Food Bioactive Ingredients

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Membrane Separation of Food Bioactive Ingredients

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Preface

Today, bioactive compounds, as functional biomolecules, are employed in food and pharmaceuticals since they offer an added value in terms of health properties. As an example, phenolic compounds are a common category of functional molecules that display specific biological activities (e.g., antioxidant properties). Additionally, carotenoids, tocopherols, and peptides are also among the natural antioxidants, which may present a further application since they can improve the sensory properties (color, taste, etc.) when embedded into food formulations. Aromas, flavors, and fragrances are another category of chemicals (>22,000 individual molecules), such as short-chain alkanes and alkenes (with or without oxygen, nitrogen, or sulfur), alcohols, esters, ketones, and organic acids. These organic solutes are responsible for typical odors in plants, fruits, fungi, and animals, which are involved in the manufacture protocols of many foods, beverages, feeds, personal care items, perfumes, and household products, among other commercial products. Interestingly, such food ingredients can be found in natural products (e.g., fruits, vegetables), by-products and co-products (such as wastes, wastewaters), and fermentation broths. However, the separation of such ingredients from the original substrates is a great challenge since many other compounds are also contained in the matrix, making the extraction and purification more complex.

At this point, membrane technologies have been pointed out as a feasible separation pathway for extraction since they use a physical perm-selective barrier to perform the separation of micro/macromolecules from complex systems. Depending on the membrane type and process, these technologies can successfully carry out the purification and concentration of a variety of biomolecules. The use of membrane techniques has been potentially extended to such complex and tough separation applications due to their multiple advantages such as:

- Low-energy demand
- High separation/recovery rates
- No degradation of thermolabile molecules
- Easy scale-up
- Simple operating parameters

- High productivity (i.e., permeation fluxes)
- No additional phases needed

The strong need for sustainability within the food industries along with the need for innovative, optimized, and tailor-made products has pushed food manufacturers to optimize membrane applications. Following these breakthroughs, this book compiles all the important development works, research, and trends on the application of various membrane techniques and membrane-assisted extraction processes for the recovery and purification of different types of food bioactive ingredients. This book contains 13 chapters addressing the current needs of food technicians dealing with the sustainable recovery of biomolecules from natural sources.

Chapter 1 introduces the membrane separation of bioactive compounds and the implied challenges and opportunities, while Chapter 2 gives an outlook of the multiple food bioactive compounds and their properties. Chapter 3 addresses the purification of phenolic compounds from agro-food by-products using pressure-driven membrane processes (e.g., microfiltration, ultrafiltration and nanofiltration), highlighting the most relevant advances in this field. Chapter 4 deals with the separation and recovery of food bioactive ingredients using a thermal-driven membrane process like membrane distillation. Chapter 5 compiles the ultimate recovery of high-added value compounds (proteins and protein fractions) from agro-food products using electrodialysis. Chapter 6 reports the application of membranes for the separation of bioactive peptides and proteins from by-products and co-products. Chapter 7 collects the recent findings of using nanofiltration for the separation of polyphenols and carotenoids. Chapter 8 provides fundamentals and application of pervaporation for the extraction of volatile aroma molecules from agro-food systems. Chapter 9 describes the current challenges of purifying bioactive metabolites from fermentation broths using membranes. Chapter 10 presents the feasibility of recovering bio-metabolites from microalgae cultivation using membrane techniques. Chapter 11 denotes the combination of membrane technologies with other emerging techniques (microwave extraction) for the purification of bioactive compounds. Chapter 12 focuses on the usage of ionic-liquid membranes (microemulsions) for the separation of bioactive compounds. Finally, Chap. 13 highlights the role of mathematical modeling for the comprehension of membrane separation and transport of bioactives.

Herein, the editors would like to thank all the contributors of the book for their collaboration and efforts in bringing together different subjects dealing with membrane separation in a comprehensive way with ultimate advances in the field. Their acceptance of our invitation in these critical and pandemic times is highly appreciated. Also, it is necessary to express our sincere thanks to all the editorial staff at Springer for their help and support throughout the project. Finally, we specially acknowledge our families for their understanding and encouragement during the editing of this great project.

Gorgan, Iran — Seid Mahdi Jafari
Nuevo León, Mexico — Roberto Castro-Muñoz

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About the Editors

Seid Mahdi Jafari received his PhD in food process engineering from the University of Queensland (Australia) in 2006. Now, he is an academic member of GUASNR (Iran) and adjunct professor at UVigo (Spain). He has published more than 350 papers in international journals (h-index=64 in Scopus) and 60 book chapters and 36 books with Elsevier, Springer, and Taylor & Francis. Selected achievements:

- One of the top 1% world scientists by Thomson Reuters (2015)
- One of the top national researchers by the Iranian Ministry of Science, Research, and Technology (2017)
- One of the world's highly cited researchers by Clarivate Analytics (Web of Science) in 2018, 2019, and 2020
- A top reviewer in the field of agricultural and biological sciences by Publons (2018 and 2019)

Roberto Castro-Muñoz holds **a PhD in biotechnology** and a **European Union Joint Doctorate Erasmus Mundus Doctorate in Membrane Engineering (EUDIME)**. Roberto has been a research fellow at the University of Chemistry and Technology Prague, Czech Republic, and early-stage researcher at **Tecnologico de Monterrey**, Mexico. He is a member of the **National Research Council of Mexico** (CONACYT,) Level 2 (out of 3). Since October 2020, Roberto is working as a guest researcher at **Gdansk University of Technology (Poland)** under the framework of **Ulam Program** from

Polish National Agency for Academic Exchange (NAWA). His project deals with the fabrication and application of sustainable membranes using deep eutectic solvents. His main research activities are also oriented to the synthesis and preparation of mixed matrix membranes for gas separation and pervaporation, among other membrane technologies. To date, he has authored over 90 scientific papers, 10 book chapters in the field of membrane technologies, and their application to environmental, food, and biotechnological fields.

Part I
General Overview of Membrane Separation Technologies for Bioactives

Chapter 1
Introduction to Membrane Separation of Bioactive Compounds; Challenges and Opportunities

Roberto Castro-Muñoz and Seid Mahdi Jafari

Abstract Today, membrane technologies are emerging techniques as efficient protocols in multiple types of separation, including chemical compounds, solvents, biomolecules, salts, ions, among others. So far, it is likely that standard membrane-based technologies driven by pressure, such as microfiltration (MF), ultrafiltration (UF) and nanofiltration (NF), have been mainly explored in the separation of biologically active compounds and food ingredients from natural products. More emergently, fractionation and concentration of bioactive compounds, such as phenolic compounds from agro-food wastes and by-products, can also be done via membrane technologies. At this point, such technologies have been fully involved within valorization and recycling protocols of various by-products. Thus, the aim of this chapter is to provide a comprehensive overview of the main agro-food by-products processed by membrane technologies for the recovery of phenolic compounds, their derivatives of different molecular weight and some other compounds. An introduction is provided in terms of separation processes, molecule properties, membrane features and other interesting phenomena that occur during their extraction. To finalize, the current challenges of membrane technologies in bioactive separation are elucidated.

Keywords Bioactives · Membrane technologies · Wastes · Natural products · Food ingredients · Fractionation

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Nomenclature

MF	Microfiltration
UF	Ultrafiltration
NF	Nanofiltration
MWCO	Molecular weight cut-off
SG	steviol glycosides

1 Introduction

The food industry faces many issues during the production of the crucial ingredients for the fabrication of food products (Gibson et al. 2004). This becomes more challenging when there is a need of satisfying the production of bioactive compounds involved in food products. According to the literature, a bioactive compound comprises any kind of chemical found in small quantities in plants, vegetables and specific natural foods (such as fruits, nuts, oils, grains, among others), which must display any actions in the body that may foster good health in the consumers (Panić et al. 2019), for example, antioxidant (such as polyphenols and carotenoids) and non-antioxidant (such as phytosterols) compounds and dietary fiber have proved a significant role in health (Saura-Calixto and Goni 2009). Thanks to the high amount of bioactive compounds in natural products, scientists and food technicians are continuously exploring several types of sources to extract such bioactives and some other food ingredients (Conidi et al. 2020). To some extent, it is quite possible that the current available natural products may satisfy the current nutritive requirements in the manufacture of food products (Burdock et al. 2006), however, the main issue concerns to the right and suitable extraction protocol towards such molecules. To date, several extraction techniques and methods have been evaluated including hot-water extraction (Rao et al. 2012), solvent extraction, irradiation-assisted extraction, adsorption (Cerón-Montes et al. 2015; Valencia-Arredondo et al. 2020), ultrasound-assisted extraction (Malićanin et al. 2014), enzyme-assisted extraction (Galiano et al. 2019), pulsed-electric field (Gachovska et al. 2010) and supercritical fluid extraction (Chemat et al. 2020; Barba et al. 2015). Most of these methods have not released enough positive results associated to relevant factors, e.g. specific bioactives, such as phenolic compounds, antioxidants carotenoids, to mention just a few of them, tend to be thermolabile that imply their degradation/denaturation related to their low stability at high temperatures, long extraction periods and the necessity of solvents in such mentioned methodologies (Cassano and Conidi 2019; Garcia-Castello et al. 2010; Castro-Muñoz et al. 2016a). Therefore, new protocols and techniques are being proposed by the research community; in which membrane technologies are pointed out as promising methods since they own multiple advantages over conventional and emerging extraction techniques, such as low energy demand, high separation efficiency, possibility of scale-up, simple operating parameters, high productivity (i.e., permeate fluxes), and the absence of phase transition

(Castro-Muñoz et al. 2021; Díaz-Montes and Castro-Muñoz 2019). Together with these advantages, the inherent properties of the membranes facilitate the separation of bioactive and food ingredients from natural systems. However, the application of membrane technologies does not only rely on molecule's extraction from natural sources, their role has also been directed towards the agro-food waste valorization (Castro-Muñoz et al. 2020a; Cassano et al. 2015a; Ochando-Pulido and Martínez-Férez 2017; Roselló-Soto et al. 2015). Food waste generation is a result of raisin global economic development, which collaborates to discard food and by-products that still contain nutritive agents and is most often related to the behavior of retailers, the foodservice sector, and consumers (Ong et al. 2018). Carmona-Cabello et al. (2018) highlighted the importance of new strategies in biorefineries based on food waste nutrients and their interactions to generate new sustainable feedstocks, as illustrated in Fig. 1.1.

In addition to this, it is well-known that the final waste disposal has become a major concern of food industries due its harmful impact on the environment. Until now, various methods have been potentially proposed attending such an issue, including dissolved air flotation, simple decantation, de-emulsification, coagulation and flocculation, enzymatic hydrolysis, fermentations, to mention just a few of them, in which their primary core is targeted to reduce the organic matter from aqueous waste stream (Maroušek et al. 2019; Ale et al. 2020) or to produce extensive valuable components (García-Depraect et al. 2021). At this point, membrane technologies, such as micro- (MF), ultra- (UF) and nano- (NF) filtration, have also assisted the treatment of food wastes (by-products, wastewaters, so on). As an outlook, it can be described that MF has been involved in macroscopic pre-treatment (MF), while UF and NF implementation has been mainly devoted to the selective separation, fractionation and concentration (Cassano and Conidi 2019; Cassano

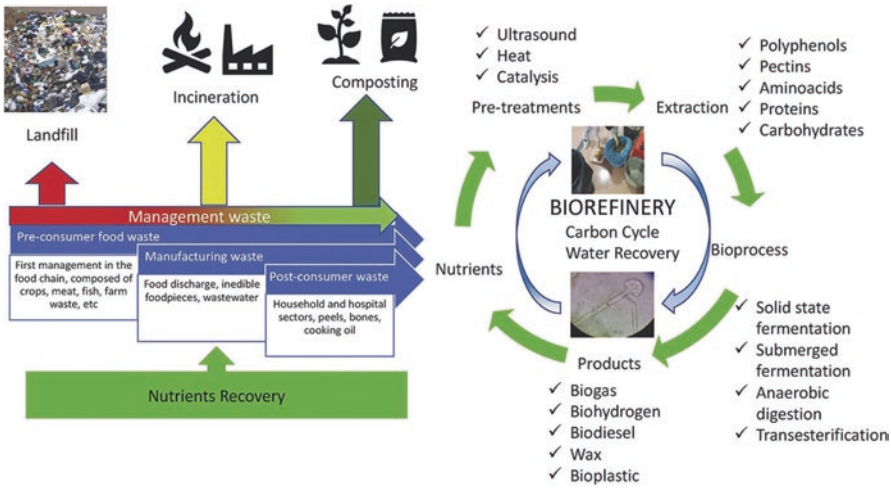

Fig. 1.1 General concept of food waste recovery based on its composition in biorefinery (Carmona-Cabello et al. 2018)

et al. 2015a; Galanakis 2015). Therefore, the main goal of this chapter is to release an overview of the bioactive compounds (mainly phenolic compounds) and some food ingredients that have been recovered from natural sources and food wastes by means of membrane-based technologies. This chapter also describes some basic principles of membrane technologies and their relevant phenomena appearing during the recovery of specific compounds, finalizing with the current challenges of membrane technologies in bioactive extraction.

2 Membrane Technologies: The Emerging Pathway for Recovering Bioactive Compounds

In principle, pressure-driven membrane technologies are generally differentiated by the membrane's molecular weight cut-off (MWCO), as represented in Fig. 1.2. Initially, the presence of a narrower pore size of the membrane will require a higher pressure demand. MF generally owns the larger pore size allowing to easily remove suspended particles, bacteria, and oil emulsion (Ochando-Pulido and Martínez-Férez 2017; Castro-Muñoz et al. 2015a), while UF is declared as one of the most efficient membrane technologies for the separation of proteins, sub-molecular organic groups, viruses, macromolecules (Russo et al. 2019; Castro-Muñoz and

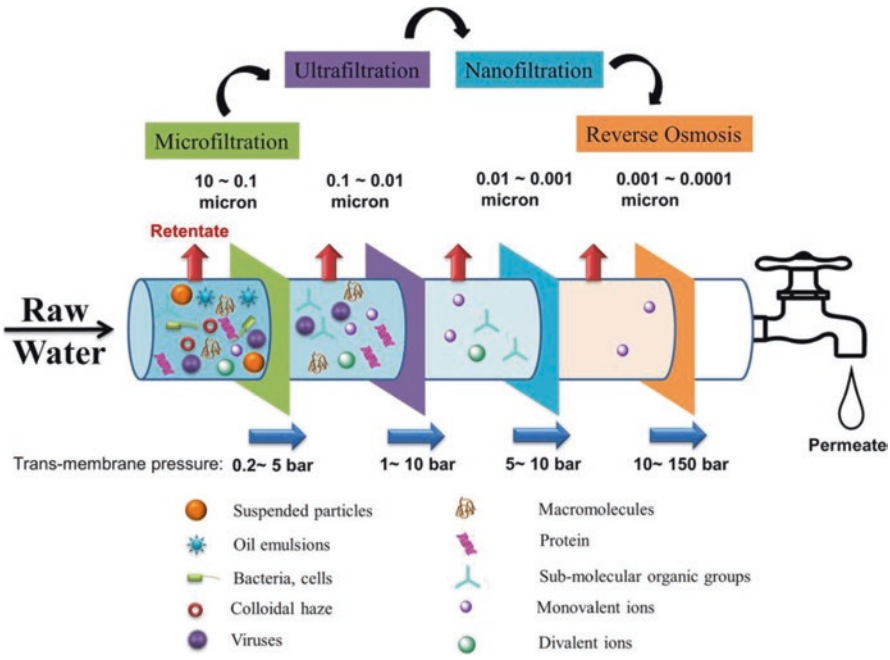

Fig. 1.2 Schematic drawing of pressure-driven membrane technologies and their role in separation (Liang et al. 2019)

Yañez-Fernandez 2015; Van Der Bruggen et al. 2003a). Evidently, the separation performance of UF becomes more efficient when membranes have tight pore sizes (Galanakis 2015; Cassano et al. 2018), it means, the UF membranes possess a MWCO in the range of 1–3 kDa, being able to effectively extract and thus concentrate low-molecular weight molecules (including anthocyanins, low molecular weight phenols, low molecular weight sugars, and peptides) (Castro-Muñoz et al. 2020a); these particular membranes are categorized in the molecular limit of the NF membranes.

Considered as the most selective technology for the fractionation and concentration of bioactives, NF technology (having pore size between 350–400 Da), together with tight UF membranes are the most recommended to achieve the recovery of low molecular weight polyphenols (Liang et al. 2019; Castro-Muñoz et al. 2019a). In the light of recovery bioactives from natural products, Table 1.1 summarizes the most extracted bioactives from natural sources using membrane technologies. It can be proved that these technologies exhibit acceptable recovery rates towards various bioactives; for instance, MF offers a rate from 47 up to ∼100% toward molecules with a molecular weight between 200 and 500 g/mol, such as anthocyanins, glutamine, isoproline, proline, betanin, isobetanin, sugars, and galacturonic acid and some phenolic compounds. Depending on the membrane's MWCO, UF can display rates between 44 and 99% of similar compounds, which have been mainly contained on the permeate side. It is important to note that some of these bioactives can be initiated to be retained by the membranes, and hence partially recovered on the retentate side. NF in turn collects mostly water on permeate side and concurrently concentrates bioactive molecules on the retentate side from 50 up to 99%. In addition to this, the application of membrane technologies has been extended to the extraction of specific food ingredients. This is the case of steviol glycosides (SGs) generally obtained from the *Stevia rebaudiana* plant (Žlabur et al. 2015). Such ingredients have recently increased their popularity since they can easily exceed the sweetening power of sucrose. Castro-Muñoz and co-workers (Castro-Muñoz et al. 2020b) have recently reviewed the current advanced in extracting SGs via membrane process. In principle, considering their molecular weight (oscillates about 318 g/mol) (Myint et al. 2020) and physiochemical properties, their extraction has been proposed using specific methods (such as solvent extraction, microwave-assisted extraction, supercritical fluid extraction, chromatographic techniques, etc) (Žlabur et al. 2015; Bursać Kovačević et al. 2018; Jaitak et al. 2009; Carbonell-Capella et al. 2017), however, their purification becomes challenging since they have exhibited specific bioactive properties (against diabetes mellitus, cancer, hypertension, gastroenteritis, cholesterol) (Ceunen and Geuns 2013), therefore, the research community has initiated to look for alternatives to preserve such bioactivity. By analyzing the literature data, Castro-Muñoz et al. stated that membranes can offer recovery yields from 25 to 80%. They also found out that the recovery rate strongly depends on various factors, such as operating parameters (transmembrane pressure, feed flow, temperature, etc.), intrinsic properties of the membranes and pre-treatment steps. However, the highest efficiencies were noticed using integrated membrane processes. For instance, Díaz-Montes et al. (2020a) demonstrated that a

Table 1.1 Bioactive compounds extracted from natural products via membrane processes

Bioactive compound	Natural source	Recovery rate	Technology	Membrane characteristics (MWCO/material/configuration)	Ref.
Antioxidant compounds	Orange juice	~98.4%	UF	15 kDa/PVDF/tubular	Cassano (2003)
	Lemon juice	~98.4%			
	Carrot juice	~98.4%			
Ascorbic acid	Kiwifruit juice	~99.5%	UF	15 kDa/PVDF/tubular	Cassano et al. (2004)
Aroma compounds (methyl butanoate, ethyl butanoate, methyl benzoate, ethyl benzoate, 3-hexen-1-ol, (E)-hexen-1-ol, 1-hexanol, 1-octen-3-ol)		N.R	UF	15 kDa/PVDF/tubular	
Betacyanins	Cactus pear juice	~63.8%	UF	10 kDa/PSF/hollow fiber	Cassano et al. (2007)
Betaxanthins		~93.5%			
Ascorbic acid		62.4%			
Citric acid		62.4%			
Glutamic acid		65.5%			
Pectins	Kiwifruit juice	60.0%	UF	30 kDa/cellulose/flat sheet	Cassano et al. (2008)
Folic acid		95.6%			
Citric acid		98.0%			
Ascorbic acid		96.4%			
Glutamic acid		~100.0%			
Total polyphenols		86.4%			
Total phenolics	Clementine mandarin juice	83.6%	UF	N.R/PSF/hollow fiber	Cassano et al. (2009)
		91.7%		N.R./PEEKWC/hollow fiber	

Flavonoids	Cactus pear juice	58.2%	UF	200 kDa/PVDF/flat sheet	Cassano et al. (2010)
Total phenolics		93.8%			
Ascorbic acid		72.4%			
Betacyanins		100.0%			
Betaxanthins		77.0%			
Proteins		100.0%			
Ascorbic acid	Pomegranate juice	69.1%	UF	10% rejection dextran 68,800 MW/PEEK/hollow fiber	Cassano et al. (2011a)
Total polyphenols (cathechin)		83.4%		10% rejection dextran 68,800 MW/PEEK/hollow fiber	
Malic acid		95.7%		10% rejection dextran 68,800 MW/PEEK/hollow fiber	
Citric acid		98.6%		10% rejection dextran 68,800 MW/PEEK/hollow fiber	
Betalains	Purple cactus pear juice	100.0%	UF	100 kDa/PSF/hollow fiber	Castro-Muñoz et al. (2015b)
Anthocyanins	Blue corn extract	~78.0%	UF	5 kDa/regenerated cellulose/ spiral wound	Cerón-Montes et al. (2015)
Hesperidin	Lemon juice	~65.8%	UF	N.R./PVDF/flat sheet	Chornomaz et al. (2013)

(continued)

Table 1.1 (continued)

Bioactive compound	Natural source	Recovery rate	Technology	Membrane characteristics (MWCO/material/configuration)	Ref.
Anthocyanins	Roselle extract	~100.0%	UF	5 kDa/PES/flat sheet	Cisse et al. (2011a)
		~90.0%	UF	1 kDa/composite polyamide/flat sheet	
		~90.0%		2 kDa/thin film/flat sheet	
		~80.0%		20 kDa/PES/flat sheet	
		~60.0%		50 kDa/PES/flat sheet	
		~90.0%	NF	N.R./composite/flat sheet	
		~100.0%		0.2–0.4 kDa/polyamide thin-film composite/flat sheet	
		~100.0%		N.R./PES/flat sheet	
		~100.0%		0.15–0.3 kDa/polyamide PSF thin-film/flat sheet	
		~100.0%		N.R./cross linked polyamide composite/flat sheet	
		~100.0%		N.R./composite/flat sheet	
Vitamin C	Roselle extract	~95.0%	MF	0.2 μm/ceramic/tubular	Cisse et al. (2011b)
Anthocyanins		~98.4%			

Total polyphenols	Bergamot juice	93.7%	UF	100 kDa/PSF/hollow fiber	Conidi et al. (2011)
Narirutin		99.2%	NF	450 Da/TiO_2/Monotubular	
Naringin		95.3%			
Hesperidin		91.7%			
Neohesperidin		96.3%			
Malic acid		99.2%	UF	100 kDa/PSF/hollow fiber	
Ascorbic acid		87.5%			
Citric acid		99.7%			
Total polyphenols	Pomegranate juice	92.0%	UF	150 kDa/cellulose triacetate/ hollow fiber	Conidi et al. (2017)
Cyanidin 3,5-O-diglucoside		90.1%			
Cyanidin 3-O-diglucoside		93.1%			
Delphinidin 3-O-glucoside		82.0%			
Pelargolidin 3,5-O-diglucoside		85.1%			
Anthocyanins		89.7%	NF	2 kDa/thin film composite/ flat sheet	
Polyphenols		86.0%			
Sucrose	Pineapple juice	74.2%	UF	100 kDa/PSF/flat sheet	de Carvalho et al. (2008)
Vitamin C	Passion fruit juice	~84.3%	MF	0.3 μm/polyamide/hollow fiber	De Oliveira (2012)
Galacturonic acid		~59.5%			
Chlorogenic acid, Cynarin, Apigenin-7-O-glucoside	Artichoke extract	>85.0%	NF	400 Da/PES/spiral wound	Cassano et al. (2015b)

(continued)

Table 1.1 (continued)

Bioactive compound	Natural source	Recovery rate	Technology	Membrane characteristics (MWCO/material/ configuration)	Ref.
Sinapic acid	Blood orange juice	94.2%	UF	100 kDa/PSF/hollow fiber	Destani et al. (2013)
p-Coumaric acid		89.9%			
Naringin		95.9%			
Hydroxybenzoic acid		95.0%			
Hesperidin		96.0%			
Ferulic acid		93.1%			
Epicatechin		95.6%			
Ellagic acid		94.7%			
Catechin hydrate		97. 0%			
Caffeic acid		94.9%			
Chlorogenic acid		99.6%			
Total phenolics	Castanea sativa leaves aqueous extract	92.1%	UF	5 kDa/modified PES/flat sheet	Díaz-Reinoso et al. (2011)
		82.5%		10 kDa/modified PES/flat sheet	
Soluble protein				5 kDa/modified PES/flat sheet	
		96.5%		5 kDa/modified PES/flat sheet	
		80.5%		10 kDa/modified PES/flat sheet	

Total phenols	Apple juice	45.8%	MF	0.45 μm/polyamide/flat sheet	Fuenmayor et al. (2014)
Malic acid		94.8%			
Fructose		76.8%			
Glucose		85.1%			
Sucrose		76.0%			
Ascorbic acid	Blood orange juice	90.7%	UF	15 kDa/PVDF/tubular	Galaverna et al. (2008)
Cyanidin-3-glucoside		97.7%			
Cyanidin-3-glucoside-6″-malonyl		97.1%			
Total anthocyanins		97.6%			
Sinapic acid		~100.0%			
Caffeic acid		~100.0%			
Ferulic acid		~100.0%			
p-Coumaric acid		~100.0%			
Narirutin		~100.0%			
Hesperidin		~100.0%			
Total polyphenols	Pineapple juice	92.8%	MF	0.1 μm/PSF/hollow fiber	Laorko et al. (2010)
		99.6%		0.2 μm/PSF/hollow fiber	
		75.0%	UF	30 kDa/PSF/hollow fiber	
		91.9%		100 kDa/PSF/hollow fiber	
Polyphenols	Propolis extract	92.8%	NF	98% rejection mg SO_4/ polyamide-polysulphone/ spiral module	Mello et al. (2010)
Flavonoids		~100.0%			

(continued)

Table 1.1 (continued)

Bioactive compound	Natural source	Recovery rate	Technology	Membrane characteristics (MWCO/material/configuration)	Ref.
Polyphenols	Blood orange juice	76.6%	UF	50 kDa/PSF/hollow fiber	Mondal et al. (2016)
		83.2%		100 kDa/PSF/hollow fiber	
		76.4%		50 kDa/polyacrylonitrile hollow fiber	
Anthocyanins		90.7%		50 kDa/PSF/hollow fiber	
		92.6%		100 kDa/PSF/hollow fiber	
		94.2%		50 kDa/polyacrylonitrile/hollow fiber	
Histidine	Cactus pear	100.0%	MF	0.2 μm/ceramic/N.R.	Moßhammer et al. (2006)
Glutamine		100.0%			
Isoproline		100.0%			
Proline		100.0%			
Betanin		100.0%			
Isobetanin		100.0%			
Gallic acid	Mate aqueous extract	75.8%	NF	150–300 Da/thin film/spiral-wound	Negrão Murakami et al. (2011)
3,4-Dihydroxybenzoic acid		94.7%			
Chlorogenic acid		89.5%			
4,5-Dicaffeoylquinic acid		~100.0%			

Chlorogenic acid	Apple juice	97.7%	UF	100 kDa/PES/cassette	Onsekizoglu et al. (2010)
Epicatechin		98.5%			
Phloridzin		99.3%			
Citric acid		88.9%			
Galacturonic acid		94.3%			
Malic acid		100.0%			
Quinic acid		96.5%			
Succinic acid		86.2%			
Fumaric acid		90.0%			
Trans-2-hexenal		79.4%			
Gallic acid	Pomegranate juice	87.4%	UF	30 kDa/PVDF/cassette	Onsekizoglu (2013)
Ellagic acid		84.6%			
Catechin		71.1%			
Chlorogenic acid		87.7%			
Caffeic acid		59.8%			
Citric acid		100.0%			
Malic acid		100.0%			
Quinic acid		92.0%			
Oxalic acid		99.6%			
Anthocyanins	Blueberry juice	47.6%	MF	0.45 μm/ZrO_2-TiO_2/tubular	Pizzolato et al. (2012)

(continued)

Table 1.1 (continued)

Bioactive compound	Natural source	Recovery rate	Technology	Membrane characteristics (MWCO/material/configuration)	Ref.
Total phenols	Blood orange juice	99.3%	UF	100 kDa/PSF/hollow fiber	Quist-Jensen et al. (2016)
Naringin		96.2%			
Hesperidin		96.8%			
Narirutin		95.8%			
Glycoside	Stevia extract	97.1%	MF	0.05 μm/Al_2O_3-TiO_2/tubular	Reis et al. (2009)
		93.7%		0.1 μm/Al_2O_3-TiO_2/tubular	
		94.7%		0.2 μm/Al_2O_3-TiO_2/tubular	
Phenols	Sideritis extract	83.7%	NF	500 Da/modified polyimide/flat sheet	Tylkowski et al. (2011)
		98.3%		400 Da/polyimide/flat sheet	
		99.2%		300 Da/modified polyimide/flat sheet	
Flavonoids		96.8%		500 Da/modified polyimide/flat sheet	
		98.8%		400 Da/polyimide/flat sheet	
		99.0%		300 Da/modified polyimide/flat sheet	
Anthocyanins	Raspberry	83.0%	MF	0.2 μm/ceramic/hollow fiber	Vladisavljević et al. (2013)
		56.9%	UF	30 kDa/PSF/hollow fiber	
Betalains	Xoconostle fruit juice	> 90.0%	UF	100 kDa/PSF/hollow fiber	Castro-Muñoz et al. (2018a)
Total polyphenols		> 90.0%			

Total polyphenols	Pomegranate juice	74.9%	UF	2500 kg Mol^{-1}/PSF/hollow fiber	Cassano et al. (2015c)
		67.3%		2500 kg Mol^{-1}/PEEKWC/ hollow fiber	
Flavonoids		75.8%		2500 kg Mol^{-1}/PSF/hollow fiber	
		66.5%		2500 kg Mol^{-1}/PEEKWC/ hollow fiber	
Total polyphenols	Pomegranate juice	73.5%	UF	15 kDa/stainless/tubular	Baklouti et al. (2012)
Total polyphenols	Strawberry juice	97%	NF	150–300 Da/PVDF/tubular	Arend et al. (2017)
Anthocyanins		99%			
Total polyphenols	Apple juice	48.2%	UF	100 kDa/PSF/flat sheet	Domingues et al. (2014)
		44.3%	UF	50 kDa/PES/flat sheet	Gulec et al. (2017)
		63.2%		30 kDa/regenerated cellulose/flat sheet	
Total polyphenols	Apple juice	59.2%	UF	100 kDa/modified PSF/flat sheet	Gulec et al. (2018)

(continued)

Table 1.1 (continued)

Bioactive compound	Natural source	Recovery rate	Technology	Membrane characteristics (MWCO/material/ configuration)	Ref.
Cyanindin-3-glycoside	Jussara fruit juice	93.6%	NF	180 Da/polyamide thin film composite/flat sheet	Vieira et al. (2018)
		97.8%		340 Da/polyamide thin film composite/flat sheet	
		89.9%		150–300 Da/polyamide thin film composite/flat sheet	
		78.8%		150–300 Da/polyamide thin film composite/flat sheet	
		79.9%		400 Da/PES/flat sheet	
		50.9%		1000 Da/PES/flat sheet	

two-step UF processes (implying 100/1 kDa membranes) was effective enough to extract rebaudioside A, as depicted in Fig. 1.3.

More specifically, the authors reported that the UF100 membrane unit worked mostly to remove total solids (ca. 42%) and carbohydrates (ca. 41%) from the crude aqueous extract, while tight UF1 membrane unit recovered about 93% of the initial rebaudioside A.

In the light of integrated membrane processes, Valencia-Arredondo et al. (2020) implemented, for the first time, an integrated membrane-adsorption protocol for anthocyanin extraction from red cabbage. In a first approach, the acidified extract, containing 32 mg cyanidin-3-glucoside per milliliter (mg ECyn-3-glu•L^{-1}), was processed using membrane technologies, such as MF and UF followed by adsorption processes, producing an enriched anthocyanin concentrate with 3221 mg ECyn-3-glu•L^{-1}. Secondly, the pigments were completely fractionated by molecular exclusion chromatography, reverse-phase vacuum liquid chromatography and semi-preparative chromatography, purifying di-acylated cyanidin. The latter is recognized among the most valuable water-soluble pigments. Its importance comprises as food additive for use in manufacturing purple-colored jam, confectionaries, and

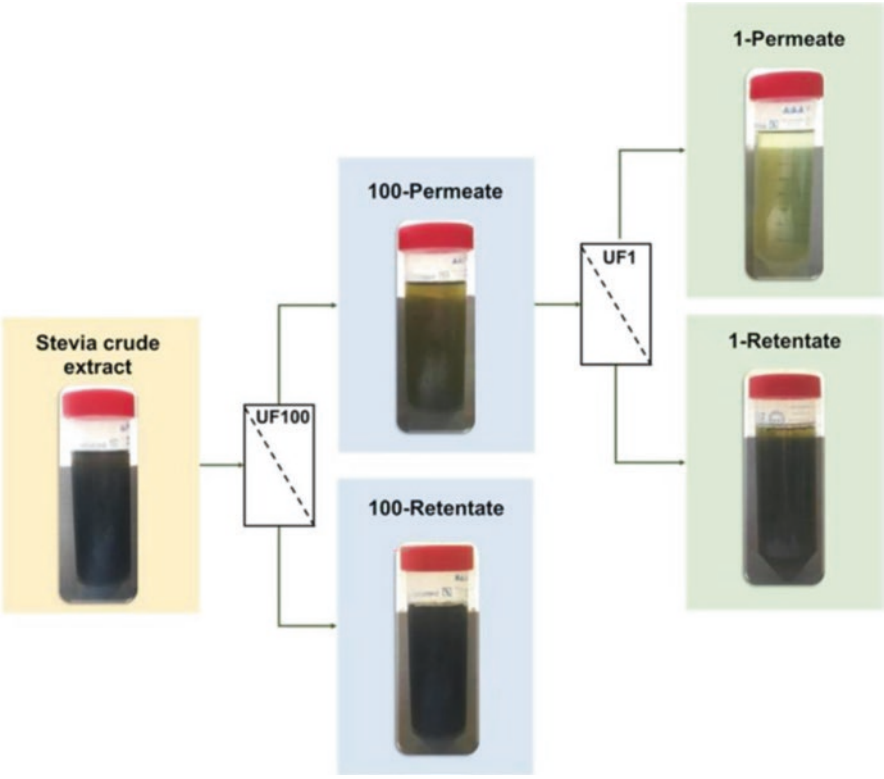

Fig. 1.3 Integrated ultrafiltration process implemented for the aqueous extraction of SGs (Díaz-Montes et al. 2020a)

beverages. It is important to mention that acylated anthocyanins are used in the food industry since they display high stability over nonacylated anthocyanins (Khoo et al. 2017). This approach opened a new window of exploration since more efficient integration processes are needed to satisfy the current demand for natural ingredients and colorants for food formulations (Carunchia et al. 2015). With the aim of extracting another food additive (like dextran) from complex aqueous systems, Díaz-Montes et al. (Díaz-Montes et al. 2020b) developed an integrated microdiafiltration-MF process for dextran extraction from fermentation broth. The usage of dextran regards as stabilizer and moisturizer (Heinze et al. 2006). Its synthesis is primarily performed via facultative bacteria *Leuconostoc mesenteroides*, cultivated in a sucrose enriched medium (Aman et al. 2012). The typical production of dextran implies separation and extraction stages, such as precipitation with polar solvents (e.g., ethanol and methanol) due to its insoluble properties in such alcohols (Vettori et al. 2011). At this point, Díaz-Montes et al. pointed out this integrated membrane approach can simultaneously extract and recover of dextran from the fermentation broth. Additionally, the authors compared the microfiltration-mediated extraction with a conventional solvent extraction protocol in terms of product yield, and physicochemical properties of the dextran. Interestingly, a successful extraction with a final yield (∼22%) was acquired using the membrane stages and resulted in less ethanol use for the final dextran precipitation, saving about 75% ethanol compared with normal ethanol precipitation.

Apart from recovery of bioactive compounds and food ingredients from natural sources, membrane technologies are contributing to the treatment of the primary by-products and wastes from food industries. Initially, these technologies were implemented for the organic matter elimination from aqueous streams, nevertheless, such a role has shifted to the valorization of agricultural waste enriched in a wide amount of bioactive molecules (Castro et al. 2018). For instance, Table 1.2 enlists the main bioactive compounds reclaimed from food wastes using membrane processes. Hydroxytyrosol, protocatechuic acid, caffeic acid, tyrosol and p-cumaric acid are among the most recovered bioactives, while olive mill wastewaters (OMW) have been found as the most investigated food waste over the last 20 years (Rahmanian et al. 2014; Conidi et al. 2014a; Galanakis et al. 2016; Cassano et al. 2016a). Russo (2007) was most probably the pioneering scientist proposing a membrane steps for the fractionation phenolic compounds from raw OMW extracts. Herein, MF and UF processes were used and produced permeates containing phenolic fractions, such as hydroxytyrosol (134,879–266,679 ppm), tyrosol (7968–11,218 ppm,) oleuropein (7765–26,698 ppm), caffeic acid (10,570–21,982 ppm) and protocatechuic acid (8871–22,601 ppm), among others. Since olive and its derived products are fundamental part of the Mediterranean diet (Bendini et al. 2007), it is obvious that by-products derived from olive processing are among the most produced wastes but also relevant source of nutraceutical molecules. The author also utilized NF and Reverse Osmosis (RO) unit operations for the fractionation and concentration of the phenolics, respectively (Russo 2007).

Unfortunately, most of the researches have concluded that the fouling phenomenon is a critical parameter when dealing with the long-term operation and stable

Table 1.2 Bioactive compounds extracted from food wastes and by-products via membrane processes

Recovered bioactive	Agro-food waste	Membrane processes	MWCO/material/configuration	Ref.
Phenolic compounds	Olive mill wastewaters	UF	30 kDa/Polyethersulfone/flat sheet	Garcia-Ivars et al. (2015)
	Winery effluents	MF	0.5 μm/PVDF/flat sheet	Giacobbo et al. (2015)
	Winery effluents	MF	0.2 μm/PVDF/hollow fiber	Giacobbo et al. (2017)
	Orange press liquor	UF	100 kDa/Polysulphone/hollow fiber	Ruby Figueroa et al. (2011) and Ruby-Figueroa et al. (2012)
Phenolic compounds	Nixtamalization wastewaters	Integrated membrane process:		Castro-Muñoz and Yañez-Fernandez (2015) and Castro-Muñoz et al. (2016b)
		MF	0.2 μm/Polysulfone/hollow fiber	
		UF	100 kDa/Polysulfone/hollow fiber	
		UF	1 kDa/Polysulfone/hollow fiber	
Phenolic compounds	Olive mill wastewaters	NF	200 Da/polymeric/spiral wound	Paraskeva et al. (2007)
Phenolic compounds	Grape seeds	UF	0.22 μm/cellulose acetate/flat sheet	Nawaz et al. (2006)
Phenolic compounds	Fermented grape pomace	UF	1000 Da/thin-film/spiral wound	Díaz-Reinoso et al. (2009) and Díaz-Reinoso et al. (2010)
		UF	1000 Da/ceramic (titania)/tubular	
		NF	250 Da/polyamide-polysulfone/spiral wound	
		NF	350 Da/polyamide-polysulfone/spiral wound	
		NF	150–300 Da/thin-film/spiral wound	

(continued)

Table 1.2 (continued)

Recovered bioactive	Agro-food waste	Membrane processes	MWCO/material/configuration	Ref.
Hydroxytyrosol, protocatechuic acid, caffeic acid, tyrosol, p-cumaric acid	Olive mill wastewaters	MF	0.2 μm/polypropylene/tubular	Cassano et al. (2011b)
		UF	4 kDa/polyethersulphone/flat sheet	
			5 kDa/regenerated cellulose/flat sheet	
			10 kDa/regenerated cellulose/flat sheet	
			10 kDa/Polyethersulphone/flat sheet	
Hydroxycinnamic acids, o-diphenols	Winery sludge from red grapes	UF	100 kDa/Polysulfone/flat sheet	Galanakis et al. (2013)
			20 kDa/Polysulfone/flat sheet	
			1 kDa/composite fluoropolymer/flat sheet	
3,4-DHPEA, p-HPEA, 3,4-DHPEA-EDA, verbascoside, and total phenols	Olive mill wastewater	Integrated membrane process:		Servili et al. (2011)
		MF	0.3 μm/polypropylene/tubular	
		UF	7 kDa/polyamide-polysulfone/spiral wound	
p-cumaric	Olive mill wastewaters	Integrated membrane process:		Conidi et al. (2014a)
		MF	0.2 μm/Polyvinylidenefluoride/flat sheet	
		UF	30 kDa/Polysulphone/hollow fiber	

Chlorogenic acid, Cynarin, Apigenin-7-O-glucoside	Artichoke wastewaters	Integrated membrane process:		Conidi et al. (2014b)
		UF	50 kDa/Polysulfone/hollow fiber	
		NF	400 Da/Polyethersulfone/spiral wound	
		NF	150–300 Da/polyamide/spiral wound	
	Artichoke wastewaters	NF	400 Da/Polyethersulphone/spiral wound	Cassano et al. (2015a)
Gallic acid, chlorogenic acid and epigallocatechin gallate	Residues from mate tree	NF	150–300 Da/thin-film/spiral wound	Prudêncio et al. (2012)
Free low MW polyphenols, hydroxytyrosol, procatechuic acid, tyrosol, oleuropein, tyrosol, caffeic acid	Olive mill wastewaters	UF	1 kDa/Polyethersulphone/spiral wound	Russo (2007)
Proanthocyanidins	Defatted milled grape seeds	UF	200 kDa/Polyvinylidenefluoride/tubular	Santamaría et al. (2002)
Hydroxytyrosol, procatechin acid, catechol, tyrosol, caffeic acid, p-cumaric acid and rutin.	Olive mill wastewaters	Integrated membrane process:		Cassano et al. (2013)
		UF	0.02 μm/Polyvinylidenefluoride/hollow fiber	
		UF	1 kDa/composite fluoropolymer/flat sheet	
		NF	Salt rejection >97%/thin-film/spiral wound	

(continued)

Table 1.2 (continued)

Recovered bioactive	Agro-food waste	Membrane processes	MWCO/material/configuration	Ref.
Isoflavones (aglycone and glucoside)	Soy processing waste	UF	1 kDa/regenerated cellulose/spiral wound	Xu et al. (2004)
Hydroxytyrosol, procatechin acid, tyrosol, caffeic acid, p-cumaric acid, oleuropein and some other low MW polyphenols.	Olive mill wastewaters	Integrated membrane process:		Garcia-Castello et al. (2010)
		UF	200 nm/Al_2O_3/tubular	
		NF	578 Da/Polyethersulphone/spiral wound	
Hydroxycinnamic acids and flavonols.	Olive mill wastewaters	UF	100 kDa/Polysulfone/spiral wound	Galanakis et al. (2010)
		UF	25 kDa/Polysulfone/spiral wound	
		UF	10 kDa/Polyethersulfone/spiral wound	
		UF	2 kDa/Polyethersulfone/spiral wound	
		NF	120 Da/Polypiperazine/spiral wound	
Anthocyanins, flavonoids	Orange press liquor	NF	180 Da/polyamide-polysulfone/spiral wound	Conidi et al. (2012)
		NF	300 Da/Polypiperazine amide thin-film composite/spiral wound	
		NF	400 Da/Polyethersulfone/spiral wound	
		NF	1000 Da/Polyethersulfone/spiral wound	
Anthocyanins (cyanidin-3-glucoside chloride, myrtillin chloride and peonidin-3-glucoside chloride), flavanones	Orange press liquor	NF	Na_2SO_4 rejection >25–50%/Polyethersulfone/spiral wound	Cassano et al. (2014)

Chlorogenic acid, Apigenin-7-O-glucoside	Artichoke wastewaters	NF	200–300 Da/polyamide/spiral wound	Conidi et al. (2015)
Oligosaccharides	Enzymatic by-product	NF	1000 Da/polyamide/spiral wound	Córdova et al. (2016)
		NF	400 Da/Polyethersulfone/spiral wound	
		NF	1000 Da/Polyethersulfone/spiral wound	
Carbohydrates	Nixtamalization wastewaters	UF	100 kDa/Polysulfone/hollow fiber	Castro-Muñoz et al. (2015c)
Oligosaccharides	Artichoke extract	Integrated membrane process:		Machado et al. (2016)
		MF	0.20 μm/Polyvinylidenefluoride/flat sheet	
		NF	150–300 Da/polyamide/tubular	
	Grape marc	Integrated membrane process:		Zagklis and Paraskeva (2015)
		UF	Pore size 100 nm/ceramic (zirconia)/tubular	
		NF	470 Da/polyamide/spiral wound	
Catechol, hydroxytyrosol, tyrosol, caffeic acid, and vanillic acid	Grape marc	Integrated membrane process:		Bazzarelli et al. (2016)
		MF	Pore size 140 nm/TiO_2/tubular	
		NF	$MgSO_4$ rejection 96%/cross-linked polyimide/spiral wound	

performance of the processes. Therefore, the concept of integrated membrane processes has also been used in these applications to reduced membrane fouling. By prepending UF and NF membranes. Cassano et al. (2013) fractionated OMWs obtaining a concentrated fraction enriched with phenolic substances (ca. 960 mg L^{-1}), which was suggested for food, cosmetic and pharmaceutical applications according to the presence of hydroxytyrosol, tyrosol, caffeic acid, p-cumaric acid, catechol and protocatechuic acid. In this work, the authors proposed a narrow pore size membrane, which in contribution with the nature of the phenolics, reached an excellent recovery. It is documented that phenolic compounds possess aromatic rings and aliphatic chains producing a hydrophobic profile increasing their volume, while concurrently attract water molecules allowing the volume increase of the polyphenols, and thus restricting their permeation due to the "polarity resistance" phenomenon (Galanakis 2015).

The winemaking is another food processing sector that produces large quantities of wastes, including grape seeds, fermented grape pomaces, lees and liquors. Díaz-Reinoso and co-workers (Díaz-Reinoso et al. 2009) recovered antioxidants from liquors. At this point, UF and NF membranes with narrow pore size were able to concentrate phenolic fractions between 0.615–1.09 mg L^{-1} from initial concentration of 0.173 mg L^{-1} in extracts. Artichoke wastewaters (AWs) are also important agro-food by-products, which have been a target of study for fractionation via integrated membrane process (Conidi et al. 2014b). In this waste, cynarin, chlorogenic acid and apigenin-7-O-glucoside were the primary molecules obtained with concentrations of 412, 612 and 400 mg L^{-1}, respectively. After evaluating their bioactivity, the complex of polyphenols displayed high antioxidant properties (ca. 40 mM Trolox).

Ultimately, an integrated membrane process was designed to extract bioactive compound compounds from Nixtamalization wastewaters (NWs) (Castro-Muñoz and Yañez-Fernandez 2015), recognized as typical by-product from the tortilla processing in America (Castro-Muñoz et al. 2017). To sum up, MF and tight UF membranes were capable to separate a phenol content of 951 mg L^{-1}. By analyzing the reported development works, this chapter has evidenced that UF and NF technologies can easily recover low molecular weight bioactives (such as phenolic compounds) from various wastewaters (Conidi et al. 2020; Cassano and Conidi 2019; Castro-Muñoz and Ruby-Figueroa 2019). Unfortunately, membrane technologies are still facing specific issues to consolidate their applications. The following section is devoted to the challenges and important factors in the framework of membrane technologies.

3 Challenges in Membrane Technologies for Bioactive Compounds Separation

The challenges of these processes deal with their weakness and limitations during the separation. In this way, it is likely that the "purity restriction" is one of the limitations of membrane technologies since most of the streams do not present pure compounds; in other words, none of the streams usually contain a minor amount of untargeted molecules (Castro-Muñoz et al. 2018b). For instance, the permeate samples can contain a significant amount of molecules aimed to concentrate in the retentate side; this is due to the fact that the membrane selectivity is not infinite. Herein, it is worth noting that the storage and handling of the membranes are crucial to extend the initial physicochemical properties and self-life, for example, if the membrane is treated by the right cleaning procedures without modifying its structure can be reutilized as long as needed. Of course, there is another important matter, like membrane fouling, to maintain the original properties of the membranes. The "fouling" is identified as the key drawback of these technologies and thus the main challenge at obtaining a more feasible and stable process, however, this is an inherent phenomenon since it depends on the types of feed bulk to be treated, basically, it is directly related to the physicochemical composition of feed (Gule et al. 2016). In addition to such factors, the fouling also becomes dependent on the membrane material and configuration, as well as operating and fluid-dynamic parameters. Particularly, the fouling, especially non-reversible fouling, can majorly restrict the permeation rate through the membranes and thus limiting their use towards specific applications.

Conventional protocols to control and regulate membrane fouling involve preliminary treatments of the feed solutions, including particle sedimentation-decantation (Fukuda et al. 2014), centrifugation (Domingues et al. 2014), flocculation (Maroušek et al. 2019), enzymatic hydrolysis (Galiano et al. 2019), screening, along with membrane surface modification (Kucera 2019), hydrodynamic optimization of the membrane module and membrane cleaning with commercial chemical or enzymatic detergents. To date, there are plenty of commercially available enzymatic (such as Ultrasil® 62 and 53, Filzym® 161) and chemical (Ultrasil® 13, OptiClean™ A, Ultrasil® 10A, AMI Chemicals® AM-55) detergents that are usually used to hydrolyze most of the pollutants, including polysaccharides, proteins, polysaccharide-like, protein-like materials and humic substances (Nguyen et al. 2010). In the field of membrane engineering, researchers are strongly working on several developments to prevent the adhesion of organic and inorganic matter that is translated to biofouling on membranes. Here, the core application has been the modification of the physicochemical properties of membranes, such as hydrophilicity, membrane charge, and membrane surface (Pichardo-Romero et al. 2020; Buonomenna 2016). Basically, the manufacture of highly hydrophilic membranes is a promising alternative since they are less prone to matter incrustation. In this regard, the preparation of nanocomposite membranes using inorganic materials and

additives seems to be the most advanced way (Castro-Muñoz et al. 2019b; Akar et al. 2013; Vatanpour et al. 2012; Zinadini et al. 2014).

Furthermore, over the course of this chapter, it has been also noted that the use of integrated membrane system can significantly contribute to reduce the early-stage fouling in membranes; a typical integrated membrane process implies the design and arrangement of multiple membrane units in sequence, contributing to mitigate fouling phenomena in the subsequent membrane stages by prepending high pore size membranes (Steeneveldt et al. 2006). Classic cases of mitigation of membrane fouling using membranes have been evidenced in the fractionation of agro-food wastes, such as artichoke wastewaters (Conidi et al. 2014b; Castro-Muñoz et al. 2018c), artichoke brines (Cassano et al. 2016b), OMWs (Russo 2007; Cassano et al. 2013), Nixtamalization (Castro-Muñoz et al. 2015a, c, 2016b; Castro-Muñoz 2019) and cellulose alkaline by-products (Cassano et al. 2016c). It is known that the implementation of integrated membrane system may require more bioseparation steps to meet high recovery rates; nevertheless, the right selection of the membranes and sequence design can give a potential strategy for the fractionation of the food and waste systems.

When dealing with the fabrication of membranes, polymers are among the main materials used in membrane preparation at industrial level. Here, there are thermal, mechanical and chemical limitations in this kind of membranes. Polymeric membrane modules cannot offer an operation at high temperature conditions since polymers do not guarantee their physical integrity at temperatures over 90–100 °C. In addition to this, most of the polymers are susceptible to chemical degradation when treating strong acid and alkaline substances, resulting in a significant reduction in membrane life. Also, specific polymeric membranes have limited mechanical stability leading to a diminish in permeability at high pressures and potential membrane failure. In this sense, it is likely that inorganic membranes, based on alumina (Al_2O_3), titania (TiO_2), silica (SiO_2) and zirconia (ZrO_2), can overcome such limitations showing greatly improved chemical, mechanical and thermal stability in comparison with polymeric membranes (Majumdar et al. 2020; Castro-Muñoz et al. 2019c). Inorganic membranes are able to operate at temperatures as high as 500 °C, with extreme pH values and they are suitable to be subjected for cleaning with chemicals, organic solvents and hot water.

Finally, as in most of the downstream processes, the energy consumption-cost relationship is a critical factor when regarding the feasibility of processes. Theoretically, pressure-driven membrane processes have been considered as low energy consumption separation techniques (Mirza 2008; Van Der Bruggen et al. 2003b), which in turn can reduce the operating costs, however, membrane modules represent the major direct capital cost of all the unit membrane separation, followed by the devices investment and their maintenance, which indeed contribute greatly to overall process costs.

4 Conclusion

In this chapter, membrane technologies have been demonstrated their ability in separation functional bioactive compounds and food ingredients from natural sources, as well as their derivative products and wastes. At this point, UF and NF membranes can be efficiently used to separate, fractionate and concentrate bioactive compounds that, according to their biological activity, have potential applications in the food and pharmaceutical industries. When compared with conventional recovery processes, these membrane-based processes are economically viable not only in terms of recovery, but also since they do not need the application of external agents. Apart from natural sources, the production of bioactive solutes from wastes is both industrially sustainable and environmentally friendly alternative.

It is quite possible that R&D will pay attention on new implementations of NF technology as the emerging tool for the recovery and concentration of phenolic-based compounds. Importantly, when further purification is required, the implementation of alternative selective methodologies, such as osmotic distillation and adsorption processes, will be needed. To finalize, this chapter also denotes the main challenges of membrane technologies in terms of purity restrictions, chemical, mechanical and thermal stability and energy consumption-cost relationship, which should be analyzed by technicians before applying at any recovery stage. Likewise, such criteria greatly play an important role in the consolidation of such technologies.

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Chapter 2
An Overview of Food Bioactive Compounds and Their Properties

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Abstract Bioactive compounds are usually described as molecules that can be found in small quantities in food and other natural matrixes that can represent an extra-nutritional contribution to the diet due to their related health effects. Membrane technology is an emerging method aimed at purifying different ingredients which has received considerable attention due to the low energy requirements in comparison to other concentration processes, wide range of applications, simplicity in continuous operation and easy integration. One of the main applications of this technique is the recovery and purification of food bioactive ingredients. Nature is an endless source of bioactive compounds that can be used for the formulation of new ingredients or other products. Therefore, it is essential to determine which are those main bioactive compounds present in food and their main properties to correctly apply this technique. The aim of this chapter is to revise those main bioactive compounds found in food, their occurrence, and main sources as well as their main properties. Furthermore, specific limitations for the application of membrane technology will be addressed whenever necessary.

Keywords Bioactive compounds · Food products · Beneficial properties · Chemical characteristics · Applications

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Abbreviations

Generic

MF	Microfiltration
UF	Ultrafiltration
NF	Nanofiltration
RO	Reverse Osmosis
TMP	Transmembrane Pressure
M_W	Molecular weight
EDPM	Porous Filtration Membranes
ED	Electrodialysis
IEMs	Ion Exchange Membranes
HCAs	Hydroxycinnamic Acids
HBAs	Hydroxybenzoic Acids
BA	Benzoic Acids
XO	Xanthine Oxidase
COX	Cyclooxygenase
IL	Interleukins
IFN-γ	Interferon Gamma
TNF-α	Tumor Necrosis Factor
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
iNOS	Nitric Oxide Synthase
GLUT-4	Glucose transporter type 4 (GLUT-4)
MA	Mevalonic Acid
MEP	Non-mevalonate or methylerythritol phosphate
PSVs	Protein Storage Vacuoles
ITCs	Resulting in isothiocyanates
BPs	Bioactive Peptides
GIT	Gastrointestinal Tract
GRAS	Generally Recognized as Safe
EFAs	Essential Fatty Acids
SCFA	Short Chain Fatty Acids
PUFAs	Poly Unsaturated Fatty Acids
ω-3	Omega-3 fatty acids
ω-6	Omega-6 fatty acids
ALA	α-linolenic acid
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
LA	Linoleic acid
GLA	γ-linolenic acid
AA	Arachidonic acid
LOXs	Lipoxygenases
EOs	Essential Oils

FOS	Fructooligosaccharides
GOS	Galactooligosaccharides
XOS	Xylooligosaccharides
LAB	Lactic Acid Bacteria

1 Introduction

The production of functional foods has increased in the latest years due to their impact on human health and prevention of certain diseases. The demand of these products is associated to the incorporation of bioactive compounds like phenolics, carotenoids, peptides and amino acids, essential fatty acids, vitamins, minerals, and certain polysaccharides. Consequently, to fulfil consumers requirements, industries are investing in processes allowing the obtaining of these ingredients from natural sources which are often present in complex matrices like plants and food by-products (Pereira et al. 2021; Otero et al. 2018; Otero et al. 2019; Garcia-Oliveira et al. 2021; Fraga-Corral et al. 2021a; Fraga-Corral et al. 2021b). Food is integrated by various structural elements with different chemistry structure, properties, and molecular size. In this context, it is important to properly select efficient separation techniques to recover and enrich these bioactive substances from complex mixtures with high selectivity. Preparative chromatographic methods have high separation resolution for compounds isolation; nevertheless, the cost of chromatography is high and needs highly qualified personal to carry out the operations (Otero et al. 2010; Alfonso et al. 2008). Currently, the purification of bioactive ingredients by membrane technologies have received considerable attention due to the low energy requirements in comparison to other concentration processes, wide range of applications, simplicity in continuous operation and easy integration (Marson et al. 2021). In addition, they are economically viable, environmentally friendly, and can be scaled up in industrial processes.

Membrane extraction technique is based on the use of a membrane as a selective separation wall and depending on the size of its pore, it is classified into microfiltration (MF), ultrafiltration (UF), nanofiltration (NF) and reverse osmosis (RO) (Fig. 2.1) (Sun et al. 2020). These constitute the most used filtration processes in the food industry, called pressure-driven separation processes since the main driving force for separation is transmembrane pressure (TMP). MF technology uses a large pore size ranging from 100 to 10,000 nm, able to purify particles in a range of 0.2 μm–2 μm (Cassano et al. 2018). This pore size usually allows the retention of bacteria, spores, fungi and yeasts; therefore, MF can be considered as a pasteurization technique that does not require heat treatments. For example, it is very common the use of MF to eliminate bacteria and spores in dairy products and to obtain and treat skimmed milk. In wine production, it is employed for clarification, elimination of yeasts and microorganisms. The technique UF uses smaller pore diameters, from 2 to 100 nm to retain molecules from 1000 to 350,000 Da and uses TMP of 1500 kPa with flows that can reach 82 kg/h*m. UF is mainly used for protein desalination and

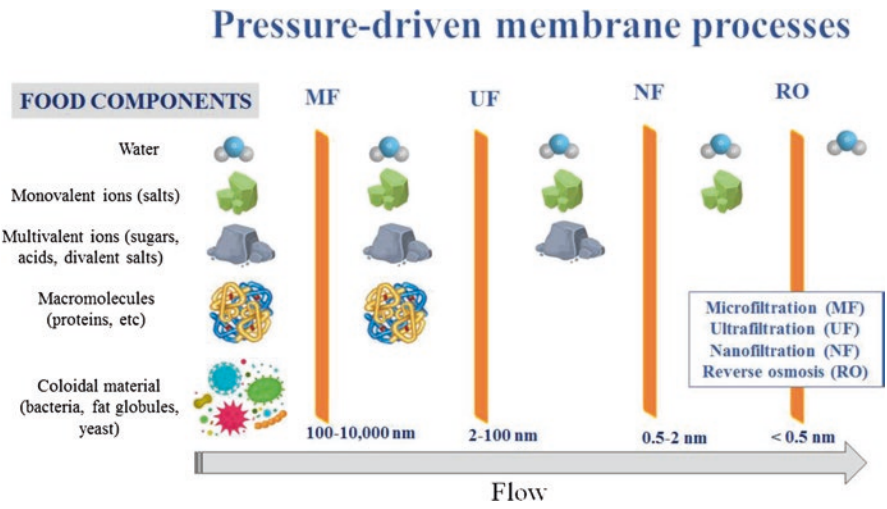

Fig. 2.1 Main membrane separation processes used in the food industry, microfiltration (MF), ultrafiltration (UF), nanofiltration (NF) and reverse osmosis (RO). Pore size range of each membrane allow to filtrate concrete food molecules

also for alcohol elimination (Liu et al. 2020a). In addition, this technology allows to isolate peptides and proteins with relatively close molecular weights (M_W) (Poulin et al. 2006). NF is another pressure-driven membrane process applied in the area between the separation capabilities of UF and RO membranes. The M_W cut off of their membranes is from 120 to 1000 Da, which pore size ranges between 0.5 and 2 nm (Cassano et al. 2018). NF can separate divalent ions like Ca^{2+}, Mg^{2+}, ions of plating industry and small molecules of sugars. NF is a suitable technique for removal of metals and for recovery of phenolic compounds and anthocyanidins from grape pomace exact (Arboleda Mejia et al. 2020), as well as for peptides separation (Poulin et al. 2006). Finally, RO processes work against osmotic pressure, *i.e.,* against chemical potential difference, so that allow filtrating mainly water. RO membranes reject about the 95% of NaCl, being a suitable technique to desalinate drinking water. For this, the operational TMP applied in RO is about 10–75 bar, much higher than in the other pressure-driven separation processes.

To sum up, different membrane pore sizes influence the access of molecules to the membrane. In addition, membranes can differ significantly in structure and types (biological source or synthetic ones). In the whole membrane process, there are three variables that define the filtration behavior: the food composition, this is the solution to be treated, the permeate (*i.e.,* the current that can pass through the membrane), which is composed of the solvent and some solutes and finally, the concentrate, meaning the current that has not passed through the membrane (Tundis et al. 1808).

Membrane technologies have extensive applications in several types of food and beverage industries, including purification for bioactive proteins from daily products, drinking water treatment and desalination of marine water. However, one of

the main limitations, especially for peptides recovering, is fouling (Marson et al. 2021). Proteins are easy foulants due to their various charged groups in a complex structure which easily bound with the membrane surface, water, and ions, affecting their real size and solubility. In addition, membrane technologies separation has low selectivity when similar-sized biomolecules are separated. Thus, it can be necessary a multi-stage membrane with different pore size to isolate the desired components, increasing the cost and decreasing the separation efficiency (Sun et al. 2020). To overcome this issue, efforts have been performed in the latest years to develop technologies aiming to increase process selectivity and production as well as to reduce membrane fouling. In this sense, electromembrane filtration process, coupling of electrical potential gradients and pressure (electronanofiltration and electrofiltration) have been shown to be suitable to improve yield and compound selectivity (Bazinet and Firdaous 2013). Furthermore, ultrasound technology has been used to enhance permeate flux. Ultrasound frequencies of 100–1000 kHz form smaller bubbles that decrease the turbulence (Marson et al. 2021). Finally, electrodialysis (electrical potential difference) with porous filtration membranes (EDPM) has been extensively studied and developed for the purification of charged bioactive proteins, fragments, or molecules from different mixtures. This new technology extends the application of electrodialysis (ED), since big molecules cannot be separated by ED due to the small pores of ion exchange membranes (IEMs). The EDPM operations can provide higher selectivity than filtration membranes for its effective separation of components with similar M_W while reducing membrane fouling (Poulin et al. 2006).

In general terms, this chapter address the challenges and perspectives involving the recovery of different size molecules present in food involved in different biological activities like antioxidant, antimicrobial, anticancer, showing also multiple applications in nutraceutical industries. It aims to describe the main sources, chemical characteristics, and their properties, as well as the main limitations regarding its recovery.

2 Phenolic Compounds

2.1 Phenolic Acids

Phenolic acids constitute a unique group of organic acids that present a benzene ring and one or more hydroxyl substituents. Concerning their biosynthesis, phenolic acids derive from phenylalanine or tyrosine through the shikimate pathway (Shahidi and Ambigaipalan 2015). They are usually found associated with the main constituents of plants such as proteins, carbohydrates by acetal, ester or ether bonds (Andreasen et al. 2000). These compounds provide protection to plants against pathogens and oxidative stress, as well as they develop allelopathic effects, that contribute to their growth and possess a positive role on the biological competence

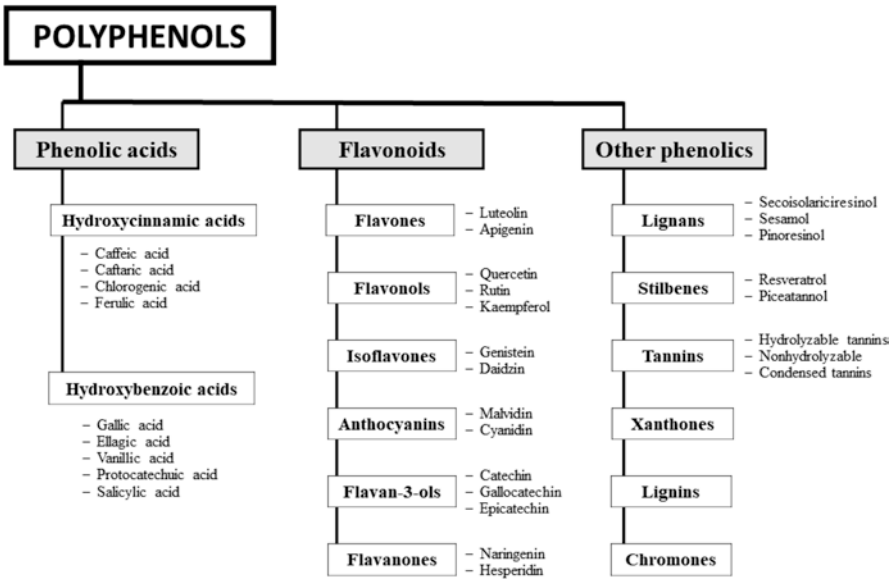

Fig. 2.2 Classification of polyphenols into phenolic acids, flavonoids and other phenolics and subclasses

against other plants. Consequently, phenolic acids are considered to promote beneficial effects on human health, mainly due to their antioxidant, anticancer, and antimicrobial properties (Shahidi and Ambigaipalan 2015). With respect to dietary sources, these compounds are mainly found in apple, cherry, blueberry, pear, peach, grapefruit, potato, spinach, tea, cider and nuts (Martins Delgado and Chammem 2019). Owing to structural criteria, phenolic acids can be classified into two subfamilies, namely hydroxycinnamic acids and hydroxybenzoic acids (Fig. 2.2).

2.1.1 Hydroxycinnamic Acids

Hydroxycinnamic acids (HCAs) are structurally characterized by a C6-C3 structure. They normally appear in conjugated forms with amino acids, peptides, and polyamines through either amide or ester bonds. In fact, as part of food products, they are included as simple esters with quinic acid and glucose, being *p*-coumaric, caffeic, ferulic, and chlorogenic acids the most relevant compounds (Mattila and Kumpulainen 2002). In addition, HCAs play essential roles in plant physiology and metabolism, as reported for *p*-coumaric acid, which is responsible for flavoring properties, as well as different bioactivities, including antibacterial and antioxidant properties, acting as a powerful free radical scavenger (Table 2.1).

Table 2.1 Examples of phenolic compounds, food sources and bioactivities

Subfamily	Compounds	Food sources	Activities	Ref.
Phenolic acids				
Hydroxybenzoic acids	Gallic acid, *p*-hydroxybenzoic acid, vanillic acid, syringic acid, protocatechuic acid	Chestnuts, peanuts, walnuts, walnuts, wheat, and spices. Blackberries, blueberries, grapefruits, grapes, mangoes, pomegranates	Anticancer, antioxidant	Martinez et al. (2017), Subramanian et al. (2015), Zhang et al. (2019), Vinothiya and Ashokkumar (2017)
Hydroxycinnamic acids	*p*-coumaric acid, caffeic acid, ferulic acid, sinapic acid, chlorogenic acid	Sunflower seeds, cereal bran, turmeric, oregano, sage, thyme, blueberries, cherries, apples, lettuce, pears, strawberries, spinach.	Antidiabetic, antioxidant, neuroprotective, anticancer	Martinez et al. (2017), Ali and Mansouri (2019), Sharma et al. (2017), Singh et al. (2020) and Zheng et al. (2020)
Flavonoids				
Flavanones	Naringin, naringenin, hesperetin, hesperidin	Tomatoes, citrus fruits (peels)	Cardioprotection, antioxidant, anti-inflammatory	(Kamran and Dangles 2014; Chanet et al. 2012; Justesen et al. 1998; Di et al. 2005; Stevens et al. 2019; Testai and Calderone 2017)
Isoflavonoids	Genistein, daidzein	Soy, beans, tofu, lupine, peanuts, some legumes	Antioxidant, anticancer, antidiabetic, cardioprotection	(Kaushik et al. 2019; Jin et al. 2010; Ahmed et al. n.d.; Farias et al. 2020)

(continued)

Table 2.1 (continued)

Anthocyanins	Cyanidin, malvidin, pelargonidin, delphinidin	Berry-type fruits, red wine	Antioxidant, anticancer, antidiabetic, prebiotic activity	(Khoo et al. 2017; Salehi et al. 2020; Fang et al. 2018; Bontempo et al. 2015; León-gonzález et al. 2018; Oliveira et al. 2020; Galvão et al. 2018; Zhou et al. 2020)
Flavones	Apigenin	Celery, broccoli, carrots, green pepper, parsley, chamomile tea, dandelion, perilla.	Anticancer, anti-inflammatory, antioxidant	(Yan et al. 2017; Wang et al. 2014; Kim et al. 2019; Dou et al. 2020; López-lázaro 2009)
Flavones, flavonols	Luteolin, quercetin	Celery, broccoli, carrots, green pepper, parsley, chamomile tea, dandelion, broccoli, black grapes, apples, black tea, onion leaves.	Anticancer, anti-inflammatory, antioxidant, cardioprotective, anti-obesity	(Yan et al. 2017; Wang et al. 2014; Kim et al. 2019; Dou et al. 2020; López-lázaro 2009; Dabeek and Marra 2019; Patel et al. 2018)
Flavonols, flavanols	Kaempferol, catechin	Broccoli, black grapes, apples, black tea, onion leaves. Green tea, cocoa, legumes, red wine	Anti-inflammatory, antioxidant, cardioprotective, anti-obesity, antidiabetic	(Dabeek and Marra 2019; Patel et al. 2018; De Pascual-teresa et al. 2000; Aron and Kennedy 2008; Stahl et al. 2009; Estefanía Márquez Campos and M-CS 2020)

(continued)

Table 2.1 (continued)

Other phenolics				
Lignans	Sesamin, secoisolariciresinol, lariciresinol, pinoresinol	Sesame, linseed, wheat bran, flax bread	Cardioprotection, antioxidant, anticancer hepatoprotective	Chen et al. (2017), Song et al. (2016), Alphonse and Aluko (2015), Tsao (2010), Dalibalta et al. (2020), Majdalawieh et al. (2020)
Stilbenes	Resveratrol		Antioxidant, anticancer	Varoni et al. (2016), Liu et al. (2017b), Ferraz et al. (n.d.), Frombaum et al. (2012)

2.1.2 Hydroxybenzoic Acids

Hydroxybenzoic acids (HBAs) present a basic C6-C1 skeleton, derived from benzoic acid (BA). They are water-soluble compounds, normally occurring as a part of the cell wall, to which is bound by their constituents, such as lignins, organic acids and sugars (Martinez et al. 2017; Oliveira et al. 2018). As plant secondary metabolites, they present different chemical substitutions to enable their accumulation, mostly including the hydroxylation and methylation of the aromatic ring. Depending on their prevalence in dietary sources, the most common HBAs are vanillic acid, protocatechuic acid, syringic acid, and *p*-hydroxybenzoic acid (Oliveira et al. 2018). The major sources of HBAs in the diet are chestnuts, peanuts, walnuts, walnuts, wheat, and some spices (Martinez et al. 2017). From an industrial point of view, it is important to note that 4-hydroxybenzoic acid and BA are authorized as food additives, being legally accepted to make part of different products (Martins Delgado and Chammem 2019).

2.2 Flavonoids

Flavonoids are the widest subfamily of phenolic compounds, as they include more than 9000 different structures of natural origin ubiquitously distributed in the Plant Kingdom (Chen and Yu 2011), synthesized from the condensation of phenylalanine with 3 subunits of malonyl-CoA (Gupta and Gupta 2015). They present a tricyclic base structure C6-C3-C6, being water-soluble metabolites that mostly appear as glycosides instead of aglycones, and which participate in essential processes related to plant defense and growth (Havsteen 2002). Flavonoids are further subdivided

into different groups, depending on their chemical structure, especially involved in the substitution degree of the central ring (mostly hydroxylations, methoxylations, prenylations, and glycosylations) (Dai and Mumper 2010), namely: flavones, flavonols, flavanones, isoflavonoids, flavanols, and anthocyanins (Brodowska 2017) (Fig. 2.2). The health benefits of flavonoids consumption is largely known, since they present important biological activities, including antioxidant, anti-inflammatory, antidiabetic, anticancer, anti-obesity and cardioprotective effects, as already reported for both *in vitro* and *in vivo* models (Havsteen 2002) (Table 2.1). Such activities are essentially due to their ability to scavenge reactive oxygen species, modulate key cell signaling pathways, as well as being powerful inhibitors of several enzymes related to oxidative stress, such as xanthine oxidase (XO), cyclooxygenase (COX), lipoxygenase, NADPH oxidase and phosphoinositide 3 -kinase (Metodiewa et al. 1997; Hayashi et al. 1988; Kim et al. 2009; Xiao et al. 2017; Rizza et al. 2011). Additionally, it is reported that they inhibit the production of pro-inflammatory cytokins, such as interleukins (IL) IL-1β, IL-2, IL-6, Interferon gamma (IFN-γ) or tumor necrosis factor (TNF-α), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and the expression of nitric oxide synthase (iNOS) (Bhaskar et al. 2016; Song et al. 2014). Regarding the antidiabetic activity of flavonoids, they are able to drive a reduction of the expression of digestive enzymes that metabolize carbohydrates, modulates glucose uptake by the expression of transporter proteins, such as Glucose transporter type 4 (GLUT-4) (Al-Ishaq et al. 2020). Furthermore, flavonoids consumption has been reported to positively modulate the gut microbiota, as proved on *in vivo* murine models (Porras et al. 2017). Concerning the health-promoting effects of flavonoids in humans, different interventional studies (Ivey et al. 2015; Liu et al. 2017a) have indicated that doses between 200 to 350 mg can reduce the risk of mortality in the general population in addition to providing preventive effects against cancer and cardiovascular diseases (Liu et al. 2017a). Therefore, they could be an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal and cosmetic applications (Kaleem and Ahmad 2018). As a consequence of the ubiquitous distribution, flavonoids are present in a wide range of foods and beverages of plant origin, such as fruits, vegetables, tea, cocoa, wine, and grains (Havsteen 2002).

2.2.1 Flavones

Flavones are characterized by having a double bond between C2 and C3 positions in the flavonoid skeleton, together with an absence of substituents at position C3 (5) and a keto group at position C4 (Hostetler et al. 2017). Regarding their role as plant secondary metabolites, they are the major pigments in white and cream-colored flowers, where they act as UV-protectors (Sen et al. 2018). Consequently, they are mainly found present in leaves, flowers, and some fruits. Among the foods with the highest flavone contents, celery, parsley, mint, ginkgo biloba, red peppers and chamomile are the most relevant sources. Moreover, it is reported that the peel of citrus fruits are rich in these compounds, mainly polymethoxylated flavones, such

as tangeretin, nobiletin, and sinensetin (Manach et al. 2004). Together with these compounds, the most relevant flavones are apigenin and luteolin. Luteolin present in apple skin, chrysanthemum flowers, and in vegetables such as broccoli, parsley, cabbages, peppers, celery, carrots (Hostetler et al. 2017). It has been used in the traditional Chinese medicine to treat hypertension, inflammatory diseases, and cancer (Galati and O'Brien 2004). On the other hand, apigenin is found in wheat sprouts, tea, oranges and in some condiments (Havsteen 2002). Regarding its biological properties, it is known that apigenin provides the antibacterial, anti-inflammatory, and antispasmodic effects associated with chamomile, in addition to important anticancer and antioxidant effects (Yan et al. 2017; Wang et al. 2014; Kim et al. 2019) (Table 2.1).

2.2.2 Flavonols

Flavonols constitute the most prevalent subfamily of flavonoids, considered as 3-hydroxyflavones, since they share the same skeleton as flavones, including an additional hydroxyl group at C-3 position (Panche et al. 2016). Among these, kaempferol, quercetin, myricetin and fisetin (Panche et al. 2016). Its dietary sources include kale, tomatoes, apples, berries, grapes, and onions, as well as wine and tea (Makris et al. 2006).

2.2.3 Flavanones

Flavanones, also known as dihydroflavones, are characterized by the saturation of B ring within the flavonoid structure. They are present in a wide range of plants, especially those from Compositae, Leguminosae and Rutaceae families. Flavanones usually are found as general constituents, making part of different structures, ranging from vegetative parts to reproductive organs. These compounds exhibit a potent antioxidant capacity as a result of the spatial configuration of the different -OH groups within their structure (Panche et al. 2016). With respect to their presence in the diet, flavanones are found in all citrus fruits like lemons and oranges. Hesperitin, naringenin, and eriodictyol are the most representative compounds of this family, to which have been attributed the flavor of citrus fruits. Regarding their health benefits as bioactive compounds, flavanones have been seen to exert anticancer effects, as manifested by the protection developed against DNA damage (Gao et al. 2006).

2.2.4 Isoflavonoids

Isoflavonoids constitute a greatly diverse subfamily of flavonoids, characterized by a 3-phenylchromen-4-one nucleus, in which the C ring is bound to the central one through the C-3 position (Szeja et al. 2017). Consequently, there are different types of isoflavonoids depending on the substitution degree of both A and B rings (Guilet

et al. 2005). Thus, isoflavonoids are water-soluble compounds, mainly found as β-glucosides (genistin, daidzin, glycitin), although four categories of isovaflonoids have been described: *(a)* aglycones, such as genistein, or daidzein; *(b)* glucosides, as previously indicated; *(c)* acetylglucosides; and *(d)* malonylglycosides (Sharma and Ramawat 2016). Indeed, genistein and daidzein are the most relevant parental compounds within this subfamily. Concerning dietary sources, isoflavonoids are found in a specific food group, such as soybeans and some legumes, as well as being present in some microbes.

2.2.5 Flavanols, Flavan-3-ols, or Catechins

Flavanols present a saturated central ring with only a hydroxyl substitution at C-3 position, thus lacking the double bond between C-2 and C-3 found in other subfamilies. This subfamily comprises complex compounds ranging from catechin, epicatechin, gallocatechin to polymeric procyanidins, known as condensed tannins (Sharma and Ramawat 2016). Among them, catechin is the most important compound since they constitute the building blocks of tannins, together with its derivatives. The main sources of catechins include tea, red wine, cocoa, apples, kiwi and cereals, whereas vegetables and legumes do not present these compounds, with the exception of lentils and beans (Gramza et al. 2005). Additionally, flavanols are found in greater proportion in the skins of seeds and fruits, despite they are usually eliminated and/or inactivated during food processing, as well as they present a limited intestinal absorption (Panche et al. 2016), thus suggesting their low bioavailability upon oral consumption.

2.2.6 Anthocyanins

Anthocyanins are water-soluble compounds responsible for the blue, red, violet and orange coloration of fruits and vegetables. They are mainly found as aglycones, structurally based on the flavylium cation, which presents several hydroxyl and methoxyl groups throughout their basic structure (Panche et al. 2016). The most prevalent anthocyanins in food sources are cyanidin-3-glucoside, delphinidin, malvidin, pelargonidin and peonidin. As a consequence of their role in plants, anthocyanins make part of the different constituents of fruits such as grapes, strawberries, raspberries, blueberries, blackberries, and currants, and they are widely used in the food industry in the formulation of different foods because of their health-promoting and organoleptic-enhancing properties (Khoo et al. 2017).

2.3 Other Phenolics

2.3.1 Stilbenes

Stilbenes constitute another subfamily of phenolic compounds, structurally characterized by a basic C6-C2-C6 skeleton, whose central double bond may give rise to two different isomers: *trans*-1,2-diphenylethylene (E-stilbene) and *cis*-1,2-diphenylethylene (Z-stilbene) (Martinez et al. 2017). As phytoconstituents, they can occur in either monomeric or oligomeric forms, usually appearing as glycosylated derivatives (Varoni et al. 2016). Within this subfamily *trans*-resveratrol has gained much attention because of their attributed biological properties, being usually identified as an anti-ageing molecule, because of its properties as free radical scanvenger, and anticancer and anti-inflammatory compound (Varoni et al. 2016; Dvorakova and Landa 2017) (Table 2.1). In a lesser extent, isorhapontigenin has been recently found as a bioactive stilbene from wine grapes (Caetano et al. 2013).

2.3.2 Lignans

Lignans are dimeric phenylpropanoids, formed by the condensation of two C6-C3 subunits at the central C-8 position. According to their structure, lignans can be divided into 'classical' lignans and neolignans, depending on the dimer configuration (Zhao et al. 2018; Andargie et al. 2021; Teponno and Kusari 2016).When incorporated in the diet, lignans are metabolized to give rise to enterodiol and enterolactone by the intestinal microflora, two estrogenic compounds that may develop hormone-like functions in humans (Teponno and Kusari 2016). Besides that, these compounds possess diverse nutritional and pharmacological applications, thanks to their biological properties, acting as hepatoprotective (Chen et al. 2017), antioxidant (Song et al. 2016) and anticancer agents (Alphonse and Aluko 2015). As flavonoids, lignans are ubiquitously found in plants, mostly in Asteraceae, Berberidaceae, Quenopodiaceae, Fabaceae, Poaceae, and Scrophulariaceae families (Teponno and Kusari 2016). Among its food sources, flaxseed is the richest source of lignans, with secoisolariciresinol, lariciresinol, pinoresinol and matairesinol as the most prevalent compounds (Andargie et al. 2021), but they are also found in legumes, black tea, soy milk, coffee, strawberries, apricots, carrots, asparagus (Teponno and Kusari 2016).

3 Other Phytochemical Compounds: Terpenes, Alkaloids and Glucosinolates

Along the wide range of plant chemicals, terpenes, alkaloids and glucosinolates can be found. Within these phytochemicals, terpenes are known to be one of the most diverse and abundant class of plant secondary metabolites (Kopaczyk et al. 2020).

Terpenes are produced via mevalonic acid (MA) and non-mevalonate or methylerythritol phosphate (MEP) pathways, and they can act as hormones, pigments and electron carriers in some mechanisms (Cox-Georgian et al. 2019; Paduch et al. 2007; Niaz et al. 2019). They can be found as hydrocarbons, presenting a branched isoprene (2-methyl-1,3-butadiene) structure as the basic building block (Kopaczyk et al. 2020), or as oxygen-containing compounds in case of adding functional groups to the tail, resulting in terpenoids, also known as isoprenoids. In turn, they are categorized based on the number of isoprene units (C5H8) connected and structural conformation, resulting in chain and cyclic terpenes (Paduch et al. 2007). Terpenes and its derivatives can be either emitted directly after their synthesis or stored in resin ducts, cavities or blisters in plants (Kopaczyk et al. 2020; Paduch et al. 2007; Dilworth et al. 2017). These molecules are more abundantly synthesized by conifers such as *Pinus sylvestris*, but are also found in other plants like *Salvia miltiorrhiza* and citrus fruits, being also present in some insects, marine microorganisms and fungi, but to a lesser extent (Kopaczyk et al. 2020; Cox-Georgian et al. 2019). Their synthesis in plants is related with plant defense as insect repellents and also as attractants for some insects, promoting cross pollination, thanks to characteristic scents and taste given by terpenes (Paduch et al. 2007; Silvestre and Gandini 2008). Moreover, terpenes have been linked with multiple biological properties beneficious for human health, such as anti-inflammatory, anticancer, antihyperglycemic, antimicrobial, antifungal, antiviral activities, as well as enhancing skin penetration of dermatopic products (Table 2.2) (Kopaczyk et al. 2020; Cox-Georgian et al. 2019; Paduch et al. 2007).

Terpenes abundance stands out even more when compared with phytochemicals of medium abundance such as alkaloids, with less than half of terpenes' molecular variety, around 12,000 species (Bai et al. 2021). Alkaloids are naturally occurring nitrogen-based compounds generally derived from amino acids, which form a complex molecular ring structure where at least one atom of nitrogen is an amine (Laghezza Masci et al. 2019; Alamgeer et al. 2020), reason why most of the alkaloids have the -ine suffix, as in berberine or tetrandrine (Alamgeer et al. 2020). These heterocyclic nitrogenous compounds are mainly found in plants, such as *Papaver somniferum* (Hao et al. 2015), as well as in animals and fungi, but this is rarely the case (Schläger and Dräger 2016; Liu et al. 2020b). Alkaloids are produced by plants as a protection mechanism against multiple pathogens and herbivores (Alamgeer et al. 2020). Additionally, these molecules have been tested as promising drugs, since they present anti-inflammatory, antiviral and muscle relaxant properties (Table 2.2) (Bai et al. 2021; Das et al. 2020).

Finally, glucosinolates are presented as naturally occurring sulfur-containing glycosides. These organosulfur compounds have a common core structure (β-thioglucoside-N-hydroxysulfate) with a varying amino acid-derived side chain (Soundararajan and Kim 2018). This side chain allows to categorize glucosinolates depending on the amino acid precursor structure, resulting in aliphatic, aromatic and heterocyclic (indolyl) glucosinolates (Ishida et al. 2014; Tacer-Caba 2019; Holst and Fenwick 2003). Hence, these molecules are the result of an amino acid chain elongation process, followed by a glucosinolate core formation and

Table 2.2 Sources, properties and applications of the most relevant terpenes, alkaloids and glucosinolates

Compound	Main groups	Sources	Properties and applications	Ref.
Terpenes	Monoterpenes, Sesquiterpenes, Diterpenes, Sesterterpenes, triterpenes, Tetraterpenes	Animals (crustaceans, egg, red fish,), flowers (canna, rose, saffron, chrysanth), fruits (citrus, tropical), microorganisms (bacteria, fungi, microalgae, yeast), grain (corn, rice), legumes, plants and trees (alfalfa, cannabis, clove, cumin, curry eucalyptus, holm oak, lavender, lemongrass, parsley, pine, rosemary, sage, sunflower, tea, thyme, watercress), seaweed, vegetables (broccoli, carrot, celery, kale, lettuce, parsley, pea, pepper, pumpkin, spinach, squash, sweet potato)	Antiaging, antiatherosclerotic antibacterial, anticarcinogenic, antidementia, antifungal, antihyperglycemic, anti-inflammatory, antioxidant, antiviral, cardiovascular enhancement, fragrance production, food dye, migraine treatment, skin penetration enhancement, ocular protection, cutaneous infections treatment, wound healing	Kopaczyk et al. (2020), Cox-Georgian et al. (2019), Paduch et al. (2007), Dilworth et al. (2017) and Silvestre and Gandini (2008)
Alkaloids	Carbazoles, Carbolines, indoles, Isoquinolines, Piperidines, purines, pyrroles, Quinolines	Algae (Chlorophyta, Rhodoohyta), microorganisms (fungi), plants (Amaryllidaceae, Annonaceae, Apocynaceae, Asteraceae, Berberidaceae, Boraginaceae, Convolvulaceae, Elaeagnaceae, Erythroxylaceae, Fabaceae, Gelsemiaceae, Liliaceae, Loganiaceae, Menispermaceae, Papaveraceae, Ranunculaceae, Rubiaceae, Rutaceae, Solanaceae, Zygophyllaceae)	Analgesia, antiarrhythmic, antibacterial, anticarcinogenic, antidiabetic, anti-hypertensive, anti-inflammatory, antioxidant, antithrombotic, cardiovascular enhancement, leukemia treatment, malaria treatment	Bai et al. (2021), Laghezza Masci et al. (2019), Alamgeer et al. (2020); Hao et al. (2015), Schläger and Dräger (2016) and Das et al. (2020)
Glucosinolates	Isothiocyanates, thiocyanates, nitriles, Epithionitriles, Goitrin	Fruit (papaya), plants (garden cress, *Drypetes* plants, Indian cress, kale, moringa, nasturtium, rocket, Rubiaceae plants, spider plant, upland cress, Violaceae plants, watercress), seeds (mustard seed, rapeseed), vegetables (broccoli, Brussel sprouts, cabbage, capers, cauliflower, horseradish, turnip)	Antiatherosclerotic, antibacterial, anticarcinogenic, antifungal, anti-inflammatory, antimicrobial, antioxidant, insecticidal	Soundararajan and Kim (2018), Ishida et al. (2014), Tacer-Caba (2019) and Holst and Fenwick (2003)

Terpenes have been classified based on the number of isoprene units connected: monoterpenes (2 isoprene units), sesquiterpenes (3 isoprene units), diterpenes (4 isoprene units), sesterterpenes (5 isoprene units), triterpenes (6 isoprene units) and tetraterpenes (8 isoprene units). Alkaloids' classification is related with the chemical structure type. Glucosinolates are classified based on the hydrolized products by the myrosinase enzyme

subsequent side chain modifications, such as oxidation, hydroxylation and reduction (Soundararajan and Kim 2018; Ishida et al. 2014). Later, these phytochemicals get accumulated into protein storage vacuoles (PSVs) of seeds in both, angiosperms and gymnosperms (Holst and Fenwick 2003; Siegmund 2015; Tan et al. 2019). Primarily, glucosinolates are found in cruciferous vegetables, such as broccoli, cabbage, cauliflower and Brussels sprouts (Tacer-Caba 2019). These molecules are naturally produced by plants as part of the defense system with antifungal, antimicrobial, and insecticidal properties, although glucosinolates do not become active until tissue damage exists. Immediately, glucosinolates are released and hydrolyzed by the endogenous myrosinase enzyme, present in the cytoplasm (Holst and Fenwick 2003; Siegmund 2015), becoming available, resulting in isothiocyanates (ITCs), thiocyanates and nitriles, among others (Soundararajan and Kim 2018; Tacer-Caba 2019). In this way, glucosinolates beneficial properties have been implemented for human health purposes, thanks to their anti-inflammatory and antioxidant activities. Whereas, these organosulfur compounds are mostly known for inducing some mechanisms of the anticarcinogenic defense system against certain cancer types (Table 2.2) (Soundararajan and Kim 2018; Tacer-Caba 2019; Siegmund 2015).

4 Carotenoids and Sterols

Carotenoids are pigments that represent one of the most recognized and widespread secondary metabolite groups, and are also known as tetraterpenes, since these are molecules built from eight isoprene units ($C_{40}H_{56}$) (Cox-Georgian et al. 2019). These fat-soluble poly-unsaturated organic (polyene) compounds consist of chains formed by 3–13 conjugated double bonds, resulting in a varied group of naturally occurring chemicals, integrated by over 700 types (Decker 2003; Šeregelj et al. 2021). These molecules are produced in chloroplasts through the MEP pathway and are classified based on the absence or presence of oxygen-containing functional groups, resulting in carotenes and xanthophylls (Rodriguez-Amaya 2015; Trono 2019). Carotenes are non-polar pure hydrocarbons, since their chemical configuration only includes hydrogen and carbon atoms, as in α-carotene, β-carotene and lycopene (Morançais et al. 2018). These molecules are known for their food coloring capabilities, providing orange and red colorations of many fruits, vegetables and cereals as well as macro- and micro- algae (Trono 2019; Morançais et al. 2018; Saini et al. 2015). Moreover, α-carotene and β-carotene are known for being vitamin A precursors, which play essential roles in vertebrates (Nagarajan et al. 2017). By contrast, xanthophylls are polar derived oxidized forms of carotenoids, so this group is integrated by oxygen-containing carotenoid forms, such as lutein, zeaxanthin, astaxanthin, cryptoxanthin and fucoxanthin (Morançais et al. 2018). These pigments provide yellow, orange and red colors in leafy vegetables, flower petals,

fruits, eggs, fish flesh, some microorganisms like yeast, bacteria and microalgae such as *Haematococcus pluvialis*, as well as in brown algae (Phaeophyceae) (Morançais et al. 2018; Breithaupt 2007; Peng et al. 2011).

Carotenoids are important pigments belonging to the light absorption system of many vegetables and fruits, being widely spread among the vegetal kingdom, and of some microorganisms. Besides their food coloring properties, these pigments have also caught the attention of food, cosmetic and medicinal industries for their beneficial bioactive capabilities applicable to human health and nutrition. Within their broad range of properties, carotenoids stand out for their antioxidant, anti-inflammatory and anti-carcinogenic activities (Rodriguez-Amaya 2015; Nagarajan et al. 2017) (Table 2.3).

Table 2.3 Sources, properties, and applications of the most relevant and common carotenoids (α-carotene, β-carotene, lycopene, lutein, zeaxanthin, astaxanthin, cryptoxanthin and fucoxanthin) and sterols (sitosterol, campesterol, stigmasterol, cholesterol and ergosterol)

Pigment	Sources	Properties and applications	Ref.
α-carotene	Flowers (chrysanth, saffron), fruits (apple, apricot, cherry, mango, orange, papaya, peach, persimmon, prune), grain (corn, rice), microorganisms (microalgae), vegetables (carrot, pepper, pumpkin, squash, sweet potato)	Anticarcinogenic, antioxidant, food dye, ocular protection	Šeregelj et al. (2021), Morançais et al. (2018), Nagarajan et al. (2017), Mohd Hatta and Othman (2020) and Jaswir et al. (2011)
β-carotene	Flowers (canna, rose, saffron, chrysanth), fruits (acerola, apple, apricot, cherry, grape, kiwi, loquat, mango, papaya, peach, pear, prune, orange, tomato, watermelon), grain (corn, rice), microorganisms (bacteria, fungi, microalgae, yeast), vegetables (broccoli, carrot, celery, kale, lettuce, parsley, pea, pepper, pumpkin, spinach, squash, sweet potato, watercress)	Antiaging, antiatherosclerotic, anticarcinogenic, antioxidant, antisunburn, cardioprotection, food dye, hepatoprotection, neuroprotection, ocular protection	Decker (2003), Šeregelj et al. (2021), Rodriguez-Amaya (2015), Morançais et al. (2018), Nagarajan et al. (2017), Mohd Hatta and Othman (2020), Jaswir et al. (2011) and Chiu et al. (2019)
Lycopene	Flowers (saffron), fruits (apricot, grape, guava, mango, orange, papaya, persimmon, Pitanga, tomato, watermelon), microorganisms (bacteria, fungi, yeast) vegetables (carrot, pumpkin, sweet potato)	Anticarcinogenic, anti-inflammatory, antioxidant, cholesterol reduction, food dye, neuroprotection, ocular protection, osteoprotection	Šeregelj et al. (2021), Rodriguez-Amaya (2015), Nagarajan et al. (2017), Mohd Hatta and Othman (2020), Jaswir et al. (2011) and Chiu et al. (2019)

(continued)

Table 2.3 (continued)

Pigment	Sources	Properties and applications	Ref.
Lutein	Animal (egg yolk), flowers (chrysanth, marigold), fruits (apple, apricot, acerola, avocado, cherry, kiwi, orange, peach, pear, persimmon, prune), grain (corn), legumes (beans), microorganisms (green algae), vegetables (beet, broccoli, Brussel sprouts, carrot, kale, lettuce, parsley, pea, pepper, spinach, squash, watercress)	Antiatherosclerotic, anticarcinogenic, antimutagenicity, antioxidant, cardiovascular enhancement, ocular protection	Šeregelj et al. (2021), Rodriguez-Amaya (2015), Morançais et al. (2018), Nagarajan et al. (2017), Mohd Hatta and Othman (2020), Jaswir et al. (2011) and Chiu et al. (2019)
Zeaxanthin	Animal (egg yolk), flowers (chrysanth, marigold, saffron), grain (corn), fruits (apricot, mango, orange, papaya, peach, persimmon, wolfberry), grain (corn), microorganisms (algae, bacteria, spinach) vegetables (alfalfa, broccoli, kale, pepper, spinach, squash)	Antiatherosclerotic, anticarcinogenic, antioxidant, food dye, ocular protection, skin pigmentation, skin protection	Šeregelj et al. (2021), Rodriguez-Amaya (2015), Morançais et al. (2018), Nagarajan et al. (2017), Mohd Hatta and Othman (2020), Jaswir et al. (2011) and Chiu et al. (2019)
Astaxanthin	Animals (crustaceans, red fish), microorganisms (algae, yeast)	Antiaging, anticarcinogenic, antidiabetic, anti-inflammatory, antimicrobial, antioxidant, cardioprotection, cholesterol reduction, food dye, neuroprotection, obesity prevention, ocular protection, skin pigmentation, skin protection	Rodriguez-Amaya (2015), Morançais et al. (2018), Mohd Hatta and Othman (2020), Jaswir et al. (2011) and Chiu et al. (2019)
Cryptoxanthin	Flowers (chrysanth), fruits (apple, apricot, acerola, cherry, loquat, mango, orange, papaya, peach, pear, persimmon, prune, tangerines, watermelon), grain (corn), microorganisms (algae), vegetables (carrot, pepper, squash)	Anticarcinogenic, antioxidant, osteoporosis prevention	Šeregelj et al. (2021), Nagarajan et al. (2017), Mohd Hatta and Othman (2020) and Jaswir et al. (2011)
Fucoxanthin	Golden-brown seaweed (Phaeophyceae), microalgae (Bacillariophyceae, Chrysophyceae, Raphidophyceae, Haptophyceae)	Anticarcinogenic, antidiabetic, antioxidant, obesity prevention	Rodriguez-Amaya (2015), Morançais et al. (2018), Mohd Hatta and Othman (2020) and Jaswir et al. (2011)

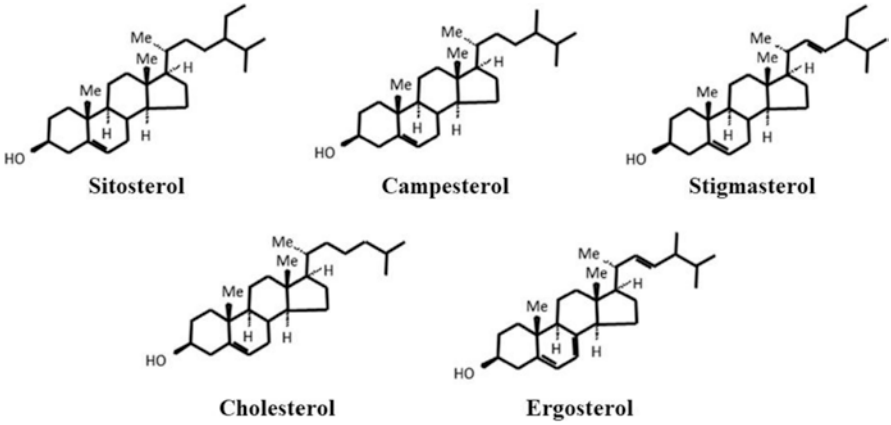

Fig. 2.3 Structural conformation of the main phytosterols (sitosterol, campesterol and stigmasterol), zoosterol (cholesterol) and mycosterol (ergosterol). Based on (Bot 2019)

Sterols, as well as carotenoids, are derived forms of terpenes. In this case, sterols are formed by six isoprene units ($C_{30}H_{48}$), so are termed as triterpenes (Cox-Georgian et al. 2019). This naturally occurring chemicals are a subgroup of steroid alcohols, which molecular structure is composed of 3 hexagonal rings and 1 pentagonal ring, with a hydroxyl group attached at position 3 of the A-ring, and a side chain at position 17 of the D-ring (Pateiro et al. 2019; Bot 2019). These molecules are classified as amphipathic lipids that can be found in the membranes of plants (phytosterols), animals (zoosterols) and some microorganisms such as fungi (mycosterols), being present in almost all living eukaryotic organisms (Bot 2019; Seçmeler and Galanakis 2019; Hazra et al. 2017; Vats 2017), although few bacteria are able to synthesize them (Wei et al. 2016). Within these groups, there are some sterols that are more abundantly found (Fig. 2.3). The most common phytosterols are sitosterol, campesterol and stigmasterol (Rodríguez-Pérez et al. 2019), while cholesterol is the most abundant zoosterol found in animal membranes (Hazra et al. 2017). In the case of fungi, ergosterol is the major membrane lipid (Bell 2006). All these triterpenes are obtained through different biosynthetic pathways that share a common biological precursor, squalene. This hydrocarbon is oxidized to oxidosqualene and later cyclization takes place to form lanosterol in animal and fungi sterols, and cycloartenol in plant sterols (Hazra et al. 2017; Wei et al. 2016).

Sterols are, therefore, essential components of animal, plant and fungal membranes that provide and define fluidity and permeability of cell membranes (Hazra et al. 2017). These structural lipids are also involved in phagocytosis, stress tolerance, sexual reproduction and cell signaling (Wei et al. 2016). In the case of phytosterols, rapeseeds and rye are their main source, being sitosterol the most abundant one, followed by campesterol (Bot 2019; Piironen et al. 2000), while the main sources of zoosterols are egg yolks, meat and fish oils, among others (Forchielli et al. 2010). Finally, mycosterols, mainly ergosterol, are usually found in yeasts. Sterols have been related with multiple beneficial activities, including anticancer,

antioxidant, antiviral and anti-atherosclerotic properties (Vats 2017). They have also been linked with a reduction of the glucose levels in blood, hence being interesting for diabetes treatment purposes (Cox-Georgian et al. 2019).

5 Bioactive Peptides and Proteins

Bioactive peptides (BPs) are natural-based compounds formed by the binding of amino acids by peptide bonds, normally containing between 2 and 20 amino acidic residues, and they have gained much attention as food additives because of their health-enhancing and disease-preventing properties (Chakrabarti et al. 2018). BPs essentially derive from the enzymatic hydrolysis of parent proteins, or by the action of fermentative microorganisms, such as bacteria belonging to Lactobacillus or Bacillus species, yeasts, and filamentous fungi (Daliri et al. 2017). However, they can be also found in their free form as constituents of their natural sources, in a lesser extent (Karami and Akbari-adergani 2019).

In this sense, due to the ubiquitous distribution of proteins in nature, the sources of BPs are heterogeneous, mostly deriving from animal, plant, extensively commercialized as dietary products, and marine origins. Thus, concerning animal-based BPs, they can be isolated from a plethora of different sources, including blood, milk, collagen, eggs, and meat, together with their derived products (Albenzio et al. 2017). In parallel, relevant plant sources of BPs are wheat, maize, soy, rice, mushrooms and pumpkins, but they can be also isolated from agro-industrial wastes (Piovesana et al. 2018). In the case of marine sources, BPs have been found as constituents of both invertebrate and vertebrate organisms, such as sponges, mollusks, ascidians, seaweeds, and algae (Ovchinnikova 2019; Jo et al. 2017). In addition to these exogenous sources of BPs, mostly incorporated as food products, it is important to note that, these compounds also present an endogenous origin, since BPs may be generated by the proteolytic activity of enzymes located along the gastrointestinal tract (GIT), during the digestion of protein-containing foods (Xu et al. 2019). Moreover, in the last years, so as to promote an efficient production of BPs with exceptional features, there has been an increasing interest on the chemical synthesis of BPs, aiming at the development of potent peptide analogues (Bechaux et al. 2019; Sharma et al. 2011).

As bioactive compounds, BPs have been revealed as multifaceted health-enhancing compounds presenting a variety of beneficial properties, acting as antidiabetic, cholesterol-lowering, anti-hypertensive, anticancer, opioid, mineral binding, antimicrobial, antioxidant, immunomodulatory, antidiabetic and osteoprotective agents (Bhandari et al. 2020). Concerning the bioactivities associated to BPs, there are a series of factors that determine the effectiveness of such properties, including the amino acidic composition of peptides, their M_W, the parental protein they derive from, and the degree of hydrolysis (Karami and Akbari-adergani 2019). Therefore, the assessment of different bioactivities to individual peptides becomes a hard task, since BPs normally occur as constituents of complex protein

hydrolysates (Piovesana et al. 2018). As a solution, the combination of rigorous peptide separation approaches with the application of bioinformatics may constitute an effective strategy to decipher cause-effects relationships between BPs and their associated bioactivities, as well as identifying active peptide sequences within the structure of different proteins (Piovesana et al. 2018).

Due to their organic nature, BPs isolated by enzymatic hydrolysis using food-grade proteases are considered as GRAS (Generally Recognized as Safe), and they can be easily incorporated to food matrices (Ulug et al. 2021). In this way, BPs are used as food additives, not only because of their beneficial effects on human health, but also because of their additional properties as providers of added value to food matrices. Thus, the addition of BPs to foods confers a positive role on the increase of their shelf-life, acting as preservatives thanks to their antioxidant properties, and on the amelioration of their sensory and rheological properties of foods, concerning taste, foaming, solubility, emulsifying, gelling and water holding capacity (Lorenzo et al. 2018). This way, many efforts are being made on BPs research, facing their sustainable production and their exploitation as ingredients of functional foods, involving novel methods such as high hydrostatic pressure processing, ultrasound and microwave-assisted extraction, pulsed electric field processing, ohmic heating, and subcritical water hydrolysis (Ulug et al. 2021).

6 Essential Fatty Acids

Essential fatty acids (EFAs) are considered a group of poly unsaturated fatty acids (PUFAs) that are incorporated to the body from exogenous dietary sources, since they cannot be synthesized by the human metabolism, although they have a direct influence on paramount physiological processes (Kaur et al. 2014). EFAs are basically distributed on two subfamilies of PUFAs, namely omega-3 fatty acids (ω-3) and omega-6 fatty acids (ω-6), depending on the carbon position presenting the first unsaturation from the end of the hydro carbonated chain within their structure: C-3 in the case of ω-3 PUFAs and C-6 in the case of ω-6 PUFAs (García-Pérez et al. 2018). Concerning the most prevalent compounds within both families, ω-3 EFAs are mostly represented by α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), whereas linoleic acid (LA), γ-linolenic acid (GLA) and arachidonic acid (AA) are considered the most prevalent ω-6 EFAs (Kang et al. 2014).

With respect to dietary sources of EFAs, both ω-3 and ω-6 fatty acids are mostly found in vegetable and marine sources. In the case of ω-3, ALA is mostly found in algae and vegetable sources, including flax, chia and paprika, among others (Cholewski et al. 2018), whereas EPA and DHA are essentially found in fish sources, such as herring, pollock roe, wild sardine, salmon and their derived products, mostly fish oil (García-Pérez et al. 2020). On the other hand, LA is considered the most predominant ω-6 EFA as part of dietary sources, which is exclusively found on vegetable sources, especially vegetable oils and their derived products, such as margarine, nuts and seeds (Innes and Calder 2018).

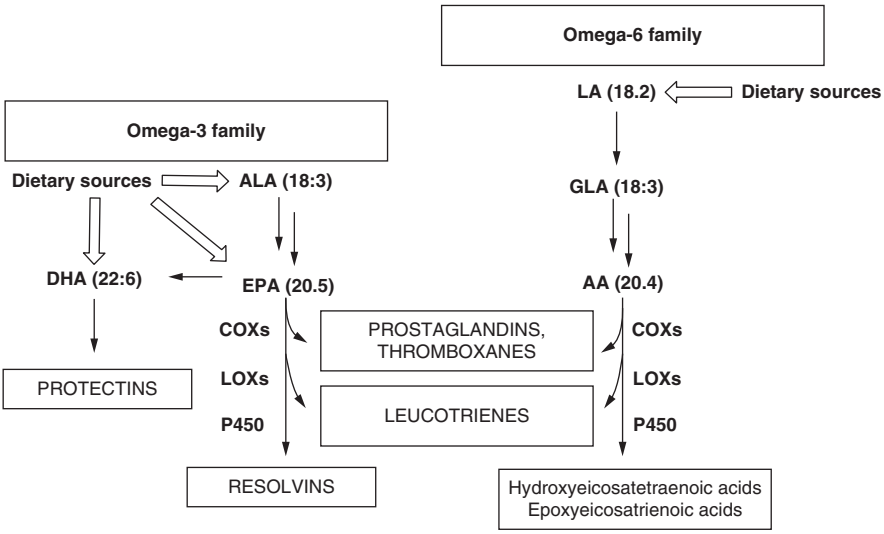

Fig. 2.4 Metabolic pathways associated with ω-3 and ω-6 EFAs. *AA* arachidonic acid, *ALA* α-linolenic acid, *COX* cyclooxygenase, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *GLA* γ-linolenic acid, *LA* linoleic acid, *LOX* lipoxygenase

Concerning their role as bioactive compounds, EFAs play an essential role on the regulation of body homeostasis, and the balance between ω-3 and ω-6 fatty acids presents a fundamental physiological influence on relevant processes involved in reproduction and development, as well as inflammation, vasodilatation, bronchodilatation and platelet aggregation (Saini and Keum 2018; Alagawany et al. 2019). Moreover, the regulatory role of both ω-3 and ω-6 fatty acids on inflammation modulates the development of inflammatory diseases, such as cardiovascular and neurodegenerative diseases, cancer and obesity (Khadge et al. 2018). Thus, different epidemiological studies have pointed that the consumption of diets with ω-3 dominance provides anti-inflammatory beneficial effects, whereas ω-6 predominant diets are associated with high risk of developing inflammatory diseases (Lands et al. 2018). Such interconnected physiological influence of EFAs is a consequence of the metabolic pathways in which they are involved, since EFA metabolism promotes the biosynthesis of oxylipins, considered as lipid mediators of inflammation (Punia et al. 2019). The production of oxylipins is catalyzed by the action of COX, lipoxygenases (LOXs), and several members of the family CYP450 on both ω-3 (EPA and DHA) and ω-6 (AA) fatty acids, thus promoting the synthesis of prostaglandins, thromboxanes and leucotrienes, which possess associated pro-inflammatory properties (Schulze et al. 2020) (Fig. 2.4).

However, in the case of ω-3 fatty acid metabolism, the pro-inflammatory effects attributed to oxylipins are countered by the synthesis of anti-inflammatory mediators, like protectins and resolvins, together with EPA and DHA that present a direct contribution on the mitigation of inflammation because of their anti-inflammatory

activity (Kwon 2020). Keeping this in mind, the essentiality associated with ω-3 and ω-6 fatty acids on human health has been assessed by the development of EFA deficiency syndrome, which is characterized by the absence of enzymes involved in EFA metabolism, thus leading to growth retardation, reproductive failure and alopecia (Anez-Bustillos et al. 2018). As a result, many efforts are being developed in the field of food science technology in order to incorporate ω-3 fatty acids on different matrices and to improve their health-promoting properties (García-Pérez et al. 2020).

7 Essential Oils

Essential oils (EOs), also known as volatile oils, are products obtained from a vegetable raw matrix by physical processes of distillation or pressing. Specifically, these ethereal oils are hydrophobic liquid concentrated which contains volatile chemical plant compounds. Moreover, they usually present mixtures of low M_W compounds (most <300 Da) and can be composed from a dozen to 300 different molecules (Baser 2009). However, most components of EOs belong to the terpene family (Modzelewska et al. 2005).

The composition of EOs can vary not only between different species, but also within the same species, mainly because of two factors: *(i)* intrinsic and *(ii)* extrinsic. Intrinsic factors are associated with the plant and its interaction with the environment (habitat, soil type and geographic area), maturity of plant and time of harvest whereas extrinsic factors are associated with extraction method and the environmental. (Dhifi et al. 2016).

These oils can be found in all parts of an aromatic plants: flowers, leaves, rhizomes, seeds, fruits, wood, and bark. However, the total content of EOs in all vegetal matrixes is less than 1% (Baser 2009). The yield and composition of EOs can be associated with several factors, many of them interrelated with each other. Seasonal variations, plant organ, degree of maturity of the plant, geographic origin, and genetics are the parameters which can affect the recovery and the chemical profile of EOs (Anwar et al. 2009). Moreover, they have been linked to numerous biological activities namely antibacterial, antioxidant, anti-inflammatory, anticancer, cytotoxicity, allelopathic and insecticidal (Dhifi et al. 2016).

In particular, some studies have suggested that EOs with a high contain of phenolic compounds (carvacrol, eugenol, and thymol) have important antimicrobial activity (Cosentino et al. 1999; Dorman and Deans 2000) (Table 2.4). Thyme, clove, and oregano EOs are some examples. However, other compounds such as terpene alcohols also present antimicrobial activity but are not as effective as those containing polyphenols. In this context, the antibacterial activity of EOs is associated with their chemical composition, the proportions of volatile molecules and their interactions (Knobloch et al. 1986).

Furthermore, EOs derived from cinnamon, nutmeg, clove, basil, parsley, oregano and thyme have some important antioxidant activities (Lobo et al. 2010), being capable not only of neutralizing free radicals, but also prevent some diseases. Their

Table 2.4 Some examples of the mainly compounds, characteristic and biological activity of essential oils (EOs)

EOs	Major compounds	Main characteristic	Biological activity	Ref.
Thyme	Thymol, carvacrol	Disruption of the cytoplasmic membrane and coagulation of cell contents.	Antimicrobial	Hammer et al. (1999), Rhayour et al. (2003) and Oliveira et al. (2007)
Clove	Eugenol			
Oregano	Carvacrol, thymol			
Cinnamon, nutmeg, clove, basil, parsley, oregano, and thyme	Thymol, carvacrol	Redox properties. Neutralization of free radicals	Antioxidant	Burt (2004)
Melaleuca alternifolia (tea tree oil)	Terpinen-4-ol	Prevention and treatment of inflammatory diseases	Anti-inflammatory: Inhibitory effect in pro-inflammatory mediator production	Hart et al. (2000)
Geranium	Geraniol, β-citronellol		Anti-inflammatory: Inhibitory effect of skin lesion induced by curdlan.	Maruyama et al. (2005)
Torreya nucifera	Limonene, δ-3-carene, α-pinene		Anti-inflammatory: Inhibitory effect on COX-2 (on prostaglandin production)	Yoon et al. (2000)
Garlic	Sulfur compounds: diallylsulfide, diallyldisulfide, diallyltrisulfide	Prevention of carcinogenic diseases.	Anticancer: decrease in the growth of neoplasms.	Milner (2001)
Myristica fragrans (nutmeg)	Myristicin		Anticancer: Inhibition of carcinogenesis induced by benzo[a]pyrene.	Zheng et al. (1992)
Citrus	*D*-limonene		Anticancer: Prevention and reduction of hepatic tumors.	Uedo et al. (1999)

antioxidant activity depends on their phenolic structure. The more active components are thymol and carvacrol (Table 2.4), but there are other components that also present antioxidant activity such as certain alcohols (linalool, geranial/neral), ethers (1,8-cineol), ketones (menthone and isomenthone), aldehydes and monoterpenes (α-terpinene, β-terpinene and α-terpinolene) (Lobo et al. 2010).

Other EOs possess anti-inflammatory activities such as geranium, *Melaleuca alternifolia* and *Torreya nucifera* oils (Knobloch et al. 1986; Hart et al. 2000; Maruyama et al. 2005) (Table 2.4). The most active components are, namely: terpinen-4-ol, geraniol, β-citronellol, linalool, limonene, δ-3-carene, α-pinene and

1,8-cineole (Hart et al. 2000; Maruyama et al. 2005; Yoon et al. 2000). All them play an important role in the prevention and treatment of inflammatory diseases by interactions involving cytokines and regulatory transcription factors and the expression of pro-inflammatory genes (Dhifi et al. 2016). These volatile oils also can present anticancer activity and play an important role in the prevention and the elimination of carcinogenic diseases. For example, sulfur compounds (diallylsulfide, diallyldisulfide, and diallyltrisulfide) of garlic EOs help preventing the production of tumors (Milner 2001); myristicin, *i.e.* a molecule which can be found in nutmeg EOs (*Myristica fragrans*), inhibits carcinogenesis (Zheng et al. 1992). Also, *d*-limonene, the main component of citrus EOs, plays an important role in the prevention and reduction of the production of stomach and liver cancer in rats through increased apoptosis and decreased DNA synthesis of these cancers (Uedo et al. 1999) (Table 2.4).

8 Vitamins and Minerals

Vitamins are organic compounds that act as catalysts in chemical reactions to maintain normal metabolic functions, growth and tissue repairing (Sardesai 2011). In this context, these complex molecules are essential micronutrients needed by the organisms in small quantities for the proper functioning of its metabolism. However, essential nutrients cannot be synthesized by the organism in sufficient quantities, so that they must be obtained through the diet (Ye and Eitenmiller 2005). Furthermore, the deficient and excess intake of a certain vitamin can cause clinically significant illness.

Most vitamins are not single molecules, but groups of related molecules called vitamers. For example, there are eight vitamers of vitamin E: four tocopherols and four tocotrienols (Traber and Stevens 2011). Some studies list fourteen vitamins, by including choline, however major health organizations list thirteen, namely: vitamin A (as all-trans-retinol, all-trans-retinyl-esters, as well as all-trans-beta-carotene and other provitamin A carotenoids), vitamin B1 (thiamine), vitamin B2 (riboflavin), vitamin B3 (niacin), vitamin B5 (pantothenic acid), vitamin B6 (pyridoxine), vitamin B7 (biotin), vitamin B9 (folic acid or folate), vitamin B12 (Cyanocobalamin), vitamin C (ascorbic acid), vitamin D (calciferols), vitamin E (tocopherols and tocotrienols), and vitamin K (phylloquinone and menaquinones) (Table 2.5) (Asensi-Fabado and Munné-Bosch 2010). Vitamins have a wide range of biochemical functions. For instance, vitamin A acts as a regulator of cell and tissue growth and differentiation; vitamin D acts as a hormone and regulates mineral metabolism for bones and other organs; the B complex vitamins work as enzyme cofactors (coenzymes) or their precursors; and vitamins C and E act as antioxidants.

On the other hand, there are two groups of vitamins, namely fat-soluble and water soluble (Lemone 2010). Regarding the first group, vitamins A, D, E and K are bound to ingested fats for absorption. They can be stored in liver and fat tissue; therefore, ingested high amounts of fat-soluble vitamins can reach levels which are toxic to human health. As regards water soluble vitamins they are C, B complex, biotin, and

pantothenic acid. These compounds can be eliminated through urine; thus they do not usually reach toxic levels (Lemone 2010; Chawla and Kvarnberg 2014).

Minerals are another type of micronutrients and can be classified in two main groups major minerals and trace minerals (Lemone 2010). Among other, calcium (Ca^{2+}), potassium (K^{+}), sodium (Na^{+}) and phosphorus (P^{3-}) are major minerals, while zinc (Zn^{2+}) and iron (Fe^{2+}) are trace-minerals (Table 2.5). Major minerals are present in large amounts in the body; however, trace minerals are found in a lesser extent. These micronutrients have important roles in our body since they are necessary for the correct functioning of the organism. For instance, Ca^{2+} and K^{+} have a high potential to control blood pressure; Ca^{2+}, Mg^{2+}, Cu^{2+} and Zn^{2+} are related with the immune system; Fe^{2+} is the responsible of the hemoglobin formation and Fe^{2+} and Zn^{2+} are part of the structure of many enzymes (Gharibzahedi and Jafari 2017) (Table 2.5).

Table 2.5 Examples of essential vitamins and minerals, sources and functions in the body

VITAMINS			
Vitamin/Mineral	**Source**	**Functions**	**Ref.**
A (Retinol, provitamin A such as carotenoids)	Retinol: Meat, butter, milk, cheese, egg yolk// Provitamin A: carrots, green leafy vegetables, sweet potatoes, pumpkin, apricots, cantaloupe.	Vision, reproduction, and immune functions. Antioxidant functions, mucous-secreting epithelial cells, normal bone development.	Sardesai (2011 and Kumar (1997)
D (Calciferol)	Fortified dairy products, margarine, fish oils, egg yolk.	Antirachitic, maintain Ca^{2+} and P^{3-} hemostasis. Calcification of bones. Normal neuromuscular activity, immune responses.	Sardesai (2011)
E (Tocopherols, tocotrienols)	Vegetable oil, margarine, shortening, green leafy vegetables, wheat germ, whole-grain products, egg yolk, butter, liver, nuts.	Antioxidant functions.	Sardesai (2011) and Meydani and Beharka (1998)
K (Phylloquinone, menaquinones)	Liver, green leafy vegetables.	Antihemorrhagic, co-factor to maintain blood clotting factors, Ca^{2+} transport and deposit in bone matrix.	Sardesai (2011)
C (Ascorbic acid)	Broccoli, peppers, collard greens, Brussels sprouts, kale, potatoes, spinach, tomatoes, citrus fruits.	Antiscorbutic, normal cellular function, intervention in the chemical processes of other enzyme systems, formation of collagen.	Lemone (2010)
B_1 (Thiamine)	Pork, peas, legumes, nuts.	Acting as co-enzyme in energy production and carbohydrate metabolism.	Lemone (2010)
B_2 (Riboflavin)	Milk, yogurt, cottage cheese, organ meats, green leafy vegetables, whole grains.	Co-enzyme (B_2 + phosphoric acid) for growth, thyroid hormone activity, glycogen synthesis, factor in adrenal synthesis of corticosteroids, bone marrow erythrocyte formation, fatty acid metabolism.	Sardesai (2011)

(continued)

Table 2.5 (continued)

B_3 (Niacin)	Liver, meat, poultry, fish, grain, peanuts, eggs.	Participation in the metabolism of carbohydrates, fats, and proteins, vasodilatation, regulation of the cholesterol levels.	Lemone (2010)
B_5 (Pantothenic acid)	Liver, kidney, fish, dairy products, eggs, avocados, legumes, mushrooms, sweet potatoes.	Formation of CoA, antimicrobial, and immunological activity.	Gheita et al. (2020)
B_6 (Pyridoxine)	Meat, poultry, fish, shellfish, green leafy vegetables, whole-grain breads and cereals, eggs, legumes.	Participation in the amino acid, carbohydrates and fats metabolism, glycogen release, synthesis of heme.	Lemone (2010)
B_7 (Biotin)	Dairy products, kidney, liver, egg yolk, vegetables, normal microflora.	Regulation of gene expression, in cell signal signaling pathways, and in histone biotinylation.	Lauw et al. (2013)
B_9 (folic acid, Folacin)	Liver, green leafy vegetables, legumes, yeast, some fruits.	DNA synthesis, maintenance of normal erythropoiesis, normal growth, reproduction, lactation, antibody formation, and fetal growth.	Rose and Mennuti (1994)
B_{12} (Cyanocobalamin)	Meat, poultry, fish, shellfish, eggs, dairy products	Production of folate, fatty acid synthesis, cell replication and hematopoiesis.	Sardesai (2011)
MINERALS			
Calcium (Ca^{2+})	Dairy products, green leafy vegetables, egg yolk, shellfish.	Physiologic effects, transmission of nerve impulses, contraction of muscles and coagulation of blood.	Sardesai (2011)
Iron (Fe^{2+})	Organ meats, brewer's yeast, wheat germ, egg yolk, oysters, dried beans and fruits, green vegetables.	Hemoglobin formation of erythrocytes and hyoglobin.	Sardesai (2011)
Phosphorus (P^{3-})	Milk, eggs, meat, fish, poultry, legumes, nuts	Bone building during growth, mineralization at new bone-forming sites.	Heaney (2004)
Potassium (K^+)	Potatoes, milk, orange juice, bananas, avocados, dried apricots, meat, fish, coffee.	Maintenance of blood pressure, reduce bone loss and renal calcium retention.	Tucker et al. (1999)
Sodium (Na^+)	Table salt, cured meats, sauerkraut, cheese.	Maintenance of the acid-base balance, total osmotic pressure of extra cellular fluids.	Consolazio et al. (1963)
Zinc (Zn^{2+})	Meat, legumes, cereals, poultry, eggs	Taste perception, wound healing, strengthen of the immune system, synthesis of RNA.	Watts (1990)

9 Dietary Fibers: Prebiotics and Probiotics

Probiotics are those living microorganisms, not pathogenic, which can provide a health benefit for the host when they are administered in adequate amounts (FAO 2002). The main probiotic microorganisms are lactic acid bacteria (LAB), both *Lactobacillus* and *Bifidobacterium*. However, other species are also considered as probiotics such as *Lactococcus, Streptococcus, Enterococcus, Propionibacterium* and *Saccharomyces* (Chugh and Kamal-Eldin 2020; McCabe 2017). Probiotics are added to different food products, generally combining several strains, but fermented dairy products being the most widely used.

Unlike medicines, most probiotic preparations are classified as food or dietary supplements and are not strictly regulated at the international level (Kolaček et al. 2017). Therefore, there is no label control or regular quality and safety evaluations of the products. This situation leads the consumer not to have reliable information to trust or validate the claims made about probiotics.

Probiotics provide beneficial effects through several mechanisms such as pH changes, competition for oxygen and nutrients, production of anti-inflammatory cytokines or bile salt deconjugation that leads to a reduction of cholesterol, among others (Table 2.6). In this sense, the beneficial effects can be, namely: *(i)* prevention or elimination of harmful bacteria of GIT, *(ii)* improvement of metabolic activities and *(iii)* antioxidant, anti-inflammatory and immunomodulatory effects (Chugh and Kamal-Eldin 2020).

The first effect is generally mediated by bacteriocins, which are peptides of low M_W peptides or complex proteins which have antimicrobial and/or antiviral properties. These peptides fight against harmful bacteria and facilitate the competition with resident microbiota. In addition, the production of short chain fatty acids (SCFA) is another important mechanism to prevent harmful bacteria since they reduce gut pH and induce antimicrobial activity (McCabe 2017). Regarding the second effect, most probiotic bacteria can produce enzymes (*i.e.,* β-galactosidase and lactase) and have different metabolic activities that can be improved when they are introduced in food products, since sometimes these activities are very low or absent in the host. At last, there are a lot of probiotic bacterial strains which produce peptides, amino acids, vitamins, phenols, lactones, and indoles which exert various biological effects. For example, tryptophan has an immunomodulatory effect and is the responsible of the reduction of allergic reactions (Kepert et al. 2017), vitamin B12 can be produced by *Propionibacterium* spp. (Piwowarek et al. 2018) and most probiotic bacteria can produce menaquinone (vitamin K1) (Patel et al. 2013) and LAB can produce long-chain linear biopolymers (*i.e.,* exopolysaccharides) which have antioxidant, anti-inflammatory, anticancer and immunomodulatory effects (Berthold-Pluta et al. 2019).

As regards prebiotics, they are indigestible food ingredients but fermented, which beneficially affect the host by selectively stimulating the growth and/or activity of a limited number of bacteria in the colon (Pandey et al. 2015; Quigley 2010). In this sense, prebiotics select which species of organisms, already present in the colon, will continue growing. Prebiotics must be resistant to gastric acidity and

hydrolysis, fermented by the gut microbiota and selectively stimulate the growth and activity of gut bacteria associated with health and well-being (Pandey et al. 2015). Most of dietary fibers are prebiotics such as inulin, resistant starch and non-starch polysaccharides and oligosaccharides such as fructooligosaccharides (FOS), galactooligosaccharides (GOS), and xylooligosaccharides (XOS) (Aachary and Prapulla 2011). Some examples of dietary fibers acting as prebiotics and their functions are shown in the Table 2.6.

Table 2.6 Examples of probiotics and prebiotics, functions and application product

Probiotics/prebiotics	Product	Functions	Ref.
Bacillus subtilis and *B. licheniformis*	Chungkookjang (fermented soybean)	Anti-inflammatory, anti-obesity, anti-diabetic, and neuroprotective effects.	Byun et al. (2016)
Enterococcus faecium CRL 183, *lactobacillus helveticus* 416	Fermented soybean food with isoflavones	Anti-inflammatory and antioxidant effects, reduced risk of cardiovascular diseases.	Cavallini et al. (2016)
Aspergillus oryzae	Kockujang (fermented red pepper paste)	Hypocholesterolemic effect	Lim et al. (2015)
Lactobacillus helveticus	Fermented milk	Antioxidant, anti-inflammatory, antitumor and antihypertensive effects.	Iwasa et al. (2013)
Lactobacillus fermentum FTL2311 and FTL10BR	Miang (fermented tea leaves)	Antibacterial and antioxidant effects.	Klayraung and Okonogi (2009)
Lactobacillus curvatus P99	Fermented oat dairy beverage	Antimicrobial activity.	Funck et al. (2019)
Lactobacillus plantarum L7	Fermented rice dairy beverage	Antimicrobial and antioxidant activity.	Giri et al. (2018)
Bifidobacterium animalis, lactobacillus bulgaricus and *L. lactis*	Fermented milk	Immunomodulatory and neuroprotective effect, control of central processing of emotion and sensation.	Tillisch et al. (2013)
Arabinoxylan oligosaccharides	Wheat	Increased *Bifidobacterium*, decreased risk of constipation, improved colonic fermentation of wheat	François et al. (2012)
Inulin + oligofructose	Fruits and vegetables	Increased *Bifidobacterium* spp., decreased fecal SCFA concentration	Salazar et al. (2015)
GOS	Dairy products, beans, root vegetables	Increased in *Bacteroides* and *Bifidobacteria,* anti-aging	Vulevic et al. (2015)
XOS	Fruits and vegetables	Increased *Bifidobacterium* and butyrate, increased activities of α-glucosidase and β-glucuronidase and decreased in acetate and *p*-cresol.	Lecerf et al. (2012)

Abbreviations: *GOS* Galactooligosaccharides, *XOS* Xylo-oligosaccharide, *SCFA* short chain fatty acids

Furthermore, in certain cases probiotics do not show sufficient benefit effect for health, thus a combination or mixture of probiotics and prebiotics, known as synbiotics, is used to overcome their possible difficulties to probiotic bacteria survival in the GIT. Increased concentration of *Lactobacillus* and *Bifidobacteria*, balanced gut microbiota, improved hepatic function and immunomodulation capacity are some benefits associated to the use of synbiotics (Pandey et al. 2015). For example, a combination of *B. coagulans* with inulin in chicken diets showed better cholesterol levels (Panda et al. 2006) or a mixture of *Lactobacillus, Bifidobacterium* and 10% FOS in rats helped to reduce the intestinal and systemic inflammation (Delcenserie et al. 2008). However, more studies are needed to find new combinations of probiotics and prebiotics that lead to the generation of maximum positive effects in the health.

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Part II
Membrane Separation of Common Food Bioactive Compounds

Chapter 3
Purification of Phenolic-Based Molecules from Agro-Food By-products via Pressure-Driven Membrane Processes

Alfredo Cassano, René Ruby-Figueroa, and Carmela Conidi

Abstract Fruit and vegetable processing industries generate huge amounts of highly polluting wastes and by-products because of their high organic load resistant to biological degradation. On the other hand, intensive researches suggest that these effluents should be regarded as a useful resource for the recovery of fine chemicals and for different biotechnological applications such as the production of important metabolites. This chapter discusses the use of pressure-driven membrane processes for the separation, purification and concentration of polyphenols from agro-food by-products in the light of increasing demand of both consumers and producers towards these compounds. Case studies related to the treatment of citrus, olive oil and wine by-products are analyzed and discussed, highlighting technological advances and improvements over conventional methodologies.

Keywords Pressure-driven membrane operations · Polyphenols · Bioactive compounds · Agro-food by-products

Nomenclature

BOD	biological oxygen demand
COD	chemical oxygen demand
MF	microfiltration
MWCO	molecular weight cut-off
NF	nanofiltration

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OMWs	olive mill wastewaters
PES	polyethersulphone
PI	polyimide
PS	polysulphone
PVDF	polyvinylidene fluoride
PVP	polyvinylpyrrolidone
RC	regenerated cellulose
RO	reverse osmosis
TOC	total organic carbon
TMP	transmembrane pressure
UF	ultrafiltration
VRF	volume reduction factor

1 Introduction

The activities of the agro-food industry are characterized by the production of large amounts of by-products and wastes with high concentrations of organic compounds whose management creates serious problems, both from the economic and environmental point of view. Additional problems are related to the variation of pH and chemical composition due to seasonal variations and changes in food processing, the microbial contamination and the high accumulation rate leading to disposal management problems (Kroyer 1995). However, these agro-residues are an extraordinary source of bioactive compounds, including phenolics, proteins, alkaloids, sugars and lipids. Among them polyphenols have received more and more attention in recent years due to their health-promoting activities and antioxidant characteristics (Visioli et al. 2011).

These compounds, widely distributed in the plant kingdom, are characterized by the presence of more than one phenol group per molecule. They are typically divided in phenolic acids, flavonoids, stilbenes and lignans (Fig. 3.1). Molecular masses range from small molecules (<100 Da), such as phenolic acids, to big molecules (>30,000 Da) of highly polymerized compounds. Their biological effects are mainly attributed to the ability to inhibit reactive oxygen and nitrogen species, transfer electrons to free radicals improving oxidative stress and inflammation, with promising effects in the prevention of various diseases including diabetes (Dembinska-Kiec et al. 2008), cancer (Khan and Mukhtar 2008), coronary heart diseases (Vita 2005), aging (Maurya and Rizvi 2009), osteoporosis (Fan et al. 2018) and neurodegenerative diseases (Ali et al. 2019).

In addition to their biological properties, phenolic compounds also find a great interest for commercial applications related to cosmetic products, food colorants, bioactive packaging, production of paints, surfactants, fertilizers, rubber, plastics and textiles (de Araujo et al. 2021).

Olive mill wastewaters, winery effluents, apple peels and pomace, berry skins, peels and seeds of tomatoes and citrus fruits as well as by-products from carrot,

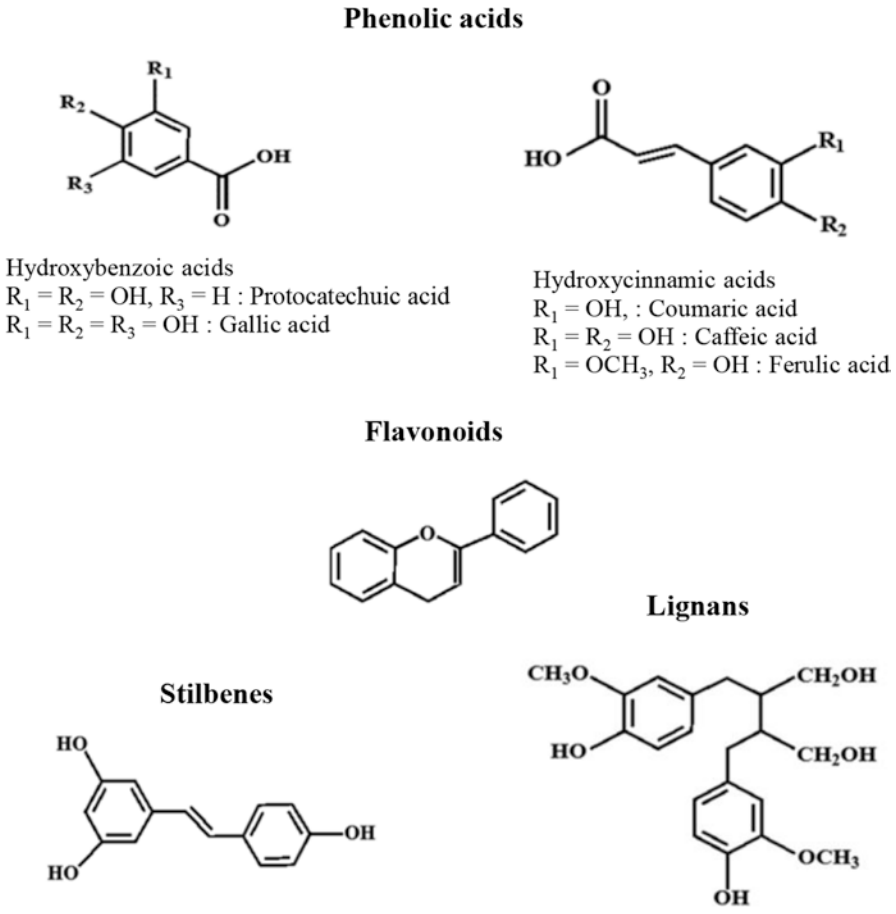

Fig. 3.1 Chemical structures of polyphenols

artichoke, cauliflower and onion processing are typical sources of phenolic compounds. These by-products present a complex physicochemical composition: therefore, the recovery of phenolic compounds from these sources require several steps (i.e. coagulation and precipitation of impurities, adsorption on resins) based on the use of chemicals, solvents and high temperatures which account for a significant part of the total costs of polyphenol production.

The reutilisation of agricultural residues is one of the fundamental goal of the circular economy. Therefore, research efforts have been focused in the last years not only on the technological applications related to the waste management, but also on the optimization of the extraction, concentration and purification of valuable compounds (Jimenez-Lopez et al. 2020).

Pressure-driven membrane operations have always been an interesting approach to reduce the content of contaminants in industrial and agro-food processing

wastewaters (Van der Bruggen et al. 2003) thanks to their intrinsic properties and typical advantages over conventional technologies (low energy requirements, high separation efficiency, easy scale-up, no use of chemical additives, high productivity, absence of phase transition among others). Nowadays, these processes are not only focused on pollution removal, but also on the recovery of high-added-value components from food processing waste and by-products (Castro-Muñoz et al. 2016, 2020; Conidi et al. 2018).

The goal of this chapter is to provide a comprehensive outlook about the research efforts focused at enhancing the separation, fractionation and concentration of phenolic compounds from agro-food by-products by membrane-based technologies. Case studies implemented on specific by-products of olive oil, citrus and wine processing industry are analysed and discussed.

2 Pressure-Driven Membrane Processes

Pressure-driven membrane operations, such as microfiltration (MF), ultrafiltration (UF), nanofiltration (NF) and reverse osmosis (RO), are physical unitary operations which allow to separate chemical species from a feed solution under a pressure difference applied between the two sides of a perm-selective membrane. This leads to the partial fractionation of the feed solution into two new streams: a permeate stream, consisting of the solvent that passes through the membrane together with solutes having molecular weight lower than the membrane's nominal molecular weight cut-off (MWCO), and a retentate stream containing all compounds partially or totally retained (higher molecular weight compounds) by the membrane.

MF membranes are characterised by pore sizes of 0.1–10 μm and are typically used to separate suspended solids, bacteria and colloids from low molecular weight compounds (Ripperger and Almann 2002). They operate under opeating pressures in the range of 0.1–2 bar.

The UF process is based on the use of asymmetric membranes with pore sizes in the skin layer of 2–10 nm. The MWCO of UF membranes is between 10^3 and 10^6 Dalton making them suitable for separation and fractionation of macromolecules. Operating pressures typically used in UF are of 0.5–10 bar (Cheryan 1998).

NF is based on the use of membranes with an intermediate separation capability between UF and RO and membranes (MWCO is in the range of 200–1000 Da). It is essentially used to fractionate salt compounds based on cation or anion valency and to separate various organic solutes with low molecular weights. The separation mechanism is based on steric, Donnan and dielectric exclusion effects. The pore size of NF membranes is in the range of 0.5–2 nm. The hydrostatic pressures used in the process can vary from 5 bar to 40 bar (Cassano et al. 2018).

RO membranes are generally used to separate low molecular weight compounds from a relatively pure solvent. The particle size for RO applications is in the range 0.1–1 nm and solutes with molecular weight greater than 300 Da are separated. The

hydrostatic pressures to obtain significant transmembrane flux can vary from 10 to 100 bar depending upon the osmotic pressure of the feed mixture (Baker 2012).

The separation capability of pressure-driven membrane operations is depicted in Fig. 3.2.

In all these processes the permeate flux through the filter medium is affected by the applied pressure difference across the membrane (between the filtrate side and the permeate side of the membrane), the resistance of the membrane and of the cake layer as well as by the viscosity of the fluid being filtered. The volumetric flux (J_v) is expressed using Darcy's law and a resistance-in-series model:

$$J_v = \frac{TMP}{\mu\left(R_m + R_c\right)} \tag{3.1}$$

where TMP is the transmembrane pressure (Pa), μ the permeate viscosity (Pa s), R_m the membrane resistance (m^{-1}) and R_c the cake resistance (m^{-1}).

The separation characteristics of membranes can be expressed in terms of membrane rejection (or retention) according to the following equation:

$$R = \left(1 - \frac{C_p}{C_r}\right) \bullet 100 \tag{3.2}$$

where R is the membrane rejection for a given component in defined conditions of hydrostatic pressure and feed solution concentration, while C_p and C_r are the concentrations of the component in the permeate and retentate stream, respectively. Rejection values are between 0% (for solutes having the highest probability to pass

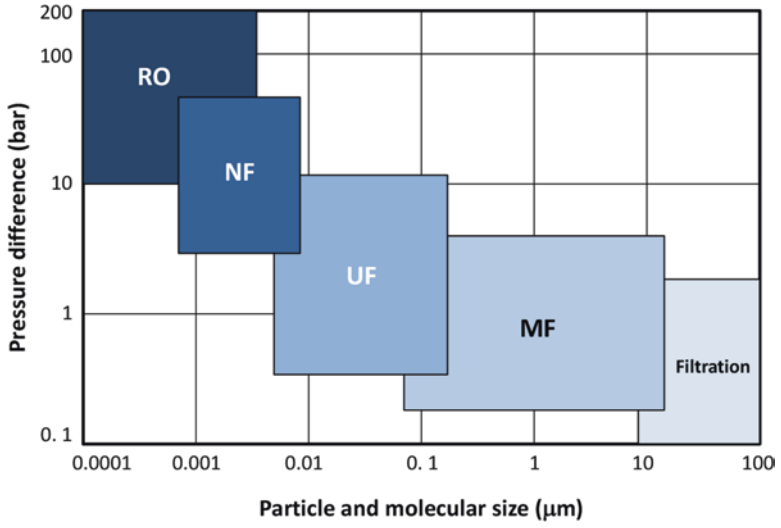

Fig. 3.2 Separation capabilities of pressure-driven membrane operations

through the membrane) and 100% (when solutes are completely retained by the membrane).

The volume reduction factor (VRF) in pressure-driven processes is defined as the ratio between the initial feed volume and the volume of the resulting retentate given by:

$$VRF = \frac{V_f}{V_r} \tag{3.3}$$

where V_f and V_r are the volume of feed and retentate, respectively.

The performance of these processes in terms of productivity (permeate flux) and selectivity towards phenolic compounds is affected by several parameters including the physicochemical composition of the feed stream, as well as operating and fluid-dynamic parameters, such as TMP, feed flowrate and temperature. In addition, membrane properties, including hydrophilicity/hydrophobicity, surface topography, charge and pore size have a strong influence on membrane-solute interactions, and hence on membrane fouling phenomena, playing a key role in the separation process (Cassano et al. 2017; Castro-Muñoz et al. 2019). Therefore, all these aspects should be carefully evaluated and optimized case-by-case for a real application and scale-up.

3 Recovery of Phenolics from Agro-Food By-products

3.1 Olive Mill Wastewaters

Olive mill wastewaters (OMWs), generated as by-product of the olive oil production, are considered one of the most polluting effluents produced by agro-food industry due to their high concentration of organic matter and nutrients, especially in terms of reduced sugars and phenolic compounds. They are characterized by an intensive violet-dark brown color with chemical oxygen demand (COD) and biochemical oxygen demand (BOD) in the range of 40–220 g/L and 35–110 g/L, respectively; the content of polyphenols (in the range of 0.5–24 g/L) is about 50% of the total phenolic content of the olive fruits (Niaounakis and Halvadakis 2006). Catechol, tyrosol, and hydroxytyrosol are the main biophenols occurring in OMWs, although verbascoside, protocatechuic acid, vanillic acid, *p*-coumaric acid, caffeic acid, 4-hydroxy-3,5-dimethoxybenzoic acid, 4-hydroxybenzoic acid and other compounds in lower concentrations have also been reported (Della Greca et al. 2004; Cardinali et al. 2011).

The utilization of membrane technologies for separating, purifying and concentrating bioactive phenolic compounds from OMWs is a topic largely investigated in the last years as alternative to the use of liquid-liquid extraction and chromatographic separations. In particular, the use of membranes with different MWCO

values in a sequential form, has been proposed as a valid approach to overcome the problem of the wide range of molecular weights of phenolic compounds which make difficult their recovery with high purities (Ochando-Pulido and Martinez-Ferez 2015).

MF and UF membranes are mainly used as preliminary step of OMWs fractionation to produce a phenolic fraction free of suspended solids. Their performance is remarkably affected by fouling phenomena which reduce permeate fluxes and modify the membrane selectivity; fouling also makes the process highly expensive owing to repeated plant shut-down for cleaning and washing the membranes. Therefore, pretreatment methods are needed to reduce the suspended solids contained in OMWs and increases the filtration efficiency of MF and UF membranes. Turano et al. (2002) proposed the use of centrifugation to remove suspended solids from OMWs before UF with polysulphone (PS) membranes. COD was reduced up to 50% after centrifugation, whereas 80% removal of suspended solids concentration and 90% COD reduction was achieved at the outlet of the integrated process. Bazzarelli et al. (2015) proposed a new approach for the pre-treatment of OMWs consisting in their pH adjustment to destabilize the suspension with the aim of achieving the coagulation and precipitation of undesired solids according to Stokes law. The maximum suspension instability was reached in a pH range of 1.5–2.5: in this range particles had zeta potential values near the isoelectric point promoting their aggregation and flocculation. On the other hand, for higher values of zeta potential there was no tendency for particles to aggregate.

The performance of the UF process in the treatment of OMWs was also improved after a pH-temperature flocculation (by adding HNO_3 70% w/w) followed by a photo-catalysis under ultraviolet irradiation (UV) with lab-made ferromagnetic-core TiO_2 nanoparticles (UV/TiO_2 PC). This treatment produced higher steady-state fluxes (18.8–34.2% increment) and higher COD rejections in comparison to a pre-treatment with solely acidification (Ochando-Pulido 2015).

Cassano et al. (2011) evaluated the fouling index of flat-sheet UF membranes with different MWCO (4, 5 and 10 kDa) and polymeric material (regenerated cellulose (RC) and polyethersulphone (PES)) in the treatment of microfiltered OMWs. Experimental results indicated that PES membranes fouled more than RC membranes; this behaviour was attributed to the higher affinity of polyphenols for PES membranes due to the formation of polar interactions and multiple hydrogen bonds towards the additive polyvinylpyrrolidone (PVP) in PES, leading to severe fouling by pore narrowing and blocking phenomena. According to the measured fouling index, RC membranes showed lower rejection values towards free low molecular weight phenolic compounds than PES membranes. For these membranes an increasing of the polyphenols/total organic carbon (TOC) ratio was also observed in the permeate stream in comparison with the feed solution. This is in agreement with an improved separation of phenolic compounds from other organic compounds of the feed solution.

Tsagaraki and Lazarides (2012) found that the operating pressure had the largest impact on permeate flux, followed by operating temperature in the UF of sieved and centrifuged OMWs with tubular PS membranes of different MWCO. A flux decline

of 60–65% due to membrane fouling was observed in the first 15–20 min of filtration despite the pretreatment of the original wastewater. Internal fouling, pore blocking and cake layer formation contributed to membrane fouling during the first 40 min of operation. After that period, cake formation appeared to play a predominant role.

The fractionation of OMWs through a combination of UF and NF or RO membranes was investigated by Paraskeva et al. (2007). OMWs were prefiltered with an 80 μm polypropylene screen and then ultrafiltered by multichannel ceramic membranes with pores of 100 nm. The UF permeate was processed with spiral-wound polymeric NF (MWCO 200 Da) or RO (MWCO 100 Da) membranes. The UF process resulted in the separation of high molecular weight constituents including suspended solid particles, while NF membranes allowed to remove more than 95% of phenolic compounds from ultrafiltered solution. A better efficiency of the OMWs treatment was achieved by applying RO after UF. Permeate fractions from NF and RO treatments exhibited quality characteristics to be discharged in aquatic systems according to EU regulations. In a further improvement of the work the RO concentrate, after a nanofiltration, was further treated with resin adsorption/desorption. Specific non ionic resins (XAD4, XAD16, and XAD7HP) were implemented for the recovery of phenols and their separation from carbohydrates (Zagklis et al. 2015). The recovered phenolic compounds were concentrated through vacuum evaporation reaching a final concentration of 378 g/L in gallic acid equivalents containing 84.8 g/L hydroxytyrosol.

Cooling crystallization has been also proposed for the selective recovery of phenolic compounds from concentrated fractions of OMWs obtained through membrane operations. In this view Kontos et al. (2016) studied the selective extraction of trans-cinnamic acid and ferulic acid (two polyphenols contained in OMWs) from their aqueous solutions by cooling crystallization achieving recovery rates of 50% and 66%, respectively.

An integrated process based on the use of MF, UF, NF and RO membranes for the recovery of bioactive compounds from OMWs was also investigated by Russo (2007). OMWs were previously acidified at pH 3–4.5, in order to prevent oxidation of polyphenols, and then treated with pectinase to hydrolyze cellulose, hemicellulose and pectin. Experimental results indicated the MF process as a critical step for the selective separation of phenolic compounds due to severe fouling phenomena and difficulties in the cleaning procedure. 6 kDa polymeric UF membranes purified the polyphenolic component contained in MF permeate reducing dried residue of 38%, total nitrogen of 68%, glucose of 37% and minerals of 33%. No differences on the selectivity of hydroxytyrosol were detected in comparison with 1 kDa ceramic membranes.

RO concentrated all the components with rejection values ranging between 96% and 99%. The final RO produced a concentrated liquid enriched in purified polyphenols of interest for pharmaceutical applications and ultrapure water suitable for beverage formulations.

In the integrated process proposed by Cassano et al. (2013), OMWs were previously ultrafiltered with hollow fiber polyvinylidene fluoride (PVDF) membranes

with pore size of 0.02 μm (HFS, Toray). The permeate stream, depleted in suspended solids, was submitted to a second UF step by using a composite fluoropolymer membrane (Etna 01PP, Alfa Laval) with a MWCO of 1000 Da. Then the UF permeate was nanofiltered through a spiral-wound polyamide (PA) membrane having a MWCO of 180 Da (NF90, Dow Filmtec). Both UF membranes allowed to recover polyphenols in the permeate fraction. However, the rejection of the 1 kDa membrane towards TOC was 72%, more than twice if compared with the rejection towards polyphenols (31%); therefore most part of organic substances were removed from phenolic compounds in the second UF step. The NF membrane retained all the analyzed phenolic compounds producing a concentrated fraction (NF retentate) suitable for cosmetic, food and pharmaceutical application and a permeate stream depleted in phenolic compounds which can be reused in the olive oil extraction process as process water or for membrane cleaning. The reuse of UF retentates, enriched in organic compounds, for the production of biogas was also suggested.

De Almeida et al. (2018) investigated the effect of operating conditions on the performance of an integrated UF/NF process in the treatment of OMWs obtained from an olive mill with traditional extraction press. Phenolic compounds were rejected for 26.8% in the UF process operating in optimized conditions of TMP and temperature (1.5 bar and 20 °C). The pH value showed to be an important variable in the retention of phenolic compounds when treating the UF permeate by NF since it influenced both the membrane charge and the dissociation of the phenolic compounds and consequently the interaction between them. The increase in pH level, within the range of operation used, led to a decrease in phenolic rejection and an increase in the permeate flux. In optimized conditions of pH, temperature and pressure (2.7, 20 °C and 18 bar, respectively), removals of phenolic compounds were of 93.1%.

NF retentates, enriched in phenolic compounds and dried using the spray dryer technique, have been tested for cell viability after oxidative stress induction on human keratinocytes model in vitro demonstrating an improved cell reparation in scratch assays assisted through time lapse video-microscopy (Alfano et al. 2018). These studies confirmed the suitability of these fractions as ingredients in cosmeceuticals and nutraceutical preparations.

The addition of a phenolic RO concentrate to the malaxed pastes during virgin olive oil extraction, gave 27–44% higher polyphenol content to the extracted virgin olive oil, adding critical health benefit to olive oil while preserving the characteristic varietal flavour (Servili et al. 2011).

Zagklis et al. (2013) analysed the sustainability of existing methods of OMWs treatment including physicochemical, biological and advanced oxidation methods. The analyses showed that membrane filtration was one of the most effective processes in terms of organics reduction and economic viability, thanks to the profit derived from the exploitation of phenolic content and the fraction rich in nutrient components. The operational costs were calculated at around 1,535,740 € for the treatment of 50,000 tons of waste, that is equivalent to 30.71 € per treated m^3 of OMWs. The possible profit for the same amount of waste were calculated at around

250,000 € for the nutrient fraction and 1,875,000 € for the phytotoxic fraction, corresponding to a profit of 42.5 €/m^3 of treated OMWs, and a net profit of 11.79 €/m^3.

Recently, a combination of pressure-driven membrane operations and adsorbent resins has been implemented on large scale for the separation and purification of phenolic compounds from OMWs resulting from a three-phase milling system (Savarese et al. 2016). The process, implemented on a plant with a capacity of 1 m^3/h of incoming effluent, consists of a pretreatment step (including lamellar flotator, decanter, centrifugal separator and filter press), a combination of spiral-wound UF, NF and RO membranes in a sequential design and a nonionic, highly cross-linked, adsorbent resin (polystyrene–divinylbenzene) (Macronet MN-202, Purolite Global Sales Limited, Milano, Italia) characterised by a high specific surface area (800–1100 m^2/g). In this approach the NF concentrate is forwarded to the section of adsorption on resin for concentration and purification of polyphenols. These compounds retained on the column during the adsorption phase are then desorbed with ethanol and the ethanolic extract is then dried in evaporator under vacuum. The NF permeate, rich in low molecular weight sugars, is sent to the RO unit to obtain purified water and a concentrate rich in sugars which is substantially free of polyphenols and could be sent to biological treatment (Fig. 3.3). This process allowed to obtain a creamy phenolic extract, with a title in phenolic compounds of about 9.5%, one-third of which (3.1%) represented by hydroxytyrosol. Total unit costs of 125.01 €/m^3 and 58.61 €/m^3 were estimated for plants of capacity of 20 m^3/day and 200 m^3/day, respectively. The income coming from the selling of the antioxidant extracts was estimated of about 200 €/kg; additional indirect benefits are represented by the avoided agronomic disposal of OMWs and the value of the biogas.

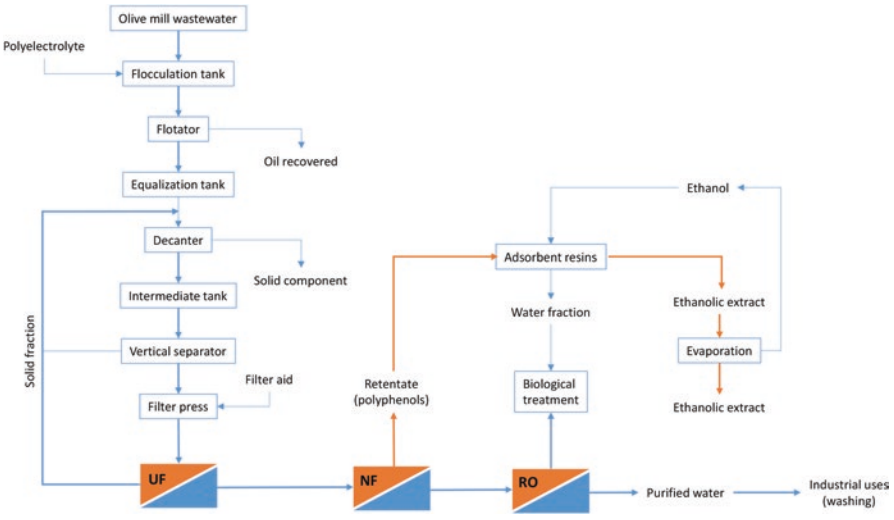

Fig. 3.3 Treatment of OMWs by combination of pressure-driven membrane operations and adsorbent resins. (Adapted from Savarese et al. 2016)

Recently, Tundis et al. (2020) analysed polyphenol-enriched fractions produced through a combination of MF, NF and RO membranes for their chemical profile and their potential antioxidant, hypolipidemic, and hypoglycaemic activities. The concentrated fraction by RO contained about 3 g/L of phenolic compounds, with hydroxytyrosol, tyrosol, and oleuropein, the most abundant compounds. This fraction showed the best antioxidant activity as well as the best hypoglycaemic activity.

The use of membrane technology for the recovery of phenolic compounds has been also studied on other olive oil by-products as well as OMWs.

Photomodified UF membranes have been used as first step for reducing color and organic load from table olive processing wastewaters in order to produce a permeate stream enriched in phenolic compounds. In particular, commercial PES membranes with MWCO of 30 kDa were UV irradiated in the presence of two hydrophilic compounds (polyethylene glycol and aluminium oxide) to enhance their fouling-resistant capability. Membranes photomodified with 0.5 wt% Al_2O_3 produced about 84% of decolourisation and 66% of COD removal and high enrichment factors of phenolic compounds in the permeate stream (Garcia-Ivars et al. 2015).

Romani et al. (2017) reported a green process for the production of phenolic extracts from olive leaves based on a hot water extraction of the vegetable material followed by MF, NF, RO and final concentration by evaporation at low temperature or spray-drying. The NF and RO concentrated fractions obtained from green leaves as starting material resulted very similar with a total polyphenols content of 3.9% w/V. The spray-dried composition of the extract, with a final phenolic concentration of 12.8% w/w contained 60.8% of secoiridoids, 18.3% of hydroxytyrosol derivatives, 13.2% of elenolic acid derivatives, 3.4% of flavonoids, 3.2% of verbascoside and 1% of hydroxycinnamic acid derivatives. The whole process was proposed for obtaining new formulations in different application fields, including the pharmaceutical, cosmetic, food, and functional food industries.

Ochando-Pulido et al. (2018) investigated the concentration and recovery of phenolic compounds from two-phase olive-oil washing wastewater and the simultaneous treatment of the effluent by NF with a thin-film composite (TFC) membrane, composed of a PA active layer on a polysulfone UF support (DK series, GE Water & Process Technologies) and with a MWCO of 300 Da. Among different pretreatment methods investigated, centrifugation was the most effective in terms of suspended solids abatement and phenolic compounds preservation. This pretreatment enhanced the performance of the NF membrane allowing to achieve steady-state permeate flux up to 64.52 L/m^{2}h, a concentrate pool enriched in phenolic compounds, a COD reduction of 86.76% and a permeate stream free of phenolic compounds. Process parameters were also optimized by RSM and were found to be: operating pressure 26.5 bar, tangential velocity 32.7 m s^{-1}, operating temperature 35 °C and pH 3.7: These conditions ensured high and stable membrane flux of about 106.2 L/m^{2}h providing a permeate stream that could be reused for irrigation purposes and a retentate stream concentrated in volume up to 6.5 times, with a total phenolic content of minimum 1315.7 mg/L (Ochando-Pulido et al. (2020).

3.2 Citrus By-products

The transformation of citrus fruit into juice is characterized by the production of large amounts of by-products, such as peels and seed residues, which may account for up to 50% of the total fruit weight. Unfortunately, this by-product is susceptible to spoilage owing to its high moisture content (78–90%), therefore it must be consumed quickly, with additional management costs due to transportation and storage capabilities.

Traditional treatments of citrus peels involve the use of lime followed by milling and pressing. The resulting press liquor contains in average a total soluble solids content of 10 °Brix including bioactive compounds, such as flavonoids and phenolic acids (Bocco et al. 1998).

MF and UF membranes represent useful techniques to separate pectins from bioactive compounds of citrus press liquor. Tubular UF ceramic membrane (ZrO_2, 30 kDa) showed a pectin rejection higher than 90% in the treatment of a pectin-containing solution extracted from citrus peel. On the other hand, the rejection of phenolic compounds was less than 20% (Lianwu et al. 2008). Therefore, this process can be a useful approach to decolorize, separate and purify pectins from these by-products producing at the same time a clarified stream with a total soluble solids content and an acidity level approximating similar to that of the press liquor.

Ruby-Figueroa et al. (2012) investigated the UF of orange press liquors by using PS hollow fiber membranes with a MWCO of 100 kDa. Operating conditions, such as TMP, axial feed flowrate and temperature were optimized through the response surface methodology (RSM) approach in order to maximize the recovery of antioxidant compounds in the permeate stream and minimize polyphenols rejection. Polyphenols rejection of 28.45% and total antioxidant activity of 32.28 mM Trolox in the clarified liquor, were estimated, respectively, in optimized operating conditions of 0.2 bar, 19.85 °C and 244.64 L/h. These conditions are those that allow to limit concentration polarization and fouling phenomena.

Spiral-wound NF membranes with MWCO in the range of 180–1000 Da were evaluated for their ability to separate phenolic compounds from sugars in orange press liquors (Conidi et al. 2012). Experimental results indicated high retention factors for anthocyanins (higher than 89%) for all selected membranes. This phenomenon was attributed to the positive charge of anthocyanins at the pH of the liquor which was of 3.4. At this pH, all the selected membranes exhibit a positive charge. Consequently, the electrostatic repulsion, independently by the MWCO of the selected membranes, contributed to the high observed rejection. On the other hand, a strong reduction in the average rejection of sugars was observed by increasing the MWCO. Among the selected membranes, a PES membrane with a MWCO of 1000 Da (NF PES10, from Microdyn-Nadir) showed the lowest average rejection towards sugar compounds and high rejections towards anthocyanins (89.2%) and flavonoids (70%). Permeate flux values at lower TMP values were also remarkably higher than the other investigated NF membranes. For this membrane the ratio between flavanones and anthocyanins decreased by increasing the VRF of the

process. This result allow to balance the flavonoid content in relation to that of the anthocyanins and, consequently, to modify the characteristics of the final product in terms of bittering capacity (for the presence of flavonoids) and coloring power (for the presence anthocyanins) (Cassano et al. 2014).

An integrated membrane process based on the use of UF and NF membranes was investigated by Conidi et al. (2011) in order to recover phenolic compounds from bergamot juice a by-product of the essential oil production from the fruit peel. The depectinized juice was clarified by UF and then treated with a UF membrane (Etna 01PP, flat-sheet fluoropolymer, 1000 Da, from Alfa Laval) and two different ceramic NF membranes (monotubular TiO_2 membranes, 750 and 450 Da, from Inopor) in order to evaluate the effect of the MWCO on the rejection of the membranes towards sugars, organic acids and flavonoids. The rejection of the NF 450 Da membrane towards flavonoids resulted in the range of 91–99%; on the other hand, the sugar rejection was of about 48% indicating for this membrane the best performance in terms of separation between sugars and flavonoids. Higher fouling indexes were measured for PES membranes (NF PES10 and N30F, from Microdyn-Nadir) in the treatment of clarified bergamot juice in comparison with a PA membrane (NF270, from Dow-Filmtec), independently by their MWCO. This behaviour was attributed to the more hydrophobic character of PES membranes (Conidi and Cassano 2015).

Recently, Ruby-Figueroa et al. (2018) evaluated the performance of four spiral-wound PA membranes with MWCO from 150 to 3500 Da (DH, GE, GH and GK, all from GE Osmonics) in the recovery of brutieridin and melitidin from clarified bergamot juice. These molecules exhibit statin-like properties and, therefore, are useful in lowering the cholesterol level in the blood (Di Donna et al. 2011). Experimental results indicated an increasing of the rejection coefficient towards both molecules by reducing the MWCO (Fig. 3.4); on the other hand, retention coefficients of glucose, fructose and sucrose were surprising higher in relation to their molecular weight due to interactions with membrane material and association with phenolic compounds.

Among the selected membranes, the Desal GE membrane showed the best performance in terms of separation between sugars and flavonoids in the clarified juice with high retentions toward flavonoids (>67% for melitidin and > 82% for brutieridin) and lower retention toward glucose (21.9%) and fructose (10.6%) at VRF 5.

3.3 Wine By-products

The wine industry produces a large amount of residues and by-products represented by leaves, stems, pomaces (including grape skins and seeds) and lees which constitute a valuable source of phenolic compounds including flavonoids, tannins, and benzoic acid derivatives (Xu et al. 2011). Grape polyphenols have attracted a great interest for their potential applications as active substances in cosmetic and pharmaceutical compositions but also for their sensory properties in wine (Pinelo et al. 2005). In this view pressure-driven membrane processes have been largely

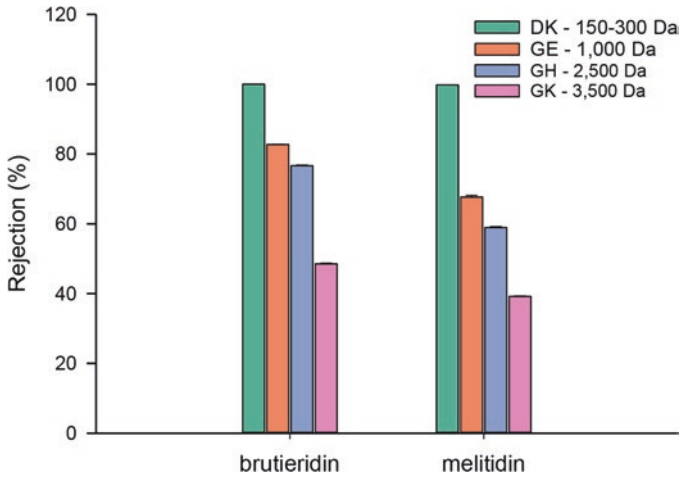

Fig. 3.4 Rejection of brutieridin and melitidin for polyamide membranes with different MWCO (operating pressure, 12 bar; temperature, 25 °C; volume reduction factor, 5). (Adapted from Ruby-Figueroa et al. 2018)

investigated, also in integrated systems, to propose viable and sustainable recovery approaches.

MF membranes can be used to reduce the suspended solids content of aqueous extracts of wine lees and the recovery of polyphenols in the permeate stream. Steady-state permeate fluxes of about 23 kg/m^{2}h were measured in the treatment of aqueous extracts with hollow fiber polyimide (PI) membranes of 0.4 μm (from PAM-Membranas Seletivas, Brazil) at a TMP of 0.5 bar and a temperature of 25 °C (Giacobbo et al. 2015). Higher dilution factors of the effluent showed higher permeate fluxes as well as higher polyphenols recovery rates in the permeate. Moreover, membranes with larger pore size showed lower permeate fluxes and consequently, more severe fouling.

UF membranes with a MWCO of 7600 Da provided a permeate stream from microfiltered winery effluents with a reduction in the TOC content by 56.6%, while the polyphenols and the polysaccharides in the retentate stream were concentrated by 6 times and 5 times, respectively (Giacobbo et al. 2013a).

Different polymeric NF membranes were tested by Giacobbo et al. (2013b) in the treatment of winery effluents and evaluated for their selectivity towards polyphenols and polysaccharides. For all selected membranes the rejection coefficients to polyphenols were lower than the ones to polysaccharides. Among the selected membranes a fluoropolymer membrane with a MWCO of 1000 Da (ETNA 01PP, from Alfa Laval) showed the lowest rejection coefficients for both polyphenols (27%) and polysaccharides (72%). On the other hand, a PA membrane with a MWCO of 400 Da (NF270 from Dow-Filmtec) exhibited the highest rejection towards these compounds (93.8% and 99% for polyphenols and polysaccharides, respectively).

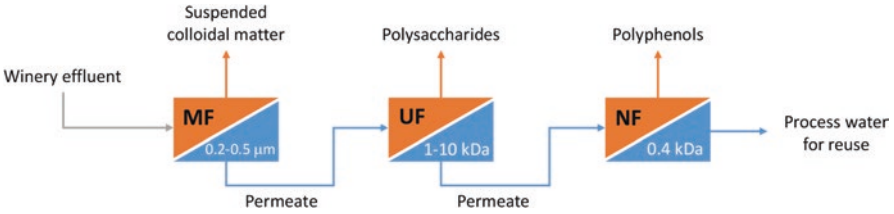

Fig. 3.5 Proposed process for the recovery of polyphenols and polysaccharides from winery effluents. (Adapted from Giacobbo et al. 2017)

Based on previous results, Giacobbo et al. (2017) proposed a conceptual process design for the fractionation of the polysaccharides and polyphenols of winery effluents from the first racking based on a sequential combination of MF, UF and NF membranes. In this approach, depicted in Fig. 3.5, suspended solids are removed by MF, while UF and NF membranes are used to concentrate polysaccharides and phenolic compounds, respectively.

A combination of pressure-driven membrane operations with adsorption-desorption processes was proposed by Díaz-Reinoso et al. (2017) in order to recover and concentrate phenolic compounds from white wine vinasses. The final dried product contained 45% of phenolics and presented a radical scavenging capacity equivalent to almost 2 g of Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid). COD and total solids were also reduced of about 85% and 92%, respectively, with significant reduction of the pollution load of the effluent.

Cassano et al. (2019) investigated the fractionation of red wine lees aqueous extracts, previously clarified by MF, by using three polymeric NF membranes namely: NP030 and NP010 (PES membranes with MWCO of 300–400 Da and 1000 Da, respectively, from Microdyn Nadir) and MPF36 (a 1000 Da PA membrane from Koch Membrane Systems). For all selected membranes anthocyanins retentions resulted higher than 93%; on the other hand, the retention of all the membranes towards phenolic compounds and resveratrol resulted lower than 34% and 30%, respectively. The MPF36 membrane showed the highest permeate flux with a steady-state value of about 17 kg/m^{2}h in the selected operating conditions (20 bar and 25 °C); this membrane exhibited the lowest retention towards resveratrol (10%) and polyphenols (26.3%) and the best separation factor between these compounds and anthocyanins. Adsorption phenomena of phenolic compounds were considered to contribute to the observed rejection together with size exclusion mechanisms. These compounds generally include aromatic (benzene) ring structures that have aliphatic carbon groups which, if undissociated in pH conditions lower than their pKa values, can be readily adsorbed on the membrane surface. This phenomenon increases by increasing the membrane hydrophobicity, such as for PES membranes (Arsuaga et al. 2010).

Recently, Arboleda Meija et al. (2019) investigated the recovery of phenolic compounds from red wine lees through a combination of microwave/hydro-alcoholic extraction and membrane operations. Suspended solids were removed

from the hydro-alcoholic extract by MF and the clarified extract was fractionated with three flat-sheet membranes having a MWCO in the range 150–1000 Da. Among the selected membranes, a PA membrane with a MWCO of 150 Da (NFT50 from Alfa Laval) presented the highest retention towards phenolic compounds. In particular, for most of phenolic compounds the rejection was higher than 70% while proanthocyanidins were completely retained by this membrane. The observed rejection was attributed, other than the steric hindrance, to adsorption phenomena due to polar, van der Waals and electron donor-acceptor interactions as well as to hydrogen bonding and hydrophobic interactions (Arsuaga et al. 2011; Ulbricht et al. 2009). The selected membranes did not show a preferential rejection of phenolic compounds over sugars.

In another work, Arboleda Mejia et al. (2020) investigated the recovery of phenolic compounds from red grape pomace through a combination of ultrasound-assisted enzymatic extraction and membrane processing with cellulose acetate NF membranes prepared in laboratory according to the phase inversion method. One of the investigated membranes (named as CA400–22) exhibited the highest permeate flux (50.58 L/m^{2}h at 20 bar and 25 °C), low fouling index (of about 23%) and the best performance in terms of separation between sugars and phenolic compounds when used in the treatment of the grape pomace extract. The observed rejections for glucose and fructose were of 19% and 12%, respectively. On the other hand, total phenolics content and proanthocyanidins were rejected for 73% and 92%, respectively.

Galanakis et al. (2013) evaluated the performance of UF membranes (two PS membranes with MWCO of 20 and 100 kDa, respectively, and a fluoropolymer membrane of 1 kDa) in the fractionation of phenolic compounds from hydroalcoholic extracts of winery sludge. Both PS membranes (GR40PP and GR70PP, from Alfa Laval, Nakskov, Denmark) showed high retention (higher than 60%) for phenolic compounds and sugars and resulted able to separate polymeric anthocyanins from monomeric ones. The 1 kDa fluoropolymer membrane (ETNA 01PP, from Alfa Laval) separated successfully hydroxycinnamic acid derivatives from anthocyanins and flavonols in both diluted and concentrated hydroalcoholic extracts. Experimental results clearly indicated that solutes retention was affected mainly by severe fouling phenomena due to polar solutes adsorption on membrane surface instead of size exclusion.

Commercial UF and NF membranes with MWCO in the range 0.25–1 kDa were used by Díaz-Reinoso et al. (2009) in the treatment of aqueous extracts from distilled fermented grape pomace. All the tested membranes presented similar rejections of total phenolics and sugars, and were suitable for concentration purposes.

Recently, Yammine et al. (2019) evaluated the rejection coefficients of several NF membranes with MWCO in the range of 150–1000 Da for several families of polyphenols from grape pomace. Membranes with MWCO between 500 and 1000 Da resulted able to recover polymeric proanthocyanidins in the retentate stream. On the other hand, membranes with MWCO between 300 and 600 Da resulted useful for the fractionation of monomeric phenolic families.

4 Conclusions and Future Trends

Pressure-driven membrane operations have demonstrated to be an interesting approach for the recovery of phenolic-based molecules from agro-food by-products. In most cases investigated on both laboratory and pilot scale the integration of these technologies in a sequential design successfully meets the requirements for the recovery, purification and concentration of polyphenols with the production of concentrated fractions of potential applications in the food, pharmaceutical and cosmetic industries.

Tailor made processes for specific by-products can be identified through a proper selection of membrane characteristics (membrane material, pore size, geometry) as well as through the optimization of operating and fluid-dynamic conditions in order to reduce and control membrane fouling phenomena which have a strong influence on membrane productivity and selectivity towards target compounds.

New perspectives and potentialities for the valorization of agro-food by-products are expected from the combination of pressure-driven membrane operations and innovative membrane unit operations such as membrane distillation, membrane emulsification and membrane crystallization or between membrane operations and conventional separation technologies (i.e. adsorption, centrifugation, evaporation). The combination of membrane filtration and cooling crystallization may be also quite promising for the development of more effective and integrated exploitation of agro-food wastewaters abiding to the zero waste targets.

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Chapter 4
Food Bioactive Ingredients Processing Using Membrane Distillation

Emilia Gontarek-Castro and Marek Lieder

Abstract Separation processes are an important part of today's food industries, especially in the case of specific bioactive components due to their health benefits. In general, processing of bioactive food ingredients assumes the introduction of integrated system directed to their separation, fractionation, and recovery. Recently, membrane distillation (MD) has been considered as an alternative membrane-based separation and concentration process in food technology. MD separates volatile components from aqueous feed solution into the permeate through microporous hydrophobic membranes, by means of the vapor pressure difference on both membrane sides. This chapter contains the analysis of the ongoing literature related to recovery and purification of food bioactive compounds using membrane distillation. Insights into the use of different MD configurations have been discussed and typical advantages and drawbacks over conventional technologies and other membrane processes have been highlighted.

Keywords Membrane distillation · Bioactive compounds · Food processing · Concentration · Polyphenols

1 Introduction

Separation processes are nowadays an integral part of agricultural and food industries. The reason is that bioactive substances in nature are hard to be find in the pure form. In general, some type of separation is applied before these substances are consumed or further processed, especially in the case of functional food and the nutraceuticals. The main objective in food bioactive processing is the development of fully integrated process to minimize the loss and diminution of bioactivity.

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Typical bioactive components that can be found in food products are anthocyanins, phenolic acids, catechins, flavonones, flavonols, non-flavonoid polyphenols and other phenolic compounds (Castro-Muñoz et al. 2016a, 2018a, b). The problem scientists need to face in the processing of bioactive components is the separation of specific components from complex matrix and their purification. The type of selected separation is usually based on physical properties of molecules such as their size, structure and physico-chemical characteristics (Díaz-Montes et al. 2020a). Each separation and purification technique should be capable of effective separation at a low cost, without any activity loss of compounds. Concentration of aqueous solutions of bioactive components is one of the most important unit operation while processing the food (Castro et al. 2020; Castro-Muñoz and Yañez-Fernandez 2015). It concerns the processing of beverages, fruit juices, vegetable and herbal extracts, milk, whey, etc. The volume reduction of concentrates through dewatering reduces their transport, storage and packaging costs and simultaneously makes them more resistant to chemical and microbial degradation. Conventional methods used for liquid concentration in food industry such as multistage vacuum evaporation (Jiao et al. 2004) are highly energy consuming and can change organoleptic and nutritional characteristics of the product due to the high operating temperatures (Varming et al. 2004; Toribio and Lozano 1986; Ibarz et al. 2011). Over the years, many industries have accepted the applications of membrane technology in some conventional processes and separation of food bioactive ingredients. In general, the advantages of membrane-based processes in bioactive components processing include the replacement of the highly energy consuming evaporation process, reutilization of wastewater, reduction of waste treatment volume and relatively low capital requirements (Cassano et al. 2010; Castro-Muñoz 2018). The disadvantages include the problems with the maintenance and durability of the membranes such as the length of operating life, replacement costs, chemical inertness, pH sensitivities and fouling problems. Various membrane processes such as microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), forward osmosis (FO), reverse osmosis (RO) and pervaporation have already gained huge interest in food processing field of research (Castro et al. 2020; Alvarez et al. 1997; Sant'Anna et al. 2012; Castro-Muñoz et al. 2020a, Castro-Muñoz 2020a). Among them, membrane distillation (MD) is an emerging thermally driven membrane process with several advantages over others. First of all, it operates with lower temperatures and pressures comparing to conventional distillation and pressure driven membranes processes (Gontarek et al. 2021). In addition, it is less susceptible to fouling than MF, UF, RO (Lawson et al. 1996; Onsekizoglu 2012).

This chapter covers the theoretical aspects of the MD process together with mathematical principles related to heat and mass transfer. Different configurations and variants of MD are presented. Secondly, the most commonly used commercial membranes will be introduced and the membrane requirements will be given with a brief overview on the optimal membrane parameters based on the recent literature data. Finally, the application of MD process in food bioactive components processing is evaluated, along with advantages and disadvantages and comparison to other membrane processes.

2 Principles of Membrane Distillation

Membrane distillation was first described by Bodell (1963) in 1963, who patented the apparatus and methods for converting non-potable aqueous fluids to potable water, where vapor and not liquid was permeating through a silicone rubber membrane. In 1967, Weyl (1967) issued another US patent that referred to the use of a porous hydrophobic membrane for improving the efficiency of desalination. In the late 1960s, Findley was the first to publish the results of the work on vaporization through porous membrane using a variety of membrane materials and basic theoretical study on direct contact membrane distillation (DCMD) (Findley 1967; Findley et al. 1969). The author noticed the potential of MD as an economical alternative of evaporation, however, he stated that first of all, low cost and long-life membranes with desirable characteristics need to be developed. At that time, the interest in MD process has temporarily decreased, subsequently, the advent of new membrane manufacturing techniques in the early 1980s, renewed the interest on this process, as the membranes with high porosity value and low thicknesses became available.

2.1 Process Fundamentals and Theory

The driving force of MD process is a vapour pressure gradient between feed and permeate solutions that is induced by the temperature difference across the membrane. The solutions are separated by microporous membrane that due to its hydrophobic character prevents the permeation of aqueous phase (Wang et al. 2016). At the entrance of each pore, liquid/gas interface is formed. Subsequently, the vapour phase is transported through the membrane to the permeate side where it condensates.

Along with the mass, the heat transfer also occurs. There are two important heat transfer mechanisms. The conductive heat transfer along the membranes pores that occurs together with the vapor diffusion causes temperature change at the both membrane boundary layers. This leads to a temperature gradient in the feed and permeate (between the bulk and boundary layer) and results in the convective heat transfer. Schematic illustration of heat flux in direct contact MD is shown in Fig. 4.1**.**

Convective heat transfer at the feed boundary layer Q_f can be described by Eq. 4.1:

$$Q_f = h_f \left(T_f - T_{f,m} \right) \tag{4.1}$$

while convective heat transfer at the permeate boundary layer Q_p:

$$Q_p = h_p \left(T_{p,m} - T_p \right) \tag{4.2}$$

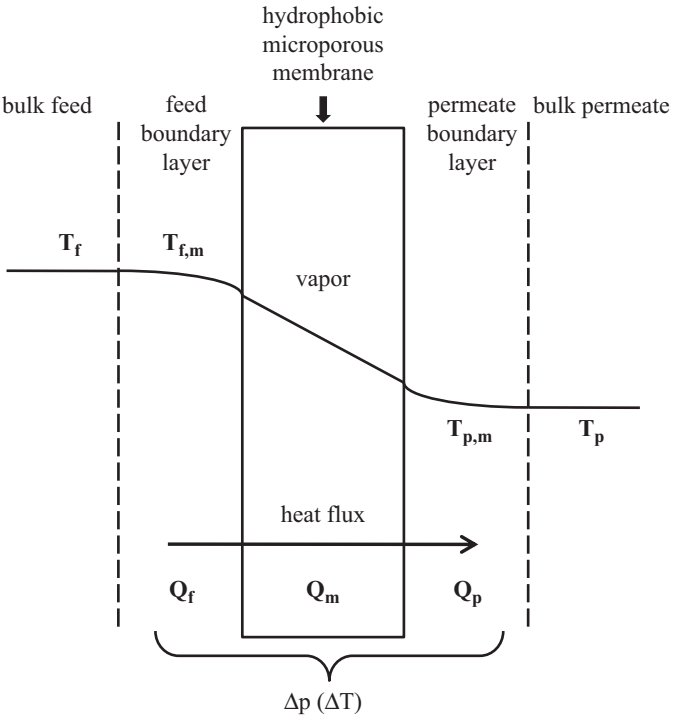

Fig. 4.1 Schematic illustration of heat flux and temperature polarization in DCMD

Conductive heat transfer across the membranes can be given by Eq. 4.3:

$$Q_m = h_m \left(T_{f,m} - T_{p,m} \right) + J \Delta H_v \tag{4.3}$$

where h_f, h_p and h_m are the heat transfer coefficients of the feed, permeate and membrane, respectively, while T_f, $T_{f,m}$, T_p and $T_{p,m}$ represent the temperature of the feed, temperature of the feed in the boundary layer, temperature of the permeate and temperature of the permeate in the boundary layer, respectively (Srisurichan et al. 2006). The temperature differences between the boundary layers and the bulk phases at both feed and permeate side reduce the driving force for mass transfer what is called temperature polarization. Increasing the feed temperature make temperature polarization phenomena more significant. Temperature polarization (ψ) is defined as follows:

$$\psi = \frac{T_{f,m} - T_{p,m}}{T_f - T_p} \tag{4.4}$$

Such equation describes the effect of heat transfer at boundary layer and the total heat transfer resistance for a given system. When the temperature polarization value

reaches 1, the feed and permeate temperature is constant and stable regardless of the distance from the membrane and the resistances of thermal boundary layer are reduced. This situation could only happen if the membrane does not conduct heat at all. When the value reaches 0, the system is controlled by large thermal boundary layer resistance. Typically, for DCMD temperature polarization value lies between 0.4 and 0.7 (Curcio and Drioli 2005). Few approaches have been proposed in the literature to reduce the temperature polarization effects such as thorough mixing, increasing flow rates or inducing turbulent flow using mesh spacers in the flow channels (Cath et al. 2004; Martínez-Díez et al. 1998; Chernyshov et al. 2005).

In the case of mass transfer in MD process it occurs due to the vapor transport that is induced by vapor pressure gradient between both membrane sides. In general MD mass transfer can be described by molecular diffusion or Knudsen diffusion model, depending on the membrane pore size (Khayet et al. 2004). The first model is applied for relatively large membrane pore size and states the predominance of collisions between molecules, as denoted by Eq. (4.6). The Knudsen model describes the systems where the mass transfer is determined by the collisions between molecule and pore walls as denoted by Eq. 4.5.

1. Knudsen diffusion model:

$$N' = \frac{1}{RT}\frac{2\varepsilon r}{3\tau}\left(\frac{8RT}{\pi M_i}\right)^{1/2}\frac{\left(p_1 - p_2\right)}{\delta} \tag{4.5}$$

where ε, r, τ, Mi and δ are porosity, pore radius, tortuosity, molecular weight of vapor and membrane thickness, respectively.

2. Molecular diffusion model:

$$N' = \frac{\varepsilon}{\tau\delta}\frac{PD_{ij}}{RT}\frac{\left(p_1 - p_2\right)}{\left|p_a\right|_{\ln}} \tag{4.6}$$

where D, P and p_a are the Fick's diffusion coefficient, total pressure in the pore and air pressure in the pore, respectively.

During MD operation the concentration of solutes in feed solution becomes higher at the liquid/gas interface than in the bulk feed. This phenomenon is called concentration polarization. Concentration polarization coefficient (CPC) is given by Eq. 4.7:

$$CPC = \frac{c_{f,m}}{c_f} \tag{4.7}$$

where $c_{f,m}$ is a concentration of the solute at the membrane surface and c_f is a concentration of the solute in the bulk feed.

2.2 Membrane Requirements

For an efficient operation of a MD process, the perm-selective barrier should present a highly hydrophobic surface, which is preferred since it may concurrently repel the water molecules in liquid state and favor the vapor transport. For this reason, superhydrophobic membranes gained special attention in MD process. The phenomena of surface wetting by a liquid and its physiochemical principle have been already well studied. A droplet resting on a solid surface can take a form of equilibrated shape and remain on the surface as a droplet or spread into a thin layer on the material surface. The behavior of the droplet depends on three thermodynamically balanced interfacial tensions that relate to the existence of an interface between liquid and vapor, solid and liquid and solid and vapor (Shirtcliffe et al. 2010). The wettability of the solid surface is dominated mainly by its chemistry and structure. It gives the possibility to easily control the surface wettability by varying one of these parameters.

Proper membrane selection is a key aspect in MD separation performance. There are various types of hydrophobic and porous membranes that meet the MD criteria. To date, the most popular materials used for MD membranes production are polypropylene (PP) (Tang et al. 2010), polytetrafluoroethylene (PTFE) (Zhu et al. 2013), and poly (vinylidene fluoride) (PVDF) (Zhang et al. 2013). Among them, PP membranes show the highest solvent resistance and crystallinity, while PVDF membranes easily dissolve in solvents such as dimethylformamide (DMF) and triethylphosphate (TEP). Despite this, PVDF exhibit good thermal and chemical resistance. PTFE membranes are considered as the most hydrophobic, however this polymer is difficult for processing.

In general, these polymeric membranes are obtained through stretching, sintering or phase inversion (Curcio and Drioli 2005). Membrane properties such as pore size, hydrophobicity, porosity, thickness, thermal conductivity and tortuosity have a direct effect on membrane separation performance (Castro-Muñoz et al. 2021; Gontarek et al. 2019). Therefore, recent works in MD area are focused on development of membranes with higher fluxes, excellent anti-wetting properties, enhanced stability and low cost (Perrotta et al. 2017; Tijing et al. 2016; Zhang et al. 2018).

Wetting Resistance During MD process, membrane is in constant contact with liquid feed solution. Usually, for this process aqueous feed solutions are used, therefore membranes should possess a strong hydrophobicity to prevent the wetting and simultaneously maintain retention of non-volatile solutes. In practice, the enhancement of the observed surface hydrophobicity is based on increasing the surface roughness and lowering solid/liquid interface energy. Membrane susceptibility to wetting can be evaluated using the liquid entry pressure (LEP) parameter, which is defined as the pressure required for the liquid to pass through the membrane. To achieve high LEP value and simultaneously good wetting prevention, membrane material should have small pore size, high surface tension and low interface energy between membrane and liquid. Selected properties affecting the wetting resistance of membranes are summarized in Table 4.1.

Table 4.1 Selected properties of membranes affecting their wetting resistance

Polymer materials:	Chemical structure	Water contact angle	Surface energy (x 10^{-3} Nm^{-1})	LEP	References
PVDF	$(CH_2CF_2)_n$	113°	30.3	21.3 kPa	Zhang et al. (2010)
PTFE	$(CF_2CF_2)_n$	126°	9.1	24 kPa	Zhang et al. (2010)
PP	$[CH_2CH(CH_3)]_n$	116-120°	30	6–28 kPa	He et al. (2011)
PE	$(C_2H_4)_n$	83-108°	28–33	0.5–0.7 bar	Zuo et al. (2016)
PVDF-HFP	$(CH_2CF_2)_n$-C_3F_6	125°	–	19.1 psi	Lalia et al. (2013)

Membrane Thickness Thickness of the membrane affects the flow in the MD process in an inversely proportional way. Thinner membrane reduces the mass transfer resistance, thereby increasing the vapour flux. On the other hand, the thickness of the membrane affects the phenomenon of conductive heat loss during the MD process. Therefore, membrane should be as thick as possible to reduce heat loss. However, this aspect conflicts with the requirement of high vapour fluxes. Hence, there is a need to optimize this parameter. According to the literature, the optimal membrane thickness for a MD process should be in the range of 30–60 μm (Laganà et al. 2000).

Membrane Porosity Porosity is defined as the ratio between volume of the pores and the total volume of the membrane. Membrane porosity is directly proportional to the evaporation surface area, hence, higher porosity of the membrane leads to higher vapour fluxes (Susanto 2011). Additionally, increase in porosity level of the membrane reduces the conductive heat loss, since the conductive heat transfer coefficient of the gases entrapped in the membrane pores is generally an order of magnitude smaller than the conductive heat transfer coefficient of the hydrophobic membrane material (Lawson et al. 1996). It has been estimated that membrane porosity value for an efficient MD should be in the range between 30–85% (El-Bourawi et al. 2006), however usually, this value is greater than 60%.

Membrane Pore Size As mentioned previously, microporous membranes are used for MD, however, the exact pore size of the membranes for the MD process must be optimized to prevent wetting of the membrane and at the same time ensure the greatest possible flux. In general, an optimum pore size value depends on MD application and the type of the feed solution. Schneider et al. (1988) estimated that for wetting prevention, a maximum pore diameter should range from 0.5 to 0.6 μm. In general, uniform pore size is preferable to maintain stability of vapour flux mechanism (Susanto 2011).

Pore Tortuosity The shape of membrane pores also affects the MD process, e.g. the deviation of the pore shape from the cylindrical structure called membrane tortuosity. It is defined as the ratio between average length of the pores and membrane thickness. When the pores in the membrane create tortuous paths, the flux of the diffusing molecules is reduced, thus for a higher vapour flux, lower tortuosity is desired. In general, the most frequently assumed tortuosity value is 2 (Phattaranawik et al. 2003).

Thermal Conductivity To minimize the heat loss during MD operation, it is important to use the membrane material with low heat conductivity. The heat loss reduction leads to higher energy efficiency, lower susceptibility to temperature polarization phenomena and higher vapour flux. Therefore, the most promising approach is the selection of highly porous membrane. As mentioned before, the thermal conductivity of polymer membrane is significantly higher than thermal conductivity of gases filling the membrane pores. Thermal conductivities of membranes materials, such as PP, PTFE, PVDF lies in the range between 0.11 for PP up to 0.27 $Wm^{-1}\ K^{-1}$ for PTFE at 23 °C (Alkhudhiri et al. 2012).

Table 4.2 shows some examples of the commercial membranes commonly used in MD by several researchers, together with their main characteristics. These membrane modules were actually designed for other membrane operations such as microfiltration. Since commercially available membranes does not meet all the MD requirements, there is a need to design novel membranes. Nevertheless, there is a certain limitation in hydrophobicity improvement of smooth surfaces. For example,

Table 4.2 Examples of commercial membranes used by research community

Polymer/ module	Trade name	Manufacturer	Thickness (μm)	Mean pore size (μm)	Porosity (%)
PVDF/flat sheet	GVHP	Milipore	125	0.2	80
PVDF/flat sheet	Durapore	Milipore	110	0.45	75
PTFE/flat sheet		Osmonics	175	0.22	70
PTFE/hollow fiber	POREFLON	Sumitomo electric	550	0.8	62
PP/flat sheet	MD080CO2N	Enka Microdyn	650	0.2	70
PP/hollow fiber	Liqui-Cel® extra-flow 2.5 × 8 in	Hoechst-Celanese	50	0.044	65
PE/hollow fiber	UPE test fiber	Millipore	250	0.2	–

in the case of smooth PVDF, a surface that is saturated by fluorinated methyl groups, it is possible to reach a maximum 120° contact angle (Liao et al. 2013). Therefore, the enhancement of the surface hydrophobicity is based on increasing the surface roughness (Tijing et al. 2016). Thus, to achieve a strong water repellent rough membrane, a proper modification must be adopted focusing on the creation of micro- and nanostructured surface. Recent studies have evaluated the potential of nanofillers incorporation into polymer membrane to modify the structure and physicochemical properties of membranes, such as hydrophobicity, porosity, surface charge density, chemical, thermal and mechanical stability (; Castro-Muñoz et al. 2019a, 2020b; Ahmad et al. 2020). The new generation of membranes modified with inorganic materials, such as carbon nanotubes (Tijing et al. 2016; Castro-Muñoz et al. 2020c), graphene (Gontarek et al. 2019; Castro-Muñoz et al. 2019b), clay (Prince et al. 2012), silica (Zhang and Wang 2013) and titanium dioxide (Meng et al. 2014), has become a promising approach for superhydrophobic MD membranes preparation.

2.3 MD Configurations

Various configurations for MD operation can be used such as direct contact membrane distillation (DCMD), air gap membrane distillation (AGMD), sweeping gas membrane distillation (SGMD) and vacuum membrane distillation (VMD). In general, the difference among MD configurations lies in the method of vapour condensation on the permeate side (Fig. 4.2).

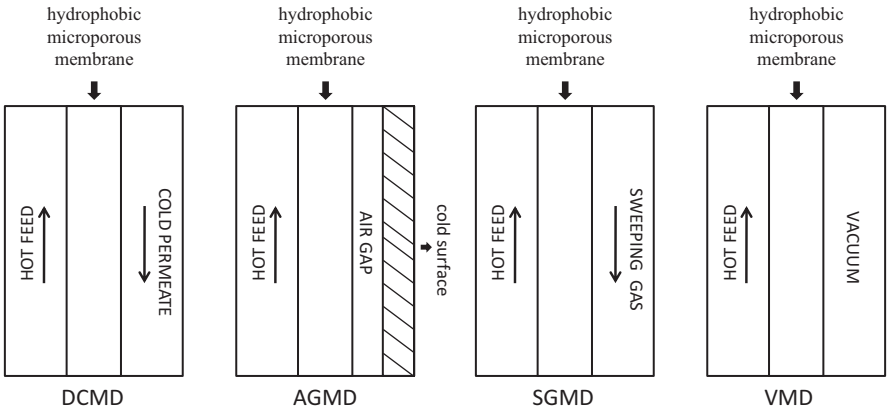

Fig. 4.2 Schemes of MD configurations

In DCMD, both feed and permeate liquids are in direct contact with the hydrophobic microporous membrane. As the permeate has lower temperature than feed it is used as a condensing fluid. Due to its set up simplicity, this configuration is most often used in laboratories. On the other hand, the direct contact of liquids with the membrane leads to heat loss across the membrane. Therefore, DCMD is characterized with the lowest thermal efficiency among the MD configurations. In AGMD the vapour passing through the membrane is condensed on the cold surface. The membrane and cold surface are separated by the air gap. This configuration reduces the heat loss throughout the membrane. In SGMD configuration, vapour passing through the membrane is sweeping and carrying by a cold inert gas outside the membrane module where condensates. Despite the obvious advantages of this configuration such as low heat loss and reduced mass transfer, it is relatively rarely used because of the higher operational cost than other configurations. In VMD, the vacuum is applied on the permeate side inducing the process driving force. Due to the low pressure, condensation takes place outside of the membrane module.

2.4 Osmotic Distillation

The osmotic distillation (OD) is a method for water evaporation and solution concentration. It is considered as a non-thermal variant of membrane distillation. Similarly, as conventional MD, the driving force is the vapour pressure gradient across the membrane, between two solutions: feed and striping solution—usually brine, however it is induced by the concentration difference. Hypertonic salt solutions of brine are usually used (Wang and Min 2011). In some cases, the feed is additionally heated to a little higher value than that of the brine, which further increases the driving force (Zambra et al. 2014). It allows to obtain higher process yields. Such a process is called osmotic membrane distillation (OMD) (Gryta 2018). As the OD process can be carried out at room temperature and atmospheric pressure, it is a great candidate for food stuffs processing without a degradation of heat-sensitive components and volatiles loss.

2.5 Membrane Modules

A membrane module for MD must meet several requirements. It should exhibit a high packing density (defined as the ratio of membrane area to the packing volume) and must provide both high feed and permeate flow rates that are usually introduced tangentially to the membrane or in cross-flow mode. Membrane module should assure the possibility of flow rate with high turbulence to provide heat and mass transfer between the bulk solution and the solution at boundary layer, thus, to mitigate the temperature polarization and concentration polarization effects. To prevent flooding of membrane pores that can be caused by a high transmembrane

hydrostatic pressure, MD module should provide low pressure drop along the membrane module length. Moreover, the MD module should ensure the maintenance uniform temperature of the liquid solutions along the module length without a heat loss to the environment. The membrane module material should be properly selected so that the used feed solutions do not cause its destruction (e.g. due to corrosion) There are several membrane modules that are commonly used by MD researchers, such as plate and frame, spiral wound, tubular, capillary or hollow fiber (Alkhudhiri et al. 2012; Castro-Muñoz and Fíla 2018a).

In the case of plate and frame module the membrane and the spacers are layered together between two plates. For this module, the membrane is usually prepared as discs or flat sheets. It is widely used on laboratory scale, as it is easy to clean and replace, moreover flat sheet membranes are easy to prepare and handle. The packing density is relatively low. Usually, the use of the membrane support is required to enhance mechanical strength. To prevent excessive concentration and temperature polarization, mass and heat transfer rates between the bulk solution and boundary layer must be sufficient. Some authors proposed the use of spacer-filled channels for the plate and frame membrane modules in both the feed and permeate side of the membrane. The use of spacers led to the flow characteristics change and promoted regions of turbulence (Martínez-Díez et al. 1998; Phattaranawik et al. 2001).

In spiral wound membranes, the flat sheet membrane, porous membrane support, feed and permeate spacers are enveloped and rolled around a perforated central collection tube. The feed solution passes across the membrane surface in an axial direction. The permeate flows to the perforated central collection tube. The spiral wound membrane is characterized by greater packing density than that of the plate and frame module, moderate susceptibility to fouling and acceptable energy consumption. Flat membrane module having a membrane area of 0.01 m^2 was used for pineapple juice concentration and clarification (Babu et al. 2008). The module consists of porous hydrophobic polypropylene membrane supported with polyester mesh between viton gasket and two stainless steel frames.

The hollow fiber module is made of connected hollow fibers that are sealed inside a shell tube. In this type of module, there are two approaches for the feed and permeate flow. One of them is inside-outside approach when the feed solution flows along the inner part of hollow fiber, while the permeate is collected outside of the membrane fiber. Another one, outside-inside approach, when the feed solution flows along the outer parts of hollow fibers and the permeate is collected in the inner part. No support is needed for this type of module, furthermore, it is characterized by high packing density and low energy consumption (El-Bourawi et al. 2006). However, it has high tendency to fouling, and the membranes are usually an integral part of the module (Pichardo-Romero et al. 2020), thus it is difficult to clean and replace them. For this reason, clarification is a crucial pretreatment step during fruit juice concentration by MD using a hollow fiber module, to mitigate the fouling and enhance MD fluxes (Cassano and Drioli 2007; Conidi et al. 2020).

In tubular membrane modules, the tube-shaped membrane is inserted between hot and cold fluid cylindrical chambers. These modules offer low tendency to fouling and provide much higher membrane surface area to module volume ratio

compared to plate and frame modules (Khayet 2011). It can be used for high viscous liquids since it is characterized by higher cross-flow velocities and large pressure drop. On the other hand, it has a high operating cost.

3 Application in Food Industry

3.1 Juices Concentration and Clarification

As mentioned previously, MD as a process that operates with mild temperatures and atmospheric pressures, can be applied for evaporation, and thus juice concentration without the risk of valuable component degradation. This hypothesis was first confirmed on the basis of preliminary studies on effective concentration of orange juice using microporous PVDF membrane in MD process, that was performed by Calabro et al. (1994). They observed very good retention of soluble solids, sugars, and organic acids. Thereafter, many papers have been published proving that MD is an effective method for concentration of fruit juices such as orange (Deshmukh et al. 2011), apple (Gunko et al. 2006), black currant (Bagger-Jørgensen et al. 2004), kiwi fruit (Cassano and Drioli 2007), pineapple (Hongvaleerat et al. 2008) and grape (Rektor et al. 2006) juices. Table 4.3 summarizes the studies on the concentration of fruit juices along with the most relevant results.

3.1.1 Effect of Process Parameters on Juice Processing

According to Cassano and Drioli (2010), the fluxes in MD are dependent on various process parameters such as: applied temperatures and temperature difference between feed and permeate, feed concentration and flow rates of feed and permeate solutions.

In general, high feed temperatures during MD process are proposed to enhance evaporation efficiency (EE). This parameter is defined as the ratio between the part of the heat which contributes to evaporation to the total heat input in the module (Smolders and Franken 1989). However, in the case of fruit juice processing, high operation temperatures are unfavorable due to the quality reduction and formation of compounds such as hydroxymethyl furfural and furan (Crews and Castle 2007; Vranová and Ciesarová 2009). In addition, increasing the feed temperature causes a higher susceptibility to the temperature polarization effect (Castro-Muñoz et al. 2020c; Hwang et al. 2011). For this reason, the optimization of operating temperature is one of the most important steps.

Jorgensen et al. (2011) examined the potential of two MD configurations for recovery of aroma compounds from black currant. They evaluated the influence of various parameter such as feed temperature and feed flow on the permeate flux and concentrate quality. Twelve aroma compounds were selected for examination of concentration factor. At the highest tested feed temperature, the highest

Table 4.3 Studies on the concentration of fruit juices using MD membranes

MD configuration and process parameters	Membrane type:	Feed	Flux:	Concentration efficiency	References
DCMD Tf: 37 °C Tp: 28 °C	Commercial plate PVDF	Orange juice	~ 0.4 kg/ m2/s *10^3	Concentration up to 400 g/L	Calabro et al. (1994)
DCMD Tf: 24 ± 1 °C Tp: 17 °C	Hollow fiber PP	Blood orange juice	0.6 kg/m^2h	65 °Brix	Quist-Jensen et al. (2016)
DCMD Tf: 70 °C Tp: 10 °C	Flat sheet PVDF	Apple juice	28 lm^{-2} h^{-1}	To 60–65 °brix	Gunko et al. (2006)
OD Tf: 35 °C Tp: 20 °C	Flat sheet PTFE	Pineapple	10 kg/m^2h	10.6 to 27.8 g 100 g-1 TSS	Hongvaleerat et al. (Hongvaleerat et al. 2008)
DCMD Tf: 30 °C Tp: 11 °C	Hollow fiber PP	Black currant	0.8 kg/m^2h	58.2 °Brix	Kozák et al. (2009)
DCMD Tf: 32 °C Tp: ~4 °C	Hollow fiber PP	Apple juice	1 kg/m^2h	64°brix	Laganà et al. (2000)
OMD Tf: 35 °C Tp: 20 °C	Flat sheet PTFE	Cactus pear juice	3–4 lm^{-2} h^{-1}	23.4 °brix	Terki et al. (2018)
DCMD Tf: 30 °C Tp: -	Capillary PP	Grape juice	2–2.5 kg/m^2h	65 °brix	Rektor et al. (2006)
OD Tf: 40 °C Tp: 40 °C	Hollow fiber PP	Cranberry juice	1.21 lm^{-2} h^{-1}	48 °brix	Zambra et al. (2014)

concentration factors have been observed. For the most hydrophobic and volatile aroma compounds the concentration factors ranged from 12.1 to 9.3 at 45 °C. The highest tested temperature of the feed and the feed flow rate equal 400 L/h resulted in an aroma recovery up to 84 vol.%. The authors compared the efficiency of the aroma recovery using SGMD and VMD. As it turns out, the SGMD process was less influenced by the flow rate, and more by the temperature. Concentration by VMD process reduced the operation time, as higher fluxes have been achieved. Due to the longer time required for SGMD for the concentration, a higher loss of aroma compounds such as anthocyanins and polyphenols was observed, comparing to the VMD.

Onsekizoglu et al. (2010) evaluated the potential of MD for the concentration of apple juice. According to their studies, the effect of the feed flow rate on transmembrane flux is inconsiderable compared to the effect of temperature difference across the membrane. During MD, the clarified apple juice with initial total soluble solids (TSS) contents of 12 °Brix was concentrated up to 65°Brix. Moreover, the

nutritional and sensorial quality of the permeate was very similar to the original juice. MD, as opposed to traditional thermal evaporation, allowed to maintain the bright natural color and pleasant aroma of concentrated juice.

During MD operation, it is important to maintain the constant trans-membrane vapor pressure to avoid a reduction in permeate flux (Laganà et al. 2000). Quist-Jensen et al. (2016) examined the concentration of clarified orange juice using DCMD. They observed the evaporation flux decay in the preconcentration step, and they explained it with the reduction of temperature difference between the feed and permeate side. However, experimental results indicated that in the final concentration step, the trans-membrane flux decay can be affected by the increase in juice viscosity. Using two-step DCMD process, the TSS content in clarified orange juice increased from 9.5 °Brix up to 65 °Brix. Gunko et al. (2006) observed an important temperature gradient dependence on the capacity of DCMD process. Their results showed that the decreasing the cooling water temperature from 30 °C to 10 °C, increases the flux almost two times (180%), when the feed temperature was 50 °C. However, similar decrease of the cooling water temperature for the feed temperature equal 70 °C causes only 10% flux increase. The highest permeate flux of around 28 L/m^2 h was obtained for the initial concentration process. When TSS content reached 50 °Brix, the permeate flux decreased to 9 L/m^2 h. Further reduction of flux was observed together with the juice concentration up to 60–65 °Brix.

Lagana et al. (2000) used polypropylene hollow-fiber DCMD modules to obtain highly concentrated apple juices up to 64 °Brix. They concluded that flux rates were mainly dependent on temperature polarization coefficient, rather than concentration polarization coefficient which is insignificant.

3.1.2 Integrated Membrane Processes

One of the main problem in fruit juices processing is the presence of colloidal particles and suspensions that may lead to clogging or blocking of membrane pores (Castro-Muñoz et al. 2016b; Castro-Muñoz and Fíla 2018b; Valencia-Arredondo et al. 2020). According to Mirsaeedghazi et al. (2009), the cake layer formation on the membrane surface causing the membrane fouling, is created within 5 min of raw pomegranate juice processing. Such a layer deposited on the membrane increases its susceptibility to wetting and can result in a liquid permeation through the membrane. Typical foulants in fruit juices are pectins, cellulose, lignin and hemicelluloses (Meng et al. 2014; Díaz-Montes and Castro-Muñoz 2019). According to He et al. (2007), the pre-clarification of the apple juice causes significantly higher fluxes during further UF operation. For pectin removal, enzymatic pretreatment can be applied as a first step of juice clarification (Galiano et al. 2019). The enzymes can hydrolyze pectins and partially hydrolyze other macromolecules and polysaccharides. An additional enzymatic pretreatment and flocculation have been proven to improve the efficiency of membrane process during apple juice clarification (Onsekizoglu et al. 2010). Lukanin et al. (2003) have evaluated the effect of an enzymatic pretreatment on the tendency of protein deposition. The protein level

deposition on the hydrophobic membrane during subsequent OD process decreased significantly after the enzymatic pretreatment.

Sort of benefits can be achieved while combining MD with pressure driven membrane separation processes, such as microfiltration (MF) and ultrafiltration (UF). Prefiltration is usually used to remove suspended solids from the fruit juices what leads to their viscosity reduction and higher fluxes during MD concentration step. Reduction of juice viscosity improve hydrodynamic conditions in the membrane channel, thereby decreasing susceptibility to concentration and temperature polarization (Lukanin et al. 2003).

Rektor et al. (2006) used MD after the MF and reverse osmosis (RO) concentration for further water removal from grape juice. The authors obtained the final juice concentration over 60 °Brix. Hongvaleerat et al. (2008) used OD to concentrate single strength and clarified pineapple juices. Preconcentration by thermal evaporation under vacuum resulted in flux enhancement during OD concentration from 6.1 kg h^{-1} m^{-2} for the single strength juice up to 8.5 kg h^{-1} m^{-2} for the preconcentrated juice. Cassano and Drioli (2007) examined the permeate quality after OD process of clarified kiwi fruit juice concentration. The raw kiwi fruit juice was first clarified using an UF laboratory pilot unit, after submitted to an OD concentration step. The clarified kiwi fruit juice was concentrated from 9.4 °Brix up to final values of 66.6 °Brix. The analytical measurements proved that concentration by OD has no influence on the acid ascorbic content and total antioxidant activity (TAA), while concentration by thermal evaporation caused a reduction of 87% of Vitamin C and 50% of TAA.

Onsekizoglu (2013) proposed the use of an integrated MD process capable of concentrating pomegranate juice under mild conditions, and evaluated the impact of coupled operation on product quality and process performance. The pomegranate juice was clarified by UF and concentrated by MD. Clarification through UF resulted in an improved clarity of the juice, simultaneously allowed to maintain organic acid content during clarification. UF step resulted in reduction of macromolecular particles in the juice, which tend to deposit on the membrane surface. Such a deposition may cause a membrane wetting and can result in a non-allowable in MD convective flow of liquid through the membrane. The use of integrated process allowed to obtain concentrated pomegranate juice (up to 57 °Brix) and to preserve its original characteristic, such as TAA, total phenolic content (TPC), total titratable acidity (TTA), total monomeric anthocyanins (TMA), pH and color.

The use of RO or FO processes, as a preconcentration step before OD or MD, has also been shown to be an effective method for high quality fruit juice concentrates production by Pagani et al. (2011) for concentration of Acerola juice, by Galaverna et al. (2008) for concentration of blood orange juice, and by Cassano et al. (2003) for concentration of citrus and carrot juices. Kozak et al. (2009) applied MF prefiltration and RO preconcentration before main black currant juice concentration by DCMD. During pretreatment it was possible to increase the concentration from 15 to 22 °Brix, while further concentration by DCMD leads to 58 °Brix using a temperature difference of only 19 °C.

Sotoft et al. (2012) proposed a conceptual process design using integrated membrane processes for the concentration of blackcurrant juice and aroma recovery. The combination of membrane processes included VMD, for aroma recovery (Castro-Muñoz 2019a), and RO, NF and DCMD for water removal was proposed as an alternative for traditional multiple step evaporators. The plant scale was based on handling 20 t/h of raw juice and the production was calculated for 17,283 ton of concentrated juice per year. Based on the mass balances, membrane areas and module numbers, the economical potential of the process was evaluated. The estimated production cost for concentration of juice from 12 °Brix to 66°Brix was 0.40 €/kg. It was 43% lower than the cost of a conventional thermal evaporation while considering the membrane lifetime of one year. To make the process even more economical, the authors proposed to increase the membrane life time up to 2 or 3 years.

3.2 Dairy Products Processing

Kezia et al. (2015) investigated the ability of DCMD to concentrate the waste effluent from the cheese making industry. They used flat sheet PTFE membrane with PP non-woven support layer, and salty whey effluent as a feed solution. The feed was composed of minerals, proteins and sugars. Even though, the feed solution was prefiltrated through MF membrane prior to DCMD concentration step, a decline in feed flux was observed due to the presence of trace protein. Adding to the prefiltration step UF membrane led to a stable flux over 10 h of operating time. Starting from 10 wt% of solids in the feed, a final total solids concentration of 30 wt% and the water recovery up to 83% was achieved. Kujawa et al. (2019) tested polymeric porous hydrophobic membranes (PP and PTFE) in AGMD process, for dairy products concentration. They found it to be an effective approach for whey and lactose solutions concentration and simultaneous production of high-quality water with retention higher than 99%. Authors compared MD results with the performance of MF, for which a rejection ranging from 80 to 90% was observed.

Moejes et al. (2020) optimized and modelled RO and AGMD network for the concentration of milk. RO was found to be favorable until its maximum achievable concentration, while AGMD was energy intensive for this type of application. This was due to the energy necessary to maintain a sufficient cross flow, which must be heated and cooled. This energy requirement is growing when the fouling phenomena occurs. To improve the performance of AGMD for milk concentration authors proposed different approaches, e.g. increasing the temperature of feed and permeate side to their maximum acceptable values and the use of available waste heat.

Numerous studies stated the occurence of fouling phenomena while processing dairy components by MD (Kujawa et al. 2019; Hausmann et al. 2013a, 2013b; Tomaszewska and Białończyk 2013). Fouling layers cause heat and mass transfer resistances leading to significant flux decline in MD process (Tijing et al. 2015). Hausmann et al. (2011) tested the possibility of MD application for dairy processing. In general, the MD requires the use of hydrophobic membranes which may lead

to interactions with any hydrophobic components, such as proteins and fats, thus result in membrane wetting. Therefore, authors evaluated the influence of the main dairy components on the membrane and overall process performance. Whole milk, skim milk, whey and lactose powder solution were tested separately in DCMD. Results showed the flux decline over time, caused by the membrane fouling. In the case of whey solution, fouling was related to time, while during skim milk solution test fouling was more related to dry-matter concentration. The fouling mechanism of dairy stream during membrane distillation has been described in detail in another paper by Hausmann et al. (2013c). In the case of skim milk and whey solutions the fouling starts with the deposition of salts and proteins. However, in the case of skim milk processing fouling occurred within a few minutes through a formation of homogeneous layer, which increases in thickness over time. Whey solution caused the formation of fouling patches that grew across the membrane area and remained reversible for much longer time periods. This type of fouling layer was less dense, thus caused smaller flux decline with time than skim milk fouling layer.

One of the possible approach to reduce membrane fouling is to make the membranes more hydrophilic (Pichardo-Romero et al. 2020; Khayet et al. 2006; Castro-Muñoz 2020b). Chanachai et al. (2010) coated hydrophobic hollow fiber PVDF membrane with highly hydrophilic chitosan. The effect of this modification was tested in oil feed solution containing limonene via OD unit. Results showed that the coating resulted in higher vapour fluxes while inhibiting the flavor loss. Moreover, uncoated membrane showed a significant flux decline after 100 min of operation. After 5 h of uncoated membrane testing 18.86 mg/l of $CaCl_2$ was found in retentate solution indicating membrane wetting. On the contrary, chitosan coated membrane showed stable flux with time and no wetting susceptibility.

3.3 Ethanol Removal

During the ethanol production and sugar fermentation several by-products are formed (Castro-Munoz et al. 2018, 2019c), which inhibit further yeast productivity leading to low ethanol concentration in fermentation broth (5–12%). An increase in the ethanol concentration may represent a lower cost of its removal through distillation, however, it is difficult to obtain due to inhibition phenomena. The MD is an economical alternative process to traditional energy intensive distillation that can be successfully applied for continuous removal of ethanol and other fermented products from the broth (Tomaszewska and Białończyk 2011; Gryta et al. 2000; Zhang et al. 2017; Fan et al. 2019). In addition, the removal of other volatile substances from fermentation broth may decrease the inhibition effect of these compounds on yeast productivity. These volatile compounds are aliphatic acids such as formic, acetic, propionic, butyric, valeric and hexanoic, alcohols (2,3-butanediol), aromatic compounds and furfural (Couallier et al. 2006). Gryta (2001) performed ethanol production in tubular bioreactor integrated with MD. The author carried out the

fermentation process with the yeast concentration of 20 g/dm^3 that resulted in the productivity level of 5.5 g/dm^{3}h of ethanol. The process efficiency almost reached the theoretical value of the fermentation. The fermentation under similar conditions, but without MD leads to the productivity decrease to 2.6 g/dm^{3}h. The fermentation efficiency decreased significantly after 10 h of process duration resulting in the final efficiency below 50%. Gryta and Barancewicz (2011) evaluated the possibility of removing not only ethanol but also other volatile compounds from fermentation broth using MD. They observed that apart from ethanol, mainly acetic acid and propionic acid were evaporated from the feed to distillate. Recent studies by Kumar et al. (2017) showed that membrane-integrated system (MF, NF and DCMD) for bioethanol production can operate for many hours without any significant concentration polarization effect and flux decline. Such a system can be driven by solar energy, representing an energy efficient and eco-friendly approach for ethanol removal and purification.

Banat and Al-Shannag (2000) evaluated the potential use of MD to recover dilute acetone-butanol-ethanol solvents from aqueous solution. The authors used multicomponent Stefan-Maxwell-based mathematical model to predict the AGMD performance. The results confirmed the effectiveness of MD in alleviating the inhibitory effect of acetone-butanol-ethanol on the microbial culture. The increase of the feed temperature led to the butanol selectivity increase, which was considered as the most toxic solvent among those mentioned. The authors found that optimum feed temperature for butanol separation was 55 °C, and interestingly, it was the most preferentially removed solvent (in spite of its high boiling point, compared to acetone and ethanol).

Several studies evaluated the potential of MD to dealcoholize alcoholic beverages (Castro-Muñoz 2019b). Varavuth et al. (2009) used microporous PVDF hollow fiber membrane for ethanol removal from ethanol diluted solution and wine using OD. They found this process to be capable of alcohol permeation, however, the study showed the significant reduction of ethyl acetate and iso-amyl alcohol (70% and 44%, respectively after 6 h of operation). Ethanol removal using OD resulted in 34% reduction of ethanol in tested wine. Similar studies by Hogan et al. (1998) showed the capability of OD to reduce alcohol content in wine up to 6% with minimum loss of its flavor and fragrance components. Purwasasmita et al. (2015) proved the possibility of VMD for beer dealcoholization process. The effect of feed and vacuum pressure on flux and selectivity was investigated. Non-porous thin-film composite polyamide was used as a membrane module. The results indicated that beer dealcoholization using VMD can reduce the alcohol content from 5%-vol. to 2.45%-vol. within 6 h, without losing any nutrients and flavoring components. A slight loss of maltose was related to the adsorption phenomena on the membrane surface, therefore, for the recovery of the flavor compound, membrane flushing was proposed.

3.4 Anthocyanins Concentration

Anthocyanins concentration using membrane technology, e.g. through ultrafiltration and nanofiltration membranes has been already studied by several researchers (Avram et al. 2017; Cassano et al. 2014; Ceron-Montes et al. 2015). However, the application of gas-filled membrane in the form of OD and MD to concentrate anthocyanins is not common. Nevertheless, there are some investigations that have considered the use of OD and MD integrated processes. Jampani and Raghavarao (2015) compared thermal evaporation with integrated aqueous two-phase extraction with membrane processes such as OMD and forward osmosis (FO) for concentration of red cabbage anthocyanins. The results showed that degradation constant of anthocyanins was lower in the case of both integrated processes when compared to anthocyanins concentration obtained by thermal evaporation. However, an integrated process involving FO was found to be the most suitable for the purification and concentration of anthocyanins. Their concentration increased from 508.05 mg/L to 3123.45 mg/L for FO integrated process, while only to 945.32 mg/L for OMD integrated process. Similar results were obtained by Nayak and Rastogi (2010). In the case of FO, the anthocyanin extract was concentrated from 49.63 mg/l up to 2.69 g/l, while in the case of OMD process, the concentration of anthocyanin achieved only 72 mg/l at the same operation time. However, migration of sodium chloride was observed during FO operation, while during OMD there was no transfer of osmotic agent. Patil and Raghavarao (2007) reported the recovery of anthocyanins from radish by performing UF, RO, and OMD processes with different combinations to evaluate the efficiency of each system. UF step was used to remove tannin, pectin, and other suspended solids, and resulted in a clear extract. RO step was used for preconcentration of anthocyanins from 1 to 4 °B. The separation by OMD resulted in concentration of extract up to 17.5 °B after 20 h using $CaCl_2$ as an osmotic agent. It took 30 h to achieve the same extract concentration using another osmotic agent (K_2HPO_4). The authors compared the OMD results with the performance of conventional evaporation process (vacuum evaporator). The concentration of anthocyanin increased up to 9 °B after three passes. The integration of UF, RO, and OMD gave a concentration increase of 25-fold higher than that of the initial feed (from 1 to 26 °B). As a result, it has been proven that the concentration of anthocyanin by integrated membrane system was more favorable than conventional or individual processes. Kozak et al. (2009) have examined the effectiveness of anthocyanin concentration using DCMD. The analytical measurements results showed that the anthocyanin content increased proportionally to the increase of the TSS from 1.868 g/L before MD, up to 3.805 g/L after MD step. Anari et al. (2019) concentrated bioactive anthocyanins from aqueous extracts of muscadine grape pomace using OD and DCMD. Due to the sensitive nature of anthocyanins (Castro-Muñoz et al. 2018a), the maximum feed temperature was limited to 40 °C and the permeate temperature was 10 °C. Concentration factor of total anthocyanins after processing using OD reached 1.07, while for DCMD it was equal 1.6. A combination of OD and DCMD gave the highest concentration factor of 2.78 and the highest

observed fluxes. The authors also highlighted other advantages of combined OD-DCMD process, such as minimal required pretreatment, reduction of equipment costs and faster processing compared to the individual OD operation. The results quoted above suggested that MD process deserves more interest in the anthocyanin concentration application as it may become an alternative to conventional method and a cost-effective unit operation. However, prior to actual manufacturing process, selection of an appropriate membrane and regeneration of the membrane must be considered and optimized.

4 Fouling and Its Control

One of the main issues of membrane-based processes including MD is membrane fouling (Pichardo-Romero et al. 2020; Cassano et al. 2015). Fouling reduces membrane performance due to the deposition of suspended or dissolved substances on the membrane surface and within the membrane pores. It deteriorates heat and mass transport across the membranes, therefore membranes have to be cleaned more frequently. For food processing, fouling becomes more complicated phenomenon due to the complexity of the processed products composition. The fouling in MD can take several forms depending on the chemical composition of the feed bulk solution, such as inorganic fouling (scaling), colloidal fouling, organic fouling and biological fouling (biofouling) (Tijing et al. 2015). Scaling is caused by the deposition of inorganic precipitates, such as calcium sulfates, calcium carbonates and magnesium carbonates. Basically, these inorganic precipitates are deposited on the membrane when their concentration in the feed solution exceeds their saturation concentrations. Colloidal fouling on the membrane surface refers to the accumulation of biologically inert particles and colloids. Organic fouling is mainly associated with the deposition or adsorption of organic matters, such as humic acid, fulvic acid, protein, polysaccharides, and polyacrylic polymers (Díaz-Montes et al. 2020b). Biofouling refers to the formation of biofilms by various microorganisms, such as bacteria and fungi, on the membrane surface. The morphology of the fouling layer determine its resistance mechanisms, e.g. non-porous layer results in both thermal and hydraulic resistances, while a porous one contributes only to thermal resistance (Gryta 2008).

Ding et al. (2008) investigated the fouling resistance during the concentration of traditional Chinese medicine via DCMD. The observed trans-membrane water flux decline due to the membrane fouling that introduced an additional thermal resistance in the boundary layer. They found prefiltration to be a more effective way than centrifugation for mitigating membrane fouling, while for effective cleaning of fouled hollow fiber membrane they proposed gas back-washing within membrane module. An intermittent back-washing could kept trans-membrane flux at relatively high level during concentration process, however, full recovery of the initial flux value was not possible as a gas of only 10 kPa gauge pressure was used for back-washing. Higher gauge pressure could cause the membrane demage. In another work Ding et al. (2011) applied bubbling as an effective startegy to control

polarization and fouling formed in concentrating traditional Chinese medicine extract through DCMD. Gas bubbling induces the flow and improves shear stress at the membrane surface. An introduction of intermittent gas bubbling to the feed side of membrane module gave possibility for effective fouling control, through deposited foulants removal from membrane surface by created two phase flow. It was also noted that the simultaneous increase of gas flow rate, gas bubbling duration, and the decrease of MD duration can improve the cleaning efficiency of gas bubbling strategy. Durham and Nguyen (1994) evaluated the effectiveness of several cleaning agents for hydrophobic membranes fouled by tomato paste in OD process. The cleaning regime was determined by the membrane surface tension. 1% NaOH was found to be the most effective cleaner for membranes with a surface tension greater than 23 mN/m, however, repeated fouling/cleaning trials lead to hydrophobic integrity demage. On the other hand, for membranes with a surface tension less than 23 mN/m, P3 Ultrasil 56 was the most effective cleaner, additionally, fouling/cleaning trials did not affect membrane performance; stable water vapour flux and no salt leakage were still observed.

5 Concluding Remarks and Future Prospects

MD gained huge interest in processing of food and food bioactive components due to its lower energy requirement and milder process conditions in comparison with conventional distillation and pressure driven membrane processes. It results in minimal thermal damage and high quality of products. Due to the possibility of effective operation at low temperatures, MD can be driven by alternative energy sources for example waste energy or solar energy, thus MD may represent an energy efficient approach for food processing. This feature makes the process more attractive for industrial implementation. Although in recent years a few pilot plants studies have been proposed for desalination, most of MD studies regarding concentration and food components processing are still at laboratory scale.

Flux decline with time due to the membrane fouling is one of the main challenges for food processing using MD technology, since membranes require regular periodic cleaning to remove foulants and keep the permeability within a given range. The risk of fouling and wetting of membrane pores affect the membrane durability and limit their applications in this field. The studies in long term MD performance needs to be done to make the MD process more promising in food industry. Effective fouling control techniques for MD must be developed. The current techniques for the control of fouling are limited to feed pretreatment and membrane cleaning.

Theoretical 100% rejection of nonvolatile solutes is one of the major advantages of MD, however, evaporation fluxes are much smaller when compared with RO and thermal evaporation. Further efforts need to be established in this field, especially on flux enhancement possibilities.

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Chapter 5
Recovery of High-Added Value Compounds from Dairy and Winery Agro-Food Industries Using Electrodialysis

X. Vecino, M. Reig, and J. L. Cortina

Abstract Electrodialysis (ED) is an established technology, which can separate ionic species applying an electrical potential. ED is widely used in water desalination for drinking water production, seawater concentration for table salt production, acid and base production from its corresponding inorganic or organic salt and the recovery of by-products from industrial effluents. However, ED is a promising and eco-friendly technology to treat agro-food streams or agricultural wastes and by-products, generated from agro-food industries, following the frame of circular economy on the management of these residues (reduce, reuse, recycle and reprocess) and in line with the industrial symbiosis principles.

This chapter presents an overview of the electro-membrane technology from the agro-industries context, as well as the application of this technology in the agro-food industries for the recovery of high-added value compounds. Among the agro-industries, dairy and winery sectors are studied in detail. These industries are selected due to their importance at Southern European and state (Spain) level as one

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of the largest industrial producers (in terms of tonnes of product). In the dairy industry, ED is mostly applied as a demineralization step of milk whey, however ED can be used for production of protein fractions, lactose recovery or lactic acid removal. Regarding winery sector, the main application of ED is in the tartaric acid stabilization of wine; but also, it can be used for tartaric acid and potassium recovery from vinasses. In this sense, the ED applications in the above-mentioned agro-industries have been summarized in this chapter.

Keywords Ion-exchange membrane · Monopolar membranes · Bipolar membranes · Selective membranes · Resource recovery · Agro-industries · Dairy · Winery

1 Introduction

1.1 Electrodialysis Principles and Applications

Electrodialysis (ED) is a membrane separation technique based on electrical potential as main driving force. For that, ion-exchange membranes (IXMs) are placed between two electrodes, forming an ED stack. ED is based on selective passage of ions through IXMs, depending on their functional group charge, due to Donnan repulsion (Doble 2016; Baker 2012). There are two IXM types: (i) cationic exchange membranes (CEMs) and (ii) anionic exchange membranes (AEMs). CEMs are negatively charged (containing $-SO_3^-$, $-POO_2^-$, or $-COO^-$ groups) and allow cations transference, while blocking anions passage through them. On the other hand, AEMs are positively charged (due to $-NR_4^+$, NR_3H^+ or $= NH_2^+$ groups) and allow anions passage, although obstruct cations transport. In other words, IXMs permit contra-ions (opposite charge) passage, while hindering co-ions (same charge) transport though them (Strathmann 2010).

To conduct electrodialysis, AEMs and CEMs are placed alternatively between a cathode and an anode, separated by spacer gaskets. Thus, by a voltage applied between both electrodes, it is possible to separate ions from an aqueous solution and uncharged compounds, obtaining two new streams: (i) diluate and (ii) concentrate (see Fig. 5.1) (Al-Amshawee et al. 2020).

As can be seen in Fig. 5.1, membranes work as barrier for co-ions, while allowing contra-ions migration through them. Then, when feed solution, containing a solute electrolyte (MX), is introduced into the ED stack and voltage is applied between anode and cathode, ion migration occurres. Cations (M^+) from feed solution are attracted by the cathode, whereas anions (X^-) are attracted by the opposite electrode, the anode. Therefore, cations move towards the negatively charged electrode, crossing CEMs (negatively charged), but not AEMs (positively charged). At the same time, anions move towards the anode, passing through AEMs, but not CEMs. Hence, ionic species are removed from the feed solution producing a diluate

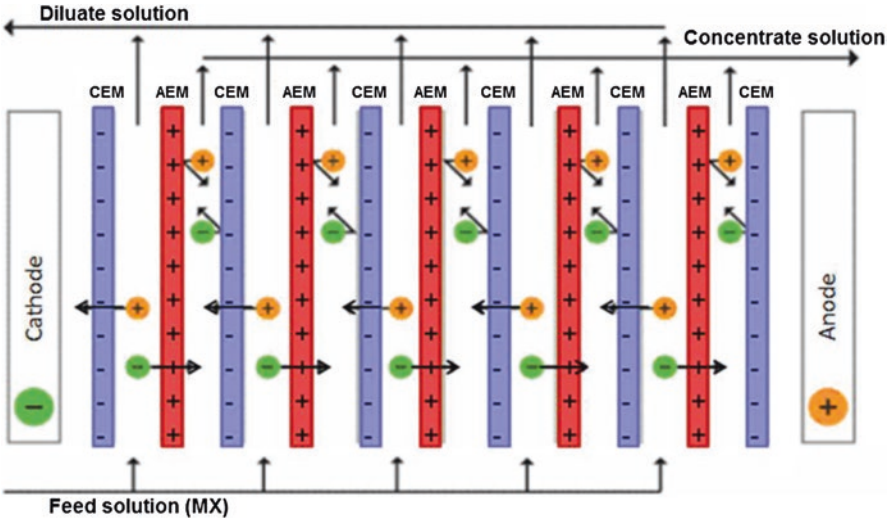

Fig. 5.1 ED membrane stack layout including the pairs of cation (CEMs) and anion exchange (AEMs) membranes and the electrodes at the extremes of the stack. (Adapted from (Arema 2017))

compartment, while a concentrate compartment is also obtained, recovering the ionic species from the feed solution. Moreover, an electrode rinse solution must circulate through both electrodes compartments, although it does not interact with the diluate and concentrate streams (Baker 2012; Strathmann 2010; Al-Amshawee et al. 2020). The electrode rinse solution keeps constant its concentration and composition over the ED procedure, since no ion transport occurred in this compartment, unless internal leaks appeared. However, solutions containing chloride ions are not recommended, due to chlorine gas formation in the electrodes compartment during the ED process. Indeed, Na_2SO_4 is one of the most widely used electrolyte (Campione et al. 2018; Reig 2016a).

As abovementioned, ion migration is the main transport phenomenon that takes place in an ED process. Nevertheless, undesired transport phenomena also take place, reducing the ED efficiency (Strathmann 2010; Pabby et al. 2009; Valdez Salas and Schorr Wiener 2012). Figure 5.2 represents all the mass transport phenomena that happen through IXMs during ED trials.

As shown in Fig. 5.2, three undesired phenomena occurred, apart from ion migration. In fact, ion migration implies electro-osmosis due to ion solvation. Then, water migration flux also occurred from the diluate to the concentrate compartment of the ED stack, diluting the final concentrated solution. Furthermore, ion diffusion and osmosis appeared after a period of ED operation, due to ion concentration gradient between both compartments. The former is the back diffusion or diffusion flux of ions from the concentrate to the diluate compartment, whereas the latter implies water transport from diluate to concentrate compartment, also known as osmosis flux.

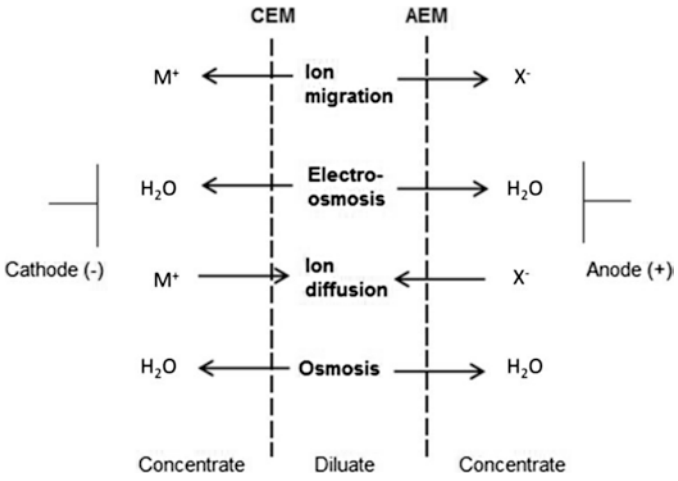

Fig. 5.2 Mass transport phenomena inside the ED stack: (i) ion migration, (ii) electro-osmosis, (iii) ion diffusion, and (iv) osmosis. (Adapted from (Reig 2016a))

An ED set-up usually consists of an ED stack, a power supply, pumps, piping and sensors. The main part is the ED stack, which is composed of IXMs, spacers and electrodes. As observed in Fig. 5.1, AEMs and CEMs are placed alternatively between electrodes. Each group of one AEM and one CEM is named cell pair. Besides, several IXMs configurations can be used for ED processes: CEM-AEM-CEM, AEM-CEM-AEM, cathode-CEM-AEM-anode or cathode-AEM-CEM-anode.

IXMs can be made by different materials, such as polyester, polyethylene, polyetheretherketone (PEEK) or polysulphone, among others (Al-Amshawee et al. 2020). Moreover, different membranes areas are used, depending on the application scale. Usually, IXMs of laboratory units have areas from 0.01 to 0.06 m^2, up to membrane areas of 1 m^2 at industrial scale (Von Gottberg 1998; Demircioglu et al. 2003; Tanaka 2015).

On the other hand, spacers can be also made from different materials, such as polypropylene/plexiglass, or polypropylene/silicone and they have the same area than the used IXMs. Besides, their thickness range is between 0.42 and 10 mm (Al-Amshawee et al. 2020).

Finally, electrodes from an ED stack can be made of titanium, titanium coated with ruthenium oxide, titanium plated with iridium, titanium coated with titanium and ruthenium oxides (70(%)RuO_2/30(%)TiO_2), platinum-plated iridium, steel 314 or graphite (Scarazzato et al. 2015; Szczygiełda and Prochaska 2017).

On the other hand, power supply is also an important device for ED tests. In fact, ED experiments do not start until current is applied between both electrodes, since ions are not attracted by the electrodes and they do not cross membranes without current applied. Thus, voltage and current should be enforced to the ED stack. However, depending on the number of cell pair, a maximum voltage could be

applied without damaging the membranes. For standard ED, 2.5 V should be considered as voltage drop in the electrodes compartment and increasing this value by 1 V for each cell pair. On the other hand, if other ED-based technologies are used, such as ED with bipolar membranes (BPMs) or selective ED, 2.5 V should be considered for electrode compartments voltage drop plus 1.5 V per each cell trio (combination of three different IXMs) plus 1 V per each bipolar membrane placed inside the stack (Ghyselbrecht et al. 2013).

There are many ED suppliers worldwide, although the main-know providers are Suez WTS, (formerly General Electric(GE) and before Ionics Inc.), Eurodia, and MEGA a.s (Valero et al. 2011).

ED technique appeared in the early 1950s for brackish water desalination applications. From then, several thousands of ED plants have been installed worldwide for water and wastewater desalination, since around 80–95% of the feed brackish water is recovered as clean water. However, a concentrate stream (5–20 times higher than the initial one) is also obtained by ED, named brine (Baker 2012). Hence, salt recovery from seawater appeared as another ED application, by valorising the ED brines (Campione et al. 2018; Reig et al. 2014). This application is widely used in Japan for table salt production.

The two already described applications are the most used by ED. Nevertheless, other applications appeared over the years, such as transition metals removal from electroplating rinse waters and hydrometallurgical processes (Zimmermann et al. 2020), energy production (Tian et al. 2020), lithium recovery (Li et al. 2019), organic acids production (Huang et al. 2007) or integrated with other technologies for increasing solutions concentration, for example in agricultural field (Vecino et al. 2020) or as part of a zero liquid discharge (ZLD) scheme (Muhammad Yaqub 2019). Finally, it is worth mentioning that ED has been also used in food industry applications (salt removal from cheese whey or soy, tannic acid removal from wine, citric acid removal from fruit juice, among others) (Baker 2012; Xu 2005).

The main drawback of conventional ED systems is membrane scaling and fouling due to colloid or insoluble salts precipitation on the IXMs. In order to prevent this issues, anti-scaling chemicals must be added to feed solution or pH adjustment must be done, together with regular membrane cleaning procedures (Strathmann 2010; Fidaleo and Moresi 2006).

Therefore, another operation mode appeared in the early 1970s: the electrodialysis reversal (EDR), designed by Ionics Inc. (USA). The main difference between conventional ED and EDR is that conventional ED systems operate unidirectional (diluate and concentrate compartments in the stack are fixed, since polarity of the electrodes is constant), whereas EDR systems are able to change – reverse – the polarity of the electrodes. Thus, by EDR the polarity of direct current applied to the electrodes is reversed time by time, exchanging also the diluate and the concentrate chambers. Thus, the precipitation accumulated on the membranes are flushed from the IXMs during the switching polarity periods, avoiding scaling or colloid obstructions on the IXMs surface. Nevertheless, the lifetime of the electrodes is reduced due to changes in polarity by EDR process (Baker 2012; Karimi and Ghassemi 2016; Murray 1995).

Apart from ED and EDR, there other ED-based technologies, that are gaining increasing attention, because of their promising possibilities of added-value compounds recovery and reuse. For instance, monovalent-selective membranes can be combined with AEMs and CEMs for separating monovalent from divalent ions, by selectrodialysis (SED) (Zhang et al. 2012a), monovalent electrodialysis (mEDR) (Atkinson 2018), or electrodialysis methathesis (EDM) (Bond and Veerapaneni 2011). Besides, acid and bases can be produced from its corresponding salts by electrodialysis with bipolar membranes (EDBM) (Koter and Warszawski 2000; Huang and Xu 2006).

In fact, ion fractioning has a potential interest for several industries, such as wastewater treatment (Reig et al. 2016a, 2018, 2019; Tran et al. 2015) or recovery of added-value from agro-food residue (Barros et al. 2019; Zhang et al. 2011; Vecino et al. 2020). For that, standard IXMs are not enough, since they can only separate ions with different charge sign (positive or negative), but they do not distinguish between different ions charges (monovalent or divalent). However, monovalent-selective membranes can make differentiation in different charge ions transport. For instance, monovalent-selective cationic membranes (MVCs) allow monovalent cations passage, while blocking the divalent cations transfer when current is applied between both electrodes (Reig et al. 2018). On the other hand, monovalent-selective anionic membranes (MVAs) allow monovalent anions to cross them, while impeding the divalent anions passage (Zhang et al. 2012a). Therefore, by using different combinations of standard IXMs and selective IXMs (SED, mEDR or EDM), it is possible to achieve two differentiated streams, one rich in divalent

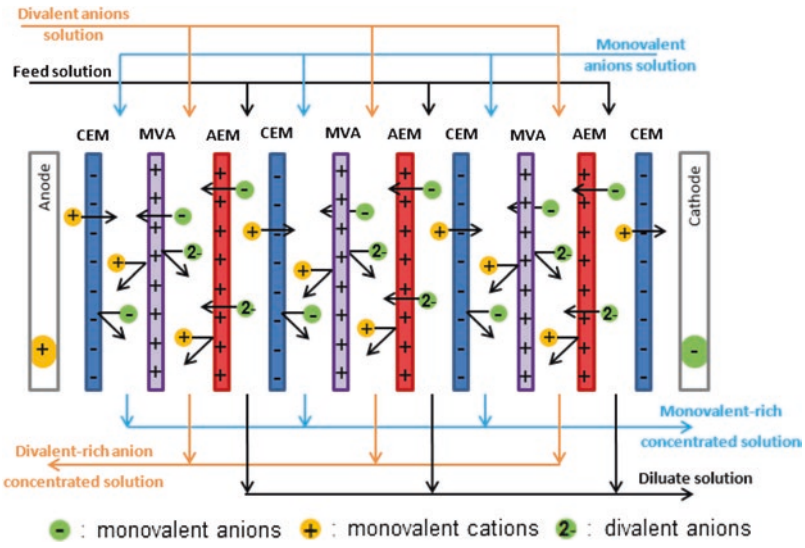

Fig. 5.3 SED membranes scheme for different charge anions separation, where AEMs and CEMs are conventional anionic and cationic ion-exchange membranes and MVAs are monovalent-selective anion exchange membranes. (Adapted from (Reig et al. 2016a))

ions and another monovalent ions-rich. For instance, Fig. 5.3 shows an example of SED for monovalent and divalent anions separation and concentration. Moreover, a diluate stream is also obtained.

Selective ED has been also applied in different fields, such as high salinity wastewater desalination (Zhang et al. 2012a), chloride and sulphate separation and concentration from industrial wastewater (Reig et al. 2016a), phosphate concentration from municipal wastewater (Tran et al. 2015), toxic metallic and non-metallic species removal from metallurgical process waters (Reig et al. 2018, 2019) or ZLD circuits (Bond and Veerapaneni 2011), among others.

For selective ED, transport phenomena are the same as when using ED. Nevertheless, other transport phenomena occurred due to membrane selectivity (using MVCs and MVAs), such as dielectric exclusion (Yaroshchuk 2000), size exclusion, charge differences and/or hydrophilicity differences between monocharged and double-charged ions, or other membrane characteristics (Zhang et al. 2012a).

For EDBM applications, BPMs are combined with CEMs and AEMs for acid and base production. A bipolar membrane is formed by a cation selective layer (negatively charged) and an anion selective layer (positively charged), with a contact region between them. This layered structure with an interfacial layer permits water splitting when current is applied, producing protons and hydroxyl ions (Pourcelly 2002; Mukiibi and Feathers 2009; Koseoglu-Imer and Karagunduz 2018). Figure 5.4 shows an EDBM membrane disposition between two electrodes.

As can be seen in Fig. 5.4, when a feed electrolyte solution (MX) is introduced into the EDBM system and current is applied, water splitting is produced in the

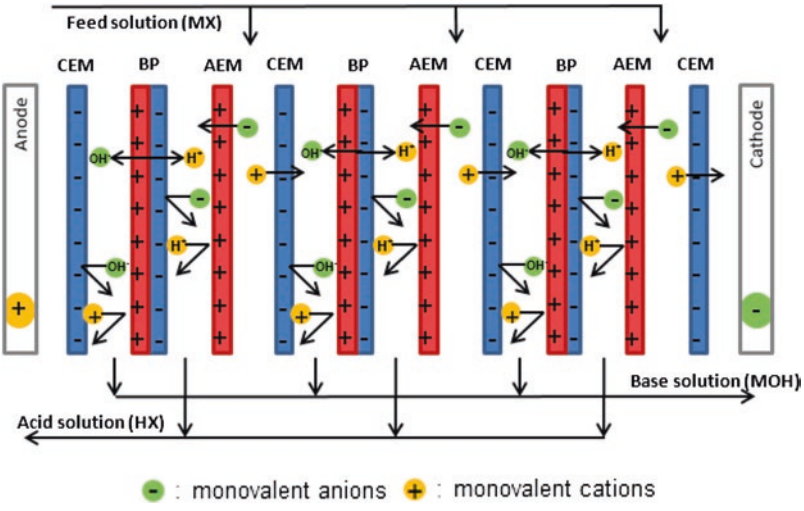

Fig. 5.4 EDBM membranes scheme for acid and base production, where AEMs and CEMs are conventional anionic and cationic ion-exchange membranes and BPMs are bipolar membranes. (Adapted from (Reig 2016b))

membrane interface (H^+ and OH^- are generated by the BPM and released through its cationic and anionic layer, respectively). Then, protons and cations moved towards the cathode, crossing the CEMs, but not the AEMs, whereas hydroxyl ions and anions move towards the anode, crossing AEMs, but not CEMs ones. Thus, cations (M^+) and OH^- are retained in the basic compartment, forming a base solution (MOH), while anions (X^-) and H^+ are retained in the acidic compartment, producing an acid solution (HX). Moreover, a diluate stream is obtained between CEMs and AEMs (not shown in Fig. 5.4) (Pourcelly 2002; Wiśniewski et al. 2004).

EDBM technique has been also used in different fields, although its main purpose is to produce acids and bases from its corresponding salt. Some applications are brines valorisation (Reig et al. 2016b, c), environmental protection (Ibáñez et al. 2004) or chemical and food processing (Fidaleo and Moresi 2006; Vecino et al. 2020). In fact, EDBM is an alternative technique for residues valorisation by chemicals production. For that reason, its implementation is growing in many industries, such as agro-food fields (Bazinet et al. 1998; Wang et al. 2018).

1.2 An Overview of Agro-Food Industries

Agriculture, food, and their combination as "agro-food", are essential sectors for human communities. In fact, agro-food is not only an important driver of economic growth in several EU countries, but also a key thematic for new industrial value chains under the Horizon 2020 program as the Bio Based Industries (BBI) Action (European Commision 2017). Agricultural products comprise three main categories: (i) animals and animal products (such as live animals, meat, fish, crustaceans and aquatic invertebrates, dairy produce, eggs, honey, and other animal origin products); (ii) crop products; and (iii) foodstuffs (Castro-Muñoz et al. 2016). In Spain, the agricultural production (EU-28 total share, 2018) was mainly highlighted in permanent crops (35.1%) and fresh vegetables (23.3%), followed by different kinds of meat, such as pig (19.0%), poultry (10.8%) and bovine (8.4%), as well as cereals (8.3%); finally the low partakes were for raw milk and root crops with 4.9% and 2.9%, respectively (European Union 2019). On the other hand, the food and beverages industries were composed mainly by (i) bakery and farinaceous products (51.7%), proceeded by (ii) meat and meat products (12.2%) and beverages (10.2%), and (iii) prepared meals and dishes, food preparations and dietetic food, sugars, cocoa, tea and coffee (9.4%). Besides, dairy products and fruit and vegetables were 4.4% and 4.2%, respectively of the EU-28 companies. In addition, there was another group that involved vegetable and animal oils and fats, grain mill and starch products, prepared animal feed and fish and fish products (7.9%). Among the EU-28 total share, Spain had the 9.3% of the food and beverages enterprises and 8.2% of persons employed in this sector (European Union 2019). In consequence, the agro-food trade in Europe reached a value of 254€ billion in 2018. Thus, EU-28 achieved the first position as the largest global exporter and second biggest importer of

agro-food products, reaching a value of 138€ billion and 116€ billion, respectively. In regard with the EU-28 agro-food exports, the overview of products included wines and vermouth (the main category); spirits and liqueurs; infant food; food preparations; chocolate; and pasta and pastry. On the other hand, the tropical fruit, coffee and fresh or dried fruits; products that are mainly used for animal feed (e.g. oilcakes and soybeans); and products which are used as ingredient in further processing (e.g. palm oil) comprised the EU-28 agro-food imports (European Commission 2018a). Among the above-mentioned agro-industries, this chapter is focused on dairy and winery sectors. Both industries are important sectors in the EU, as well as in Spain. In fact, dairy industry represents the second major agro-food industry in Europe (Di Berardino 2019). In 2018, the EU produced 172.2 million tonnes of raw milk on farms, 97% of which was from cows (166.7 million tonnes); followed by milk from ewes (2.8 million tonnes), goats (2.3 million tonnes) and buffalos (0.3 million tonnes). The vast majority of raw milk was delivered to dairies (160 million tonnes); whereas only 12.2 million tonnes of milk was used on farms, either being consumed by the farmer and his/her family, sold directly to consumers, used as animals feed or processed directly. From 160 million tonnes of milk delivered to dairies, 156 million tonnes were milk from cows, being the rest a combination of ewes', goats' and buffalos' milk. From the milk used by the diaries, 0.4 and 0.2 million tonnes were raw milk imported and exported, respectively. On the other hand, with the milk used in diary industry, 118.4 million tonnes of fresh and manufactured products can be obtained. Fresh products comprise drinking milk products (30.1 million tonnes) and other fresh products (15.7 million tonnes). From the 30.1 million tonnes of drinking milk, 12.6 million tonnes are skimmed milk and a further 17.3 million tonnes are whole milk. In regard with manufactured products, they can be divided mostly into whey (54.8 million tonnes), followed by cheese (10.3 million tonnes), milk powder (3.1 million tonnes), butter (2.4 million tonnes) and other manufactured products (2.0 million tonnes). In addition, Spain represented the 4.6% (eighth position), of the EU-28 total share from the 156.0 million tonnes, collection of cows' milk by dairies (European Union 2019).

On the other hand, the EU is a big player on the world's wine market. Indeed, between 2014 and 2018 it accounted for 65% of global production, 60% of consumption and 70% of exports, with 45% of the wine-growing areas in the world (European Union 2019). Particularly, 13% of the global area is occupied for Spain wine production (7.4 million of hectares), which are mainly destined for the production of wine grapes (table grapes or dried grapes) (IOV 2019), whereas Spain represented 26% of grapes for wines from the total harvested production of grapes in the EU-28 total (European Union 2019).

From the world production of grapes in 2018 (77.8 million of tons), the majority was used for wine grape (57%), preceded by table grape (36%) and dried grape (7%). In this context, the global production of wine was 292 million of hectolitres in 2018 (including sparkling and special wines and excluding juice and musts), being Spain the third largest wine producer (44.4 Mhl) just behind Italy and France (IOV 2019).

Apart from that, agro-food industries are responsible of a large part of global greenhouse gas (GHG) emissions. The agricultural sector produced 426,473 ktonnes of CO_2 eq of GHG (not including land use), about 10% of the EU's total GHG emissions (in 2015) (Eurostat 2019); whereas the entire food supply chain generated 26% of global GHG emissions (~13.7 billion metric tons of CO_2 eq). Additionally, food production caused ~32% of global terrestrial acidification and ~ 78% of eutrophication in 2018 (Poore and Nemecek 2018). Indeed, the implemented traditional agricultural practices result in high productivity but are strongly dependent on natural resources, such as water, nutrients (e.g. phosphorus), and fossil fuels. Actually, it has been estimated that between 30 and 50% of all food produced around the world is food losses or food wastes. In addition, agro-food industries, such as both diary and winery industries, produce huge amounts of wastes. In the case of dairy industry, whey, dairy sludge and wastewaters (from processing, cleaning and sanitary steps) are the main wastes generated, having the latter the major environmental impact of the sector. Indeed, around 6–10 m^3 of wastewater per m^3 of processed milk is generated by dairy industries. Furthermore, processing of dairy products, from milk fermentation or by-products from the processing, can result in wastes, that could be used in the preparation of other dairy products, like whey concentrates from cheese whey. Commonly, dairy wastes (sludge and effluents) have high level of suspended solids and organic matter, high content of nutrients (nitrogen and phosphorous), high concentration of dissolved organic components (e.g. lactose, minerals, fat and whey protein), fatty acids, oil and greases. Furthermore, they can contain residues of the cleaning products used in utensils and equipment cleaning (e.g. detergents and biocides). However, the main by-product of dairy industry is whey, which is a source of food protein and produced during cheese and casein manufacturing. Due to the milk whey composition (lipids, carbohydrates, soluble vitamin, minerals as well as proteins), it has already been integrated for human consumption in many products (Ahmad et al. 2019; Reig et al. 2021).

Regarding to winery industry, during the winemaking process different kind of residues are produced. For instance, vineyard pruning wastes (also named trimming vine shoots) from harvest step, grape stalks from the de-stemmed of grapes, bagasse (also called grape marc or grape pomace) from pressing steps, wine lees obtained after different decanting steps, sediments obtained during clarification step, and wastewater generated from vinification lees (Devesa-Rey et al. 2011). In fact, Oliveira and Duarte (Oliveira and Duarte 2016) provided that from 1 ton of processed grape around 0.13 t of grape marc, 0.06 t of wine lees, 0.03 t of stalks and 1.65 m^3 of wastewater are generated. Additionally, to recover ethanol and produce distilled beverages, the grape marc and wine lees must be sent to alcohol distilleries companies according to the European Council Regulation (EC) 479/2008 on the common organization of the wine market. During the distillation process, a liquid waste called vinasses is produced (Devesa-Rey et al. 2011; Pérez-Bibbins et al. 2015). Distilled vinasses are an environmental challenge if they are not treated properly, since they are acidic effluents with a large amount of organic matter and high solid content from dead yeast, grape pulp, skin and seeds. Vinasses are also composed by acids, sugars, phenols, proteins, lipids, as well as significant nutrients

(such as nitrogen, phosphorous, and potassium) (Devesa-Rey et al. 2011; Vlyssides et al. 2005).

In view of the aforementioned, a change for sustainable agricultural practices, in the agro-food system, is necessary to reduce the environmental impacts. The interdependency between infrastructure, production, distribution and environmental resources would allow the agro-food sustainability (Matthews 2017). Thus, the global interest about environmental protection in food, about several aspects such as climate change, resource depletion, human health risk or ecosystem damage are now considered as a priority by both society and governments in industrialised countries, as well as social and environmental organisations, businesses and academics (Scherer et al. 2020; Rico et al. 2020). In fact, the priority order in waste prevention and management legislation and policy should be as follows: (1) prevention; (2) preparing for re-use; (3) recycling; (4) other recovery, e.g. energy recovery; and (5) disposal, according to the Directive EU 2018/851 on waste (European Commission 2018b). Traditional direct disposal and treatment techniques, such as landfilling or incineration, are still vastly used but they are not suitable options; while re-use and recycling are the most favored choices (Capson-Tojo et al. 2016). The seventh EU Environmental Action Programme until 2020 (European Union 2013) identified waste prevention and management as one top priorities, being the main objective that the economic growth would not result in a disproportionate increase in waste generation. The huge impact that these residues have on the environment is not only due to the GHG emissions, related to climate change or to the loss of resources, but also to the complex mix of materials that compose them.

The households and processing sectors are the ones that generated the most food waste, being the 72% of EU-28 food waste (Stenmarck et al. 2016). For instance, the Spanish economy produced 132.1 million tonnes of waste in 2017, 2.3% more than the previous year. Among them, 3.2 million corresponded to hazardous waste (1.6% more than in 2016) and 128.9 million to non-hazardous waste (2.0% more), meaning the 2.4% and the 97.6% of the waste generated, respectively. By sectors, animal and vegetal wastes were generated mostly by agriculture, livestock, forestry and fishing (5.6 million tonnes). Regarding of the total generated waste to final waste treatment in Spain, 53.9% ended up in landfill, 38.9% was recycled, 3.7% was reused in backfilling operations and 3.5% was incinerated (Instituto Nacional de Estadística 2019). However, in line with the demands from the European Commission, industries should give a second thought to their current residues disposal practices. Instead of burning the wastes generated in their production chains or sending to landfill, it would be more interesting to develop strategies to transform them into valuable by-products. Because of that, the agricultural waste and by-products generated from the agro-food industries require a change from a linear to a circular economy concept that create innovative ways of valorisation to convert these waste materials into high-value products (Devesa-Rey et al. 2011; Donner et al. 2020). For that reason, apart from the classical 3Rs (reduce, reuse and recycle) of the waste management strategies, it has been introduced a fourth R, “Reprocess”, which consists on the development of completely new processes to reuse the wastes as resources (Melikoglu et al. 2013).

Therefore, not only agro-food products must be considered added-value products, but also generated waste from the agro-food processing industry should be utilized to reduce the environmental impact and to increase the potential benefits for the industries (Castro-Muñoz et al. 2020). Thus, process technologies for conventional process improvement and for producing novel products have been developed for both purposes: (i) agro-food products treatment and (ii) agro-food waste recovery. Among them, membrane technology has been successfully employed in agro-food processing and valorisation (Daufin et al. 2001; Lipnizki 2010a, b; Castro-Muñoz and Fíla 2018; Castro-Muñoz et al. 2018, 2019, 2020). In fact, membrane technologies are well-known as clean technologies for agro-food treatment and they are economically feasible when either the waste management is high-cost or when a high-quality product is desired. For example, in the dairy industry, membrane technologies have been implemented in the milk and dairy processing chains, such as milk reception, cheese making, whey protein concentration, fractionation of protein hydrolysates, waste stream purification and effluents recycling and treatment (Di Berardino 2019; Daufin et al. 2001; Tavares and Malcata 2016; Reig et al. 2021). It is worth mentioning that the innovative application of membrane technology in the dairy industry was the conversion of whey into refined proteins for commercial use by ultrafiltration process (UF). In this sense, the top pressure-driven membrane processes in the dairy industry are microfiltration (MF) and UF, followed by nanofiltration (NF) and reserve osmosis (RO) (Lipnizki 2010a, b; Conidi et al. 2020). Regarding electro-membrane technologies, ED is commonly applied in the demineralization of whey (Daufin et al. 2001; Vecino et al. 2020).

On the other hand, must correction by RO (in terms of sugar content) was the first potential application in the wine production and lately for alcohol reduction in wine; then MF was used for clarification of wine after fermentation; the rejuvenation/lifting of old wine has been carried out with RO and DF (diafiltration); pervaporation (PV) has been used for recovery of wine aromas (Castro-Muñoz 2019); and the well-known application of ED in the wine industry is as a stabilizing stage in the tartaric precipitation in wines (Daufin et al. 2001; Lipnizki 2010a, b; Vecino et al. 2020).

2 Applications for Agro-Food Sectors

The agro-food industry encompasses diverse and complexes activities whose challenge includes a wide range of processes and operations as food activities from the agricultural to our table. However, as aforementioned, agro-industries also produced huge amount of wastes. Thus, ED is a promising and eco-friendly technology to treat agro-food products streams, as well as agricultural wastes and by-products, generated from agro-food industries, following the frame of circular economy on the management of these residues and in line with the industrial symbiosis. Therefore, as represented in Fig. 5.5, the following chapter sections cover an overview of the application of ED technology in agro-food products treatment as well as in the recovery of by-products/wastes generated from two of the major agro-food

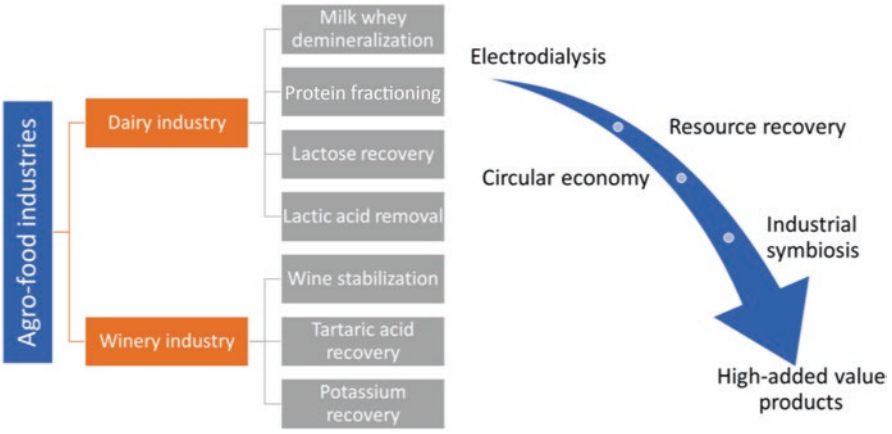

Fig. 5.5 Electrodialysis technology for high-added value compounds recovery from agro-food industries – chapter overview

industries: dairy and wine. In this case, sections were divided to show in detail the recovery of high-added value compounds by ED from the above-mentioned agro-food industries.

2.1 Dairy Industry

The major by-product from dairy industry, mainly of cheese and casein manufactures, is whey. Whey is a yellow-green liquid fraction drained from the curd, which can be easily acidified. Thus, two whey types can be distinguished: sweet whey ($pH \geq 5.6$) and acid whey ($pH \leq 4$) (Fidaleo and Moresi 2006; Wang et al. 2018). The main difference between cow milk and whey composition is lactic acid content in sweet whey (0.03–0.04% w/w) and acid whey (0.42–0.49% w/w), in comparison with cow milk, which does not contain lactic acid (Fidaleo and Moresi 2006). Furthermore, another whey type can be found, namely salty whey. This whey, which is salt-rich (50–60%), is produced in the cheese salting process and it is usually treated by UF. By this technique is possible to recover the whey proteins, although a high amount of minerals is retained in the UF permeate, making this stream not suitable neither for human, nor for animals feed and presenting environmental concerns if disposed directly, without any treatment. For this reason, salty whey is a waste by-product that increases disposal costs for dairy industries (Talebi et al. 2019). Thus, the main restriction for dairy by-products (mainly whey and ultrafiltration permeates) commercialization is the high minerals content in cow milk (3.37% w/w raw proteins, 3.9% w/w fat, among others). Moreover, due to whey biochemical oxygen demand (BOD_5) content (31–35 kg/m^3), it cannot be discharged into sewage. Furthermore, if whey is desalted, then it could be used in food production

(Fidaleo and Moresi 2006). For these reasons, the main ED application (with monopolar and bipolar membranes) in dairy industries is whey treatment (Tavares and Malcata 2016; Chen et al. 2018), mainly milk effluents demineralization, whey deacidification or alkalinisation, as well as proteins and caseinates production (Bazinet 2005). However, due to its high lactic acid content, acid whey processing is blocked at industrial scale and it is one of the main challenge in dairy industries treatment (Kravtsov et al. 2020a; Dufton et al. 2020). Indeed, whey demineralization can be carried out by ED, achieving a demineralization rate from 50 to 95% (Daufin et al. 2001).

On the other hand, ED has many advantages for whey treatment, such biological substances demineralization, substance separation, minimal valuable components (proteins, lactose, among others) losses, no chemical addition, low energy consumption (< 1 kWh/kg ash removed, when demineralization degree is 50%–75% (Ahlgren 1972)) and high industrial capacity (easy operation equipment, modular design, processed at ambient temperature, automation, among others). Thus, ED is an economic and efficient method for whey processing (Tavares and Malcata 2016). In this case, although standard ED, with monopolar membranes, is the most common used technology in dairy industries, EDBM is also used for whey treatment (Kravtsov et al. 2020a, b; Dufton et al. 2018; Merkel et al. 2018) and proteins production (caseins and caseinates) (Mikhaylin et al. 2018; Masson et al. 2018). Table 5.1 summarises the main operational conditions, such as flow rates or electricity inputs into the EDBM stack, as well as the ion-exchange membranes used, the EDBM set-up, the main treated streams, the studied parameters and also the main results obtained in each study.

As can be seen in Table 5.1, Mikhaylin et al. (2018) and Masson et al. (2018) studied the effect of an EDBM system for proteins production from an ultrafiltrated milk fraction. In both cases, an EDBM set-up Model MP, from ElectroCell Systems AB Company was equipped with food grade Neosepta membranes (CMX-SB, AMX-SB and BP-1) with 100 cm^2 membrane area. Moreover, constant current of 2 A was applied in both cases and NaCl was used as additional stream. The former work (Mikhaylin et al. 2018) developed a life cycle assessment in order to study caseinate powder production from skim milk, whereas the latter (Masson et al. 2018) studied the advantages of UF, followed by EDBM for caseins separation, in comparison with conventional chemical acidification. The more outstanding result in both studies was NaOH production by EDBM, which could be used to solubilize the casein obtained during the EDBM process and be able produce caseinates. Thus, not only the skim milk stream was acidified during the process, but also caseinates were produced without the need of chemical addition, such as NaOH. Then, sodium caseinate powder could be produced on-site. Finally, it is worth to mention that by both methods (EDBM and conventional acidification with HCl) it was possible to produce whey. However, when using EDBM, the obtained whey was already demineralized and also some co-products were obtained: a lactose enriched solution and a Ca^{2+}/Mg^{2+}-rich solution.

On the other hand, Dufton et al. (2018) and Kravtsov et al. (2020b) studied acid whey demineralization and deacidification by EDBM (Table 5.1). The former work

Table 5.1 EDBM applications in dairy industries: review of applications and process performances

Main purpose	Feed solutions: Diluate stream (treated solution)	Feed solutions: Concentrate stream I Concentrate stream II Electrode rinse	CEM AEM BPM	EDBM set-up Membranes	Operational conditions: Flow rates (L/h)	Operational conditions: Constant voltage or current Temperature Experimental time (min)	Studied parameters	Main results	Ref
Milk protein production	0.5 L – UF milk fraction (containing mainly lactose and minerals)	0.5 L – 2 g/L NaCl – 0.5 L – 20 g/L NaCl	Food grade Neosepta CMX-SB (Astom) Food grade Neosepta AMX-SB (Astom) Food grade Neosepta BP-1 (Astom)	Model MP (ElectroCell Systems AB Company) 100 cm^2; 3CEM, 1 AEM, 1 BPM	Diluate and concentrate: 9 Electrode solution: 30	20 mA/cm^2 – 100	Life cycle assessment (LCA) Caseinate powder production from skim milk	Skim milk acidification Casein production Co-products: Demineralized whey, lactose – rich and Ca/Mg-rich solution NaOH to solubilize the casein	(Mikhaylin et al. 2018)
Production of calcium- and magnesium-enriched caseins and caseinates	0.5 L – UF pasteurized skim milk (Pur filtre; Parmalat, Toronto, Canada).	0.5 L – 2 g/L NaCl – 0.7 L – 30 g/L NaCl	Food grade Neosepta CMX-SB (Astom) Food grade Neosepta AMX-SB (Astom) Food grade Neosepta BP-1 (Astom)	Model MP (ElectroCell Systems AB Company) 100 cm^2; 3CEM, 1 AEM, 1 BPM	Diluate: varied Concentrate: 12 Electrode solution: 36	2 A – –	Separation of caseins by conventional chemical acidification vs UF + EDBM	pH decreases from 6.7 to 4.8 Caseins content: Ca = 0.22%; Mg = 0.011% Caseinates content: Ca = 0.18%; Mg = 0.010% Caseinates production by solubilizing Caseins with NaOH from EDBM	(Masson et al. 2018)

(continued)

Table 5.1 (continued)

Main purpose	Feed solutions: Diluate stream (treated solution)	Feed solutions: Concentrate stream I Concentrate stream II Electrode rinse	CEM AEM BPM	EDBM set-up Membranes	Operational conditions: Flow rates (L/h)	Operational conditions: Constant voltage or current Temperature Experimental time (min)	Studied parameters	Main results	Ref
Neutralization of the desalinated whey after ED (pH correction of milk whey)	1 kg – Nanofiltrated acidic milk whey (NFW) from curd producing (MADETA milk factory, Czech Republic) + ED treated stream (ED70 and ED90)	Conf 1: 0.5 kg – tap water – 0.25 kg – 10 g/L $NaNO_3$ Conf 2: 0.5 kg – 13.56 mS/cm 0.5 kg – 7.47 mS/cm 0.25 kg – 10 g/L $NaNO_3$	Food-grade CM-PP (MemBrain ltd.) Food-grade AM-PP (MemBrain Ltd.) Heterogeneous food-grade BM-PP (MemBrain ltd.)	Pilot unit EDR-Z/10–0.8 (MemBrain ltd.) 64 cm^2; BM-AM-BM (conf 1)-10 cell pairs; BM-AM-AM-BM (conf 2) – 20 AM, 11 BM	Diluate and concentrate: 58 Electrode solution: 50	20 V (conf 1); 25 V (conf 2) 15 ± 3 °C 150 (NFW); 120 (ED70); 30 (ED90)	Milk whey samples from ED demineralization Two EDBM configurations	EDBM capacity (kg/m·h): NFW = 8.2–14.8; ED70 = 7.6–10.4: ED90 = 31.0–49.3 pH increase: NFW = 4.8 to 5.7; ED70 = up to 6.3; ED90 = up to 6.7 Lactic acid concentration (g/L): NFW = 16.8 to 7.6; ED70 = 12.9–6.1; ED90 = 2.6–1.4 Wh/kg feed: NFW = 11.3–7.4; ED70 = 3.8–6.5: ED90 = 1.0–1.9	(Merkel et al. 2018)
Lactic acid deacidification and demineralization	2000 mL – AW from a dairy processing plant owned by Parmalat-Canada (Canada)	2000 mL – 5.5 g/L KOH 2000 mL – 5.5 g/L NaCl 2000 mL – 20 g/L Na_2SO_4	Commercial food-grade CEM (Astom) Commercial food-grade AEM (Astom) BPM (Astom)	Laboratory-scale cell (Model MP, ElectroCell Systems AB Company) 100 cm^2; BACBAC configuration	Diluate and concentrate (I and II): 240 Electrode solution: 240	100 A/m^2 Around 20 °C 180	EDBM vs ED	Lactic acid deacidification: 44% AW demineralization: 67%	(Dufton et al. 2018)

Acid whey demineralization and deacidifcation	300 mL – AW from the cottage cheese production at the MKS dairy plant (Russia). Two types: 1) AW: 7% total solids 2) concentrated AW: 20% total solids	300 mL – Main water, conductivity 0.43–0.48 mS/cm – 300 mL – 20 g/L $NaNO_3$	Heterogeneous RALEX CMH-PES (MEGA a.s.) Heterogeneous Ralex AMH-PES (MEGA a.s.) BM 2.0 (MEGA a.s.)	Laboratory-scale unit P EDR-Z (MEGA a.s.) 64 cm^2; 21 membranes	Diluate and concentrate: 70 Electrode solution: 100	12.5 V demineralization; 25 V deacidification 22 ± 2 °C 65 (AW); 100 (concentrated AW)	AW and concentrated AW treatment	Degrees of AW demineralization: 70% (AW) and 90% (concentrated AW) Energy consumption: 76 kWh/t dry matter (70%) and 45 kWh/t dry matter (90%)	(Kravtsov et al. 2020b)
Alkalinization of acid whey in terms of lactic acid removal	800 mL – AW from a dairy processing plant owned by Parmalat-Canada (Canada)	800 mL – 0.5 mS/cm KCl – 1 L – 20 mS/cm $NaNO_3$	CMX (Neosepta) AMX (Neosepta) BP-1 (Tokuyama corporation)	Laboratory-scale cell (Model MP, ElectroCell Systems AB Company) 100 cm^2	Diluate and concentrate: 24 Electrode solution: 54	10 V Room temperature (22 ± 2 °C) 140 (conf 1); 80 (conf 2)	Two cell configurations: 1) 2 CEM, 1 AEM, 1 BPM; 2) 2 AEM, 1 BPM	AW alcalinization: pH up to 6.5 Lactic acid removal: 26% (conf 1), 24% (conf 2) Demineralization: 34% (conf 1), 24% (conf 2) 28 kWh/kg (conf 1), 21 kWh/kg (conf 2)	(Kravtsov et al. 2020a)

AW: Acid whey

treated an acid whey from a dairy processing plant owned by Parmalat-Canada, whereas the second one treated an acid whey from the Cottage cheese production at the MKS dairy plant in Russia. In this case, different EDBM set-up, with different membranes (from Astom and MEGA, respectively) and different membrane areas (100 and 64 cm^2, respectively) were used. Moreover, the first study used constant current, whereas the latter kept voltage constant during the EDBM process. In both cases, the main purpose was achieved, with a demineralization degree of 67%, lactic acid deacidification of 44% (Dufton et al. 2018), and 70% to 90% acid whey demineralization with an energy consumption varying from 45 to 76 kWh/t dry matter, depending on the initial acid whey concentration (Kravtsov et al. 2020b).

Finally, Merkel et al. (2018) and Kravtsov et al. (2020a) studied EDBM for acid whey alkalinisation in terms of lactic acid removal. The first work treated an acid whey from a dairy processing plant (Canada), whereas the second work used three different feed streams: a nanofiltrated acid whey (NFW, Czech Republic) from curd processing, and two desalinated ED streams (ED70 and ED90). Different membranes (Membrain (Merkel et al. 2018), Neosepta (CEMs and AEMs) and Tokuyama Corporation (BPMs) (Kravtsov et al. 2020a)) with different membrane areas (64 and 100 cm^2, respectively) were used. In both studies, constant voltage was applied and different EDBM configurations were tested. Results showed that acid whey pH increased up to 5.7 (when treating NFW), 6.3 (for ED70 feed stream), 6.7 (for ED90 input), and 6.5 (when using acid whey from Canada), whereas lactic acid was removed (from 46 to 55% (Merkel et al. 2018) and values around 25% (Kravtsov et al. 2020a)). Moreover, as reported in Table 5.1, energy consumption results depended on the initial feed stream and also EDBM configuration.

On the other hand, as above-mentioned, ED is widely used for whey treatment in dairy industry applications, mainly for demineralization purposes or lactic acid removal, as summarized in Table 5.2.

As summarized in Table 5.2, acid whey, sweet whey and salty whey have been processed by ED, mainly for lactic acid removal and demineralization purposes. Indeed, Chen et al. (2016) and Talebi et al. (2020) studied lactic acid reduction by ED when treating raw acid whey samples and ultrafiltrated fresh raw acid whey solutions, respectively, with a FuMA-Tech ED module, Neosepta IXMs and applying constant voltage. The aim of removing lactate or reducing its concentration from acid whey allows to recover proteins and lactose for sale, by processing the acid whey without lactic acid, as sweet whey. There were some differences between both studies: the former was carried out at lab scale (36 cm^2 active membrane area) and two working temperatures were studied (5 and 45 °C), whereas the latter was carried out at pilot scale (100 cm^2 of active membrane area) and ED was studied in combination with other membranes techniques, such as UF or NF. In this case, UF was used as a pre-treatment for protein removal and NF as a pre-treatment to achieve greater lactic acid removal levels. The first work showed that best results were obtained at high temperature (45 °C), achieving 80% lactic acid removal, 90% minerals removal and 3 times less ED experimental time than at 5 °C, and with an energy consumption of 0.014 kWh/kg acid whey when achieving 90% demineralization. On the other hand, the second work obtained the best results when

Table 5.2 Whey treatment by ED in dairy industries: review of applications and process performances

Main purpose	Feed solutions		CEM AEM	ED set-up Membranes	Operational conditions		Studied parameters	Main results	Ref
	Diluate stream (treated solution)	Concentrate stream Electrode rinse			Flow rates (L/h)	Constant voltage Temperature Experimental time (min)			
Removal of lactic acid from acid whey	1.2 L – raw acid whey samples from a dairy processing company (Australia)	1.2 L – 5.5 g/L NaCl 1.2 L – 20 g/L Na_2SO_4	Neosepta CMB (Astom) Neosepta AHA (Astom)	FTED-40 module (FuMA-Tech GmbH) 36 cm^2; 2 cell pairs	Diluate and concentrate: 7.5 Electrode solution: 60	7 V 5 and 45 °C 180	Temperature pH increase (4.6–6)	45 °C: more lactate ions Removal 45 °C: 3 times shorter ED than at 5 °C, to achieve the same lactate removal 80% lactate ions removal; 90% minerals removal 0.014 kWh/kg whey → 90% demineralization	(Chen et al. 2016)
Removal of lactic acid and minerals from acid whey	5 L – UF fresh raw acid whey (Tatura Milk Industries, Australia)	Tap water 20 g/L Na_2SO_4	Neosepta CMB (Astom) Neosepta AHA (Astom)	FT-TS40 module (FuMA-Tech GmbH) 100 cm^2; 10 cell pairs	Diluate, concentrate, electrode solution: 200	24 V 35 ± 4 °C 60	(i) UF + ED (ii) UF + NF + ED (iii) UF + dia-NF + ED	Best results: UF + dia-NF + ED maximum lactic acid removal: 88% lowest lactic acid/lactose ratio: 0.017 g/g) 7.8 kWh/t feed	(Talebi et al. 2020)

(continued)

Table 5.2 (continued)

Main purpose	Feed solutions: Diluate stream (treated solution)	Feed solutions: Concentrate stream Electrode rinse	CEM AEM	ED set-up Membranes	Operational conditions: Flow rates (L/h)	Operational conditions: Constant voltage Temperature Experimental time (min)	Studied parameters	Main results	Ref
(i) Sweet whey demineralization (ii) Salty whey permeate demineralization (lactose and salt separation)	(i) 2 L – skimmed sweet whey from dairy companies (Australia) (ii) 4 L – UF salty whey permeate from dairy companies (Australia)	(i) 2 L- salty whey permeate or 0.1 M NaCl (ii) 1 L – salty whey permeate or 0.1 M NaCl	CMB and CIMS (Astom) AHA and ACD (Astom)	FTED-40 unit (FuMA-Tech GmbH) 36 cm^2; 3 cell pairs	Diluate and concentrate: 30 Electrode solution: 60	(i) 7 V (ii) 55 mA/cm^2 or 5, 10, 15 V (i) 44 ± 2 °C (ii) 26 ± 2 °C (i) 180 (ii) 480	Sweet demineralization using UF salty whey as concentrate stream Monovalent-selective IXM for salty whey demineralization	(i) 75% demineralization 7.4 kWh/t whey (ii) 6.5–22-33% demineralization at 5, 10 and 15 V 0.9–2.1-3.6 kWh/t NaCl at 5, 10 and 15 V Ca concentration (concentrate stream) half reduced with selective IXMs	(Talebi et al. 2019)
Demineralization of whey	2.2 kg – Nanofiltrated acidic milk whey (NFW) from curd producing (MADETA milk factory, Czech Republic)	0.5 kg – Tap water 0.25 kg – 10 g/L $NaNO_3$	Heterogeneous food-grade CM-PES (MemBrain ltd.) Heterogeneous food-grade AM-PES (MemBrain ltd.)	Pilot unit EDR-Z/10–0.8 (MemBrain Ltd.) 64 cm^2; 10 cell pairs	Diluate and concentrate: 58 Electrode solution: 50	12 V 15 ± 3 °C 348 (ED70); 438 (ED90)	ED with 70% (ED70) and 90% (ED90) of demineralization	ED capacity (kg/m·h): ED70 = 5.8: ED90 = 4.2 pH increased (4.5 to 5.0) Lactic acid concentration decreased (17 to 3 g/L) Wh/kg feed: ED70 = 5.7; ED90 = 10.0	(Merkel et al. 2018)

Lactic acid deacidification and demineralization	2000 mL – AW from a dairy processing plant owned by Parmalat-Canada (Canada)	2000 mL – 5.5 g/L NaCl 2000 mL – 20 g/L Na_2SO_4	Commercial food-grade CEM (Astom) Commercial food-grade AEM (Astom)	Laboratory-scale cell (model MP, ElectroCell systems AB company) 100 cm^2; CACAC configuration	Diluate and concentrate: 240 Electrode solution: 240	100 A/m^2 ~ 20 °C 180	ED vs EDBM	Lactic acid deacidification: 44% AW demineralization: 67%	(Dufton et al. 2018)

AW: acid whey

combining UF, dia-NF and ED, since the dia-NF retentate was 3.5 times more concentrated than the UF permeate. Thus, it was possible to remove 88% lactic acid with an energy consumption of 7.8 kWh/t feed.

Talebi et al. (2019) had also studied the demineralization of sweet whey and salty whey permeate treatment from dairy companies by ED. The aim of this study was not only to recover the demineralize lactose-rich stream – which could be used for lactose powder production, but also to produce a concentrated salt solution – which could be used in the chlor-alkali industry. For sweet whey demineralization, ultrafiltrated salty whey was used as concentrate solution using a 36 cm^2 membrane area module from FuMA-Tech. In this case, standard IXMs from Astom were used at constant voltage to obtain 75% of demineralization with an energy consumption of 7.4 kWh/t whey. For salty whey processing, monovalent-selective IXMs from Astom were used. These membranes selectively separate monovalent ions, such as sodium and chloride ions from divalent ions, such as calcium. Then, it was possible to generate a pure salt concentrate stream and a lactose-rich stream, with nutritional content of calcium. Moreover, demineralization values from 6.5 to 33% were achieved at different constant voltages (5–15 V) with an energy consumption ranging from 0.9 to 3.6 kWh/t NaCl.

Finally, Merkel et al. (2018) and Dufton et al. (2018) studied acid whey demineralization by ED. The first work utilized MemBrain heterogenous food-grade IXMs to demineralize nanofiltrated acidic milk whey from curd producing by an EDR pilot with 64 cm^2 of membrane area at constant voltage. Results showed that the conductivity decreased (lactic acid concentration varied from 17 to 3 g/L), whereas the pH increased (from 4.5 to 5.0) over time. On the other hand, the second work was carried out to study lactic acid deacidification and acid whey demineralization by commercial food-grade membranes from Astom (100 cm^2 of active membrane area) and a laboratory ED cell from ElectroCell Systems. In this case, constant current density was applied obtaining lactic acid deacidification of 44% and acid whey demineralization of 67%.

Furthermore, ED has been studied and applied for other applications, such as skimmed milk demineralization, desalination of ultrafiltrated milk permeate, demineralization of nanofiltrated retentate when treating lactose-free milk production or preparation of low-lactose milk powder. These examples have been summarized in Table 5.3.

As can be seen in Table 5.3, to the best of our knowledge, Andrés et al. (1995) were the first proposing the use of selective IXMs for commercial skimmed milk demineralization. In this case, they compared the results when using (i) standard IXMs (from Stantech) and (ii) selective IXMs (from Tokuyama). Moreover, different stacks were used: (i) a 100 cm^2 laboratory unit with 10 cell pairs and (ii) a 1568 cm^2 semi-pilot scale unit with 4 cell pairs, both tested at constant voltage. Results showed slightly better demineralization percentages when using standard ED membranes (45% vs 42% when using selective ED). However, it was possible to obtain quicker monovalent ions removal, when using selective IXMs, achieving higher Ca/Na selectivity (1.6 vs 1.2). Finally, energy consumption was also lower when using the selective membranes (0.94 kWh/kg vs 1.2 kWh/kg).

Table 5.3 ED applications in the dairy industry: review of applications and process performances

Main purpose	Feed solutions		CEM AEM	ED set-up Membranes	Operational conditions		Studied parameters	Main results	Ref
	Diluate stream (treated solution)	Concentrate stream Electrode rinse			Flow rates (L/h)	Constant voltage Temperature Experimental time (min)			
Skimmed milk demineralization with (i) standard ED, (ii) selective ED	Commercial skimmed milk from Central Lechera Asturiana (Spain)	7 g/L Na_2SO_4 20 g/L Na_2SO_4 (acidified to pH = 2 with H_2SO_4)	(i) SC- 1 (Stantech) (ii) Special grade Neosepta CMS (Tokuyama) (i) SA 1 (Stantech) (ii) Special grade Neosepta ACS (Tokuyama)	(i) Stackpack laboratory unit (Stantech) (ii) Semi-pilot scale TS-2 1OP (Eurodia) (i) 100 cm^2; 10 cell pairs (ii) 1568 cm^2; 4 cell pairs	–	Constant voltage (not exceeding 20–25 mA/cm^2) 24 °C 60	Selective IXMs vs standard IXMs	Demineralization: 45% ED and 42% selective ED Quicker monovalent ions removal with selective ED Ca/Na: 1.57 selective ED and 1.22 ED Current efficiency: 77% selective ED; 63% ED ED: 0.94 kWh/kg selective ED: 1.2 kWh/g	(Andrés et al. 1995)

(continued)

Table 5.3 (continued)

Main purpose	Feed solutions		CEM AEM	ED set-up Membranes	Operational conditions		Studied parameters	Main results	Ref
	Diluate stream (treated solution)	Concentrate stream Electrode rinse			Flow rates (L/h)	Constant voltage Temperature Experimental time (min)			
Desalination of UF milk permeate	(i) UF permeate from skim milk from a dairy plant (Czech Republic) (ii) UF milk permeate, concentrated by RO (3 times)	3% HNO_3 10 g/L $NaNO_3$	RALE X -CEM RALE X-AEM	P EDR-Z/10–0,8 (MemBrain s.r.o) 64 cm^2; 10 cell pairs	Diluate and concentrate: 60 Electrode solution: 50	15 V 15 ± 2 °C (i) 65; (ii) 130	Feed sample: (i) UF milk permeate and (ii) concentrate UF milk permeate by RO	(i) 90% desalination by 65 min; 2.21 Wh/kg (ii) 90% desalination by 130 min; 6.95 Wh/kg (i, ii) final products had similar compositions	(Shakhno et al. 2019)
Demineralization of NF retentate (lactose-rich)	2 L – NF retentate (NFR) from a lactose-free milk production (Esbjerg, Denmark)	2 L – 2 g/L NaCl 0.25 L – 20 g/L Na_2SO_4	CEM-PES (Membrain) AEM-PES (MemBrain)	P EDR-Z/10–0.8 (MemBrain) 64 cm^2; 10 cell pairs	Diluate and concentrate: 50 Electrode solution: 60	5, 10, 15 V 25 °C 120	Applied voltage NFR concentration; undiluted, dilution ratios 1.5 and 2	Demineralization rate > 90% Higher demineralization efficiency at 15 V and higher dilution ratio No significant changes or loss of lactose	(Rasmussen et al. 2020)

Preparation of low-lactose milk powder ED: Remove and recover mineral salts from UF permeate	10 L – UF pasteurized milk (Hangzhou Meijian Co., Ltd.)	Ionized water Na_2SO_4	CEM-type II (FUJI film) AEM-type II (FUJI film)	MP type cell (Electro Cell Systems AB) 189 cm^2, 6 cell pairs	Diluate, concentrate, electrode solution: 40	15, 20, 25 V Room temperature 60	UF + ED + NF	Volume reduction: 1 L of concentrate from 10 L of feed More voltage → + salt rejection rate, − desalination time 98% desalination at 30 min	(Zhang et al. 2020)

Furthermore, as observed in Table 5.3, the newest works (Rasmussen et al. (2020) and Zhang et al. (2020)) carried out during 2020, are focused in lactose-free/low-lactose dairy products, due to the growing lactose intolerance in society. The aim of the first work was to demineralize a nanofiltrated retentate from a lactose-free milk production in Denmark. In this case, the NF retentate, which was lactose-rich, was tested by an ED set-up from MemBrain and standard CEMs and AEMs from the same company, with an active membrane area of 64 cm^2. Several constant voltages were studied (5, 10 and 15 V) and also different dilution ratios of the NF retentate were tested. In all cases, demineralization percentages above 90% were achieved, without significant changes or lactose loses. Nevertheless, it was concluded that higher demineralization efficiencies were achieved at 15 V and higher dilution ratio of the ED feed.

On the other hand, Zhang et al. (2020) studied ED to remove and recover mineral salts from an ultrafiltrated permeate from pasteurized milk. The idea of the UF pretreatment was to retain macromolecules (proteins and fats). Then, ED was used for mineral salt removal (desalting) and also as a concentration step of the UF permeate stream (salts were re-added into milk). Finally, NF was also added in the proposed treatment train for lactose recovery. Moreover, to close a circular scheme, NF permeate could be recirculated into the UF stage. For that, CEMs and AEMs from FUJI Film were used in an ED stack from Electro Cell Systems applying several constant voltages (15, 20, 25 V). Results showed a high-volume reduction (from 10 L of feed to 1 L of concentrate) and a maximum desalination percentage of 98% at 30 min of ED operation. Besides, it was demonstrated that higher applied voltage, implied more salt rejection rates and less desalination time. All in all, it can be indicated that the proposed membrane treatment train could be a promising scheme for low-lactose milk powder preparation and lactose recovery.

Finally, ED has been studied for other treatments in dairy industries, such as to separate added-value proteins (e.g. lactoferrin and immunoglobulins from other proteins of crude dairy streams (Wang et al. 2020)) or to increase the *Lactococcus lactis* NZ133 starter culture biomass production by lactate removal in dairy applications (Boonmee et al. 2007). In the former work, poly(vinyl) alcohol membranes were prepared to achieve a high selectivity between lactoferrin and other proteins. Moreover, a crosslinking agent was used to increase the membranes water resistance. Synthetic solutions were tested by ED, mimicking an ultrafiltrated milk, that represented the buffered salt mixture in a common dairy whey. In this case, an ED Gradipore Gradflow BF400 System (Memphasys Limited, Sydney) was used, with an active membrane area of 16 cm^2. All tanks (diluate, concentrate and electrode rinse) were filled with the same feed solution. Diluate and concentrate stream compartments used 10 mL of ultrafiltrated milk in a recirculation mode at 17 mL/min, whereas the electrode rinse compartment was filled with 1 L of feed solution, which was also recirculated, but at 3.4 L/min. Then, a constant voltage of 100 V was applied between ED electrodes. Results showed that it was possible to isolate large proteins, such as lactoferrin and immunoglobulins from dairy whey by ED. In this case, smaller proteins passed through the membrane, while larger proteins were retained (Wang et al. 2020). Finally, Boonmee et al. (2007) incorporated an ED

system into a batch fermentation grown on 80 g lactose/L. The ED set-up consisted on 3 cell pairs of CEMs and AEMs from BDH Chemicals (Australia), with a membrane area of 100 cm^2. In this case, 0.25 L of diluate (fermented stream) and initial concentrate solution (tap water) were circulated into the ED stack at 3.6 L/h. Moreover, 0.25 L of 0.1 M H_2SO_4 were used as electrode rinse solution, circulating at 2.85 L/h. Different experiments were carried out at constant voltage of 40 V, or at constant current. Results showed that it was possible to remove lactate ions, which are a growth inhibitory metabolic end-product. Nevertheless, it seems that ED is not the most adequate technology to be incorporated in a fermentation process due to its limitations in lactate ions removal and low increase of the biomass production of the dairy starter culture *Lactococcus lactis* NZ133. Indeed, lower starter culture concentrations were obtained, compared with the conventional fermentation process (Boonmee et al. 2007).

As a summary, ED, selective ED and EDBM have been used for several purposes in dairy industries, such as, whey and milk demineralization, production of protein fractions, lactose recovery or lactic acid removal (Himstedt and Hestekin 2011; Bazinet 2015; O'Mahony and Tuohy 2013; Hestekin et al. 2010).

2.2 Wine Industry

The main application of ED in wine industry is the tartaric acid stabilization in wines (Lasanta and Gómez 2012; Gonçalves et al. 2003; Gómez Benítez et al. 2003; Soares et al. 2009; Bories et al. 2011; Corti and Paladino 2016; Henriques et al. 2019). The wine instability is caused by some sediments of tartaric salts, potassium bitartrate (KHT) and less frequently calcium tartrate (CaT), when the wine is bottled and stored at low temperatures. The precipitation of both tartaric salts occurs during the alcohol fermentation of wines, producing a supersaturated solution in them. Thus, the crystals deposits are neither desirable for wine production, nor for consumers (Low et al. 2008). Hence, the most widely used and traditional technique for wine stabilization is the cold treatment. It consists in cooling the wine to a temperature close to its freezing point and storing it between 3 days and 3 weeks, being 1 week the most often. However, it is a time-spending and energy-consuming method (Lasanta and Gómez 2012). In addition, cold treatment does not allow a precise control of the final KHT concentration and the wine quality can be affected by simultaneous polysaccharides and polyphenols precipitation together with the KHT salts (Gonçalves et al. 2003; Soares et al. 2009). For that reason, ED is proposed as a suitable membrane technique not only to remove KHT and tartaric acid (H_2T) in almost the same way observed in the conventional cold stabilization process, but it also permits a specific reduction degree of organics acids (e.g. lactic and malic acids) as well as cationic species (Mg^{2+}, Ca^{2+}, and Na^{+}) (Fidaleo and Moresi 2006). In this context, some ions from wines, such as potassium, calcium and tartrate were extracted by ED, which helps to reduce the over saturation level of tartaric acid salts (Daufin et al. 2001). In fact, Gonçalves et al. (Gonçalves et al. 2003)

highlighted that calcium removal is crucial to achieve tartrate stability in terms of both KHT and CaT. Nevertheless, in the ED treatment other molecules like polyphenols (anthocyanins and tannins), polysaccharides, amino acids and volatile compounds were unaffected (Daufin et al. 2001).

Tartaric stabilization of wines by ED is industrially conducted. To achieve the required level of K^+, the wine is circulated in the diluate compartments of the ED stack. Under an electrical field influence, the organic anions (containing tartrate, lactate and maleate) move towards to the anode permeating through the AEMs, whereas the cations (principally K^+, but also Mg^{2+}, Ca^{2+}, and Na^+) drive towards to the cathode crossing the CEMs. The concentrate compartments are filled with a salt solution (e.g., NaCl or KHT). In addition, a slight decrease in the pH of wine is commonly observed (0.15–0.25 pH units), since the anions permeation is slower than for the cations (Mondor et al. 2012).

The main advantage to use ED is that the energy cost of tartaric stabilization is very low; since the total electricity consumption is between 0.5 and 1 kWh/m^3 of treated wine (including pumping). Comparing with traditional methods, in which refrigeration is used, the energy required is about 10 times less by ED process. Additionally, the sensorial and organoleptic properties in wines were not modified by the ED process (Daufin et al. 2001). For instance, Gonçalves et al. (Gonçalves et al. 2003) commented that the organoleptic characteristics of wines (colour, aroma and taste) showed no differences when wines were treated by ED or conventional cold stabilization processes. For that reason, ED is a process implemented in several industrial treatment units of different capacities (4000–10,000 L/h) in France, Italy and Spain since 1997 (Daufin et al. 2001).

Forsyth (2010), from the Australian Wine Research Institute, made a comparison between ED and cold treatment, as a method to produce potassium tartrate stable wine. Results showed that ED offered considerable assets in power consumption (77 kWh for ED vs 1761–2968 kWh for cold treatment), time taken to process wine (17 h vs 384 h), and in wine losses minimization (136 L vs 424 L). Besides, there was no sensorial difference in the wines treated by ED in comparison with the cold technique. Nevertheless, wastewater volume (7683 L vs 1581 L) and labour requirements (17 h vs 9 h) were higher for ED than for the cold method. This report concluded that, based on the obtained results, ED appeared to offer a sustainable alternative method for tartrate stabilization in wines.

Several examples of tartaric acid stabilization in wines by using ED process are collected in Table 5.4. For practical considerations, to predict the degree of deionization (DD) that renders the wine stable, it is necessary in advance the removal of potassium and bitartrate ions from wine by ED (El Rayess and Mietton-Peuchot 2016). Two assays, based on rapid response conductivity techniques, such as saturation temperature and mini-contact test, can be used to determine the tartaric stability. First, the tartaric acid stability can be determined by the saturation temperature (T_s) in KHT, contained in the wine, being high stability at low values of T_s. The saturation temperature is obtained by measuring the electrical conductivity during a cycle by increasing the temperature of two samples, a control (without KHT) and other adding KHT. The T_s is reached when the conductivity of the two samples is

Table 5.4 ED applications from tartaric acid stabilization in wines: review of applications and process performances

Feed solutions				Operational conditions			
Diluate stream (treated solution)	Concentrate stream Electrode rinse	CEM AEM	ED set-up Membranes	Flow rates	Constant voltage or current Temperature Experimental time	Main results	Ref
24 L of white wine and 14 L of red wine – "Vinho Verde" wines	0.2 g/L NaCl –	CMX Sb (Tokuyama Soda) AMX Sb (Tokuyama Soda)	EUR2C-7P18 unit (Eurodia) 2 dm^2; 7 cells	–	1 V/cell 25 °C 2.5 h	DD for white wines: 4.7–30.1% DD for red wines: 5.5–20.6% KHT removal: 24% H_2T removal: 10.9% (at T_s = 14.8 °C and DD = 14.5%) Ca removal: 39% Lactic and malic acids contents were almost constant	(Gonçalves et al. 2003)
Sherry wines	– –	– –	– 25 m^2	25 hL/h	– – –	DD for "Fino" wine: 19.6–40.4% DD for "Medium" wine: 20.8–30.1% DD for "Cream" wine: 18.3%	(Gómez Benítez et al. 2003)
3 L – white, rose, red, and fortified wines	3 L – 0.2 mol/L KHT (pH = 3) 3 L – 0.2 mol/L K_2SO_4	CMX Sb (Tokuyama) AMX Sb (Tokuyama)	EUR2C-7P18 unit (Eurodia) 2 dm^2; 7 cells	180, 250, and 400 L/h for concentrate, diluate, and electrode rinse solution, respectively	1.5 V/cell 25 °C 18 min, 4 h, 24 h and 65 h	DD: 10–30%	(Soares et al. 2009)

Table 5.4 (continued)

Feed solutions				Operational conditions			
Diluate stream (treated solution)	Concentrate stream Electrode rinse	CEM AEM	ED set-up Membranes	Flow rates	Constant voltage or current Temperature Experimental time	Main results	Ref
White, rose, red, and fortified wines	– –	– –	Pilot device: 150 cells (Inra/Eurodia) Industrial unit: Two stacks of 150 cells (semi-automatic Eurodia)	Pilot scale: 15 hL/h Industrial scale: 30 hL/h	– – 7 h	Overall electrical energy consumption at industrial scale: 0.21 kWh/hL Water consumption: 5.5 L/hL wine	(Bories et al. 2011)
10,500 L – White and red wines	– –	– –	Model ED15 (Juclas) 30 m^2; 150 cells	15 hL/h	– –-	DD of white wines: 21–23% DD of red wines: 16–18%	(Corti and Paladino 2016)

the same (Lasanta and Gómez 2012). However, this parameter is not very accurate due to the huge metastability of KHT and the presence of crystal growth inhibitors. Therefore, a test, called mini-contact, has been developed, which consists in cooling a wine sample (0 °C) and measuring its conductivity for 4 h after the addition of KHT (4 g/L) that causes salt precipitation. The difference between conductivity at the beginning and at the end of the experimental time gives an estimate of the DD required to stabilize a wine by ED (Lasanta and Gómez 2012; Soares et al. 2009; Henriques et al. 2019; El Rayess and Mietton-Peuchot 2016). For example, Soares et al. (2009) developed a study to predict the required DD to stabilize wine by ED based on the mini-contact test. Then, they evaluated the tartaric stability of wines by the freezer test, the long-term storage test, and saturation temperature. In the study, the DD was predicted using the mini-contact test, which simulates the cold treatment with seeding, at a bench-scale during 65 h with two different particle size distribution of KHT crystals. Otherwise, freezer test is the traditional method to check when crystalline sediments appear during the thawing of a previously frozen wine sample. Different wine samples with DD between 10% and 30% were obtained by ED. They also observed, with mini-contact assays, that the DD required for tartaric acid stability of the electrodialysis-treated wine was strongly dependent on experimental time and was also influenced by KHT crystal granulometry. Furthermore, it is important to mention that it is necessary to use KHT, with a controlled size distribution, to enhance the mini-contact test repeatability. Afterwards, wines that overcame from the freezer test (with no prefiltration) were stable during 6 months of storage at 6 °C. Recently, Henriques et al. (2019) proposed both active and passive controlled freeze-thawing tests to predict the deionization degree required for tartaric stabilization by ED, and then compared it with the mini-contact test. In this study, the wine was frozen (−20 °C) and thawed (0 °C) in controlled conditions. They showed that freeze-thawing assays gave reproducible results, that were between 5 and 9% higher DD than the corresponding values obtained by the mini-contact test at −4 °C during 4 h. Because of that, they concluded that the controlled passive freeze-thawing test could be a reliable and low-cost alternative to the mini-contact test that can yield in 24 h an estimation of the DD of wines for tartaric stabilization by ED.

In regards with ED applications for tartaric acid stabilization in wines, Gonçalves et al. (2003) studied the KHT removal performance for wine tartaric stabilization by using ED. The wine saturation temperature was used to assess the tartaric stability. The study was carried out in a pilot scale (from Eurodia) with an ED stack composed by 7 cells with 2 dm^2 effective area (9 cationic CMX Sb and 7 anionic AMX Sb membranes, all from Tokuyama Soda). The wine samples used were two "Vinho Verde" wines, a white and a red, from grapes harvested in 1998 (Portugal). Results showed that the wine saturation temperatures varied linearly with the deionization degree. Regarding with white wines, it was possible to achieve a DD of 14.5% and a tartaric acid removal of 10.9% when the saturation temperature was 14.8 °C and stability up to 0 °C. In addition, the lactic and malic acids contents were kept almost constant, while the calcium content was reduced by 39%. For red wines, the saturation temperature was 9.2 °C, indicating a more stable wine.

Gómez Benítez et al. (2003) compared the efficacy of cold treatment and ED for tartrate stabilization, at industrial scale, of three sherry wines ("Fino", "Medium" and "Cream"). The difference in the studied wines was the sugar content, being <2 g/L, 40 g/L and 100 g/L of sugar, respectively. Conductivity techniques for rapid tartaric stability control, such as saturation temperature and mini-contact test, were used. They checked that the mini-contact test provided accurate information on stability in comparison with saturation temperature assay. Additionally, in the three studied wines, the cold treatment guaranteed the tartrate stability; while for ED, to obtain a similar stability it was necessary to apply a DD value higher than 26% in the "Fino" wine and lower than 20% for "Medium" and "Cream" wines. Authors also noted that the sulphate content was reduced more than the tartrates, and the sensory characteristics of sherry wines were slightly affected, depending on the applied DD.

Bories et al. (2011) evaluated the environmental impacts of tartaric acid stabilisation processes for wines using ED (pilot and industrial scale) and cold treatment. In the case of ED at industrial scale (30 hL/h), a RO unit was coupled to treat the generated brines in the ED process, and then to recycle the permeates from RO into the ED device. It is worth noting that this ED-RO hybrid process allowed the reduction of 65% of the overall water consumption in comparison with the ED without brine treatment. Comparing ED and cold method, results showed that ED presented less wine loss and minor waste generation because of the filtration step with diatomaceous earth involved in the cold technique. Besides, the overall electrical energy consumption for tartaric stabilisation by ED (2.1 kWh/m^3) resulted in eight times lower than the cold stabilisation treatment.

Besides, Daufin et al. (2001) stated that the integration of ED and MF, as one-step process and in a continuous system, is an innovative hybrid process to solve some issues in wine industry as follows: (i) microbiological stability, (ii) clarification, and (iii) tartaric stabilization with an excellent protection against oxidation without any additive.

On the other hand, ED is also proposed as a grape must rectification step for wine production. The conventional process for concentrate grape must production is evaporation, followed by ion-exchange resins for rectification; however in these processes numerous aromas compounds and organic acids are removed (Bazinet and Firdaous 2011). As an example, Correia de Pinho et al. (2006) patented a NF and electrodialysis hybrid process to simultaneously concentrate and partially rectify grape must. In this application, ED can be performed before the NF, after the NF or both, before and after the NF. They proposed the ED before the concentration step by NF, when the processing grape musts presented high potassium bitartrate concentration, to decrease from 10 to 40% of grape must ions. Thus, by reducing the precipitation of tartrate salts, it was possible to avoid NF membranes fouling after the ED stage. Also, ED could be used after the NF concentration step, when the initial concentration of potassium bitartrate in the grape must is low, to control the concentration of organic acids in the final grape must concentrate. It is important to note that the process does not require thermal separation and can be operated at room temperature or at temperature ensuring the preservation of volatile and aromas

compounds. As suggested by the authors, the process can be used for concentration and rectification of pulps and juices of fruits.

ED, with monopolar membranes, is also employed to recover tartaric acid (Zhang et al. 2011; Andrés et al. 1997; Kaláb and Palatý 2012; Eliseeva et al. 2012) and to reduce potassium content (Barros et al. 2019; Decloux et al. 2002) in vinasses as an effective way of wine waste treatment. Furthermore, ED with bipolar membranes, is used to produce acid (e.g. H_2T) and base (e.g. KOH) solutions from the salt (KHT) found in the vinasses (Zhang et al. 2009, 2012b; Vecino et al. 2020). Some examples about the vinasses valorisation by using ED and EDBM are summarized in Table 5.5.

Andrés et al. (1997) studied the ED process as an alternative method to purify and concentrate tartaric acid from IX (ion-exchange) regeneration waters obtained in grape juice industry. In that work, it was possible to reach a final tartrate concentration about 50 g/L from an initial tartrate concentration in the grape juice wastewaters about 5 g/L; so a concentration factor of 10 was achieved after 3.7 h, by using an ED configuration (anode)-CEM-AEM-(cathode) with 10 cell pairs and an effective membrane area of 0.2 m^2.

Zhang et al. (2011) evaluated the production of tartaric acid by EDM (QianQiu Environmental Protection & Water Treatment Corporation) applying different current densities (300 to 600 A/m^2) adding a resin or without adding it in the EDM process. The concentration factor obtained was 3.25 using 2 cell pairs ((anode)-AEM-CEM-(cathode) configuration) in presence or absence of the resin at 300 A/m^2 with a membrane area of 25 cm^2 after 5 h.

Kaláb and Palatý (2012) investigated mathematical models to predict tartaric acid concentration in the diluate and concentrate streams by ED with a CEM-AEM-CEM configuration. The IXMs used were Ralex-CMH-PES and Ralex-AMH-PES and were supplied by the Mega Inc. Company (Czech Republic). A concentration factor of 3.8 was achieved for tartaric acid in the concentrate compartment, under a range of current densities from 50 to 130 A/m^2, by using an ED-set-up with 10 cell pairs.

Eliseeva et al. (2012) studied the ED process of tartaric acid solutions and its salts, achieving tartaric acid percentage removal of 62% from an initial tartaric acid solution. A stack with 7 cell pairs was used, with a membrane area of 20 cm^2, and a (anode)-AEM-CEM-(cathode) as membrane configuration.

Barros et al. (2019) tested different configurations in the ED process for vinasses desalting and potassium recovery. ED system comprised 2 cell pairs and an effective membrane area of 16 cm^2. The membranes used in this study were Neosepta® homogenous selective monovalent cation (CMS) and anion (ACS) exchange membranes from Astom Co. (Japan), and non-selective heterogeneous HDX membranes (HDX 100 (cationic) and HDX 200 (anionic)) supplied by Hidrodex®. The vinasses were obtained from a sugarcane juice distillery plant and the configurations were as follows: (anode)-CEM-AEM-(cathode) for both monovalent-selective membranes or both non-selective membranes; and a mix configuration as (anode)-CEM (non-selective)-AEM (non-selective)-CEM (selective)-(cathode). Using all three configurations during 8 h, the maximum removal from raw vinasses was around 90% for K^+ and SO_4^{2-} and about 80% for Ca^{2+} and Mg^{2+}. Additionally, with the ED mixed

Table 5.5 ED and EDBM applications for vinasses revalorization: review of applications and process performances

ED								
Main purpose	Feed solutions		CEM AEM	ED set-up Membranes	Operational conditions		Main results	Ref
	Diluate stream (treated solution)	Concentrate stream Electrode rinse			Flow rates	Constant voltage or current Temperature Experimental time		
Potassium tartrate concentration	1L distilled vinasses (synthetic solution)	1 L distilled vinasses (synthetic solution)/1 L distilled vinasses (synthetic solution)	CEM Type II (Fujifilm), PC SK (PCCell)/ AEM Type II (Fujifilm), PC-100D (PCCell)	ED64-4 (PCCell, Germany)/64 cm ; 3 cell pairs	Diluate and concentrate: 15-20 L/h; Electrode rinse: 90-100 L/h	5.5 V/ 23 ºC/6 h	KHT desalting = 89.4 %; CF (KHT) = 2.2	Vecino et al. 2020
Tartaric acid recovery and concentration	45 L – fruit juice wastewater (10 kg/m^3 H_2T and 60 kg/m^3 glucose)	2 L – 10 kg/m^3 H_2T 10 L – 20 kg/m^3 Na_2SO_4 (pH = 2)	SC-1 (Stantech) SA-1 (Stantech)	LT-1 stack (Stantech) 0.2 m^2; 10 cell pairs	–	120 A/m^2 25 °C 3.7 h	H_2T final concentration = 53.2 kg/m^3 H_2T purity ~60%	(Andrés et al. 1997)
Potassium content reduction	Beet molasses stillage	2 L – 5 g/L NaCl 2 L – 21 g/L KNO_3	CMXbs AMXsb	EUR 2B lOP30 pilot unit (Eurodia) 0.2 m^2; 10 cells	–	17 V 19–26 °C 40 min	77.8% of K reduction CF = 7	(Decloux et al. 2002)

Tartaric acid production	Synthetic solution of KHT (0.5 M)	0.05 M H_2T 0.5 M Na_2SO_4	Heterogenous CEM (Qianqiu Environmental Protection & Water Treatment Corporation) Heterogenous AEM (Qianqiu Environmental Protection & Water Treatment Corporation)	– 25 cm^2; 2 cell pairs	–	300 to 600 A/m^2 – 5 h	H_2T CF = 3.25	(Zhang et al. 2011)
Tartaric acid production	Synthetic solution of H_2T (0.2 to 0.35 kmol/m^3)	0.05 to 0.35 kmol/m^3 H_2T 0.2 kmol/m^3 H_2T	Ralex-CMH-PES (Mega) Ralex-AMH-PES (Mega)	ED-Z mini (Mega) 64 x10^{-4} m^2; 10 cell pairs	Diluate and concentrate: 65 L/h Electrode rinse: 75 L/h	50 to 130 A/m^2 25 °C –	H_2T CF = 3.8	(Kaláb and Palatý 2012)
Tartaric acid production	Synthetic solution of H_2T[a] (0.05 mol/L, pH = 1.95) or KHT[b] (0.01 mol/L, pH = 5) or lysine hydrotartrate[c] (0.05 mol/L, pH = 2.75)	– Na_2SO_4	Heterogeneous MK-40 (Shchekinoazot) Heterogeneous MA-41 (Shchekinoazot)	B5–50 unit 20 cm^2; 7 cell pairs	0.1 cm/s (velocity)	[a]0.5–5 mA/cm^2 [b]0.25–2 mA/cm^2 [c]5–14 mA/cm^2 – –	H_2T extraction = 62%	(Eliseeva et al. 2012)

(continued)

Table 5.5 (continued)

Vinasses desalting and potassium recovery	1 L – distilled vinasses (raw and ultrafiltrated) from sugarcane juice	– 1 L – 0.03 M Na_2SO_4 (pH = 8)	Selective monovalent NEOSEPTA® CIMS and NEOSEPTA® ACS (ASTOM) Non-selective heterogeneous HDX (Hidrodex®)	– 16 cm^2; 2 cell pairs	10 L/h for all streams	0–210 A/m^2 – 8 h	72% of potassium recovery applying 60 A/m^2 (mixed configuration) Energy consumption = 9 kWh/m^3 Current efficiency = 54%	(Barros et al. 2019)
EDBM								
Main purpose	Feed solutions		CEM AEM BPM	EDBM set-up Membranes	Operational conditions		Main results	Ref
	Diluate stream (treated solution)	Concentrate stream I Concentrate stream II Electrode rinse			Flow rates	Constant voltage or current Temperature Experimental time		
Tartaric acid production	1L concentrate vinasses by ED	1 L 0.05 M H T/ 1 L 0.05 M KOH/1 L concentrate vinasses by ED	CEM Type II (Fujifilm)/ AEM Type II (Fujifilm)/ PC-bip (PCCell)	ED64-4 (PCCell, Germany)/64 cm2; 3 cell trios	Diluate, acid and base: 15-20 L/h; Electrode rinse: 90-100 L/h	10 V/ 23 ºC/16 h	9.9 g/L H T, 69.7% purity and 5.6 g/L KOH, 77.3% purity	Vecino et al. 2020

Tartaric acid production	Synthetic solution of KHT (0.5 M)	0.05 M H_2T 0.2 M KOH 0.5 M Na_2SO_4	Homogeneous FT-FKB CEM (FuMA-tech GmbH) Heterogenous AEM (Qianqiu Environmental Protection & Water Treatment Corporation) FT-BP (FuMA-tech GmbH)	– 25 cm^2; 1 cell trio	–	300 to 700 A/m^2 – 5 h	H_2T final concentration = 14 g/L at 300 A/m^2 (CF = 2.8) H_2T final concentration = 16 g/L at 400 A/m^2 (CF = 3.2) H_2T final concentration = 20 g/L at 500 A/m^2 (CF = 4.0) H_2T final concentration = 25 g/L at 700 A/m^2 (CF = 5.0)	(Zhang et al. 2009)
Tartaric acid production	Synthetic solution of KHT (0.5 M)	0.05 M H_2T 0.05 M KOH Na_2SO_4 (0.5 M)	Heterogenous CEM (Qianqiu Environmental Protection & Water Treatment Corporation) Heterogenous AEM (Qianqiu environmental protection & water treatment corporation FT-BP (FuMA-tech GmbH)	– 150 cm^2; 4 cell trios	15 L/h	66.7 to 200 A/m^2 – 5 h	H_2T final concentration = 55 g/L at 66.7 A/m^2 (CF = 3.7) H_2T final concentration = 95 g/L at 133.3A/m^2 (CF = 4.75) H_2T final concentration = 135 g/L at 200 A/m^2 (CF = 5.4)	**(Zhang et al. 2012b)**

CF: concentration factor

configuration, an energy consumption of 9 kWh/m^3 was reached for K^+ recovery (72%) at 60 A/m^2.

Respect to EDBM examples, Zhang et al. (2009) carried out different assays varying the current density (300–700 A/m^2) and adding a resin or without adding it in the EDBM process. The membranes used were heterogeneous AEMs supplied from QianQiu Environmental Protection Water Treatment Corporation (China), and a homogeneous FT-FKB CEM and a FT-BPM commercialized by FuMA-Tech GmbH (Germany). Fixing the current density value at 300 A/m^2 and using the following configuration (anode)-BPM-AEM-CEM-BPM-(cathode), independently of the presence or absence of the resins, the produced tartaric acid concentration was about 14 g/L after 5 h. Nevertheless, increasing the current density up to 700 A/m^2, it was possible to reach 25 g/L of H_2T.

In another work, Zhang et al. (2012b) evaluated ion conductive spacers for energy-saving production of tartaric acid instead of conventional spacers. CEMs and AEMs, were supplied by QianQiu Environmental Protection & Water Treatment Corporation, whereas the BPMs were commercially obtained from FuMA-Tech GmbH (Germany). The initial concentration of H_2T and KOH were 0.05 M in the acid and base compartments, respectively, and the configuration used was (anode)-CEM-BPM-AEM-CEM-(cathode). Under the above-mentioned conditions, it was possible to reach a concentration factor of 3.7 regardless of the spacer type (ion conductive or conventional) using a current density of 66.7 A/m^2 after 5 h. However, by increasing the current to 200 A/m^2, it was possible to achieve 135 g/L of tartaric acid providing a concentration factor of 5.4.

On the other hand, by using EDBM process the acidification and de-acidification of musts and wines are possible (El Rayess and Mietton-Peuchot 2016; Comuzzo and Battistutta 2018). High pH (about 4) is presented in wines not only because of the deficit of organic acids, but also due to cations excess such as potassium (El Rayess and Mietton-Peuchot 2016). In this context, the natural acidity in musts and wines can be caused by the climatic conditions in the viticulture region or due to oenological practices that lead to a decrease in natural acidity (Castelluci 2010). Several properties such as microbiological stability, physico-chemical, colour stability and organoleptic quality of wines depend on the wine acidity. For that, tartaric acid was proposed as an acidulant to correct the pH of musts and wines, being 1.5 g/L and 2.5 g/L the maximum dosage for them, respectively (El Rayess and Mietton-Peuchot 2016; Moldes et al. 2017).

In 2010, according to the International Organisation of Vine and Wine (OIV), the use of EDBM was accepted as an acidification method to treat musts and wines. The goals of this method consist of: (i) increasing of titratable acidity and actual acidity (decrease of the pH); (ii) obtaining wines with balanced taste characteristics; (iii) promoting a good biological evolution and proper storage of the wine; and (iv) remedying insufficient natural acidity (Castelluci 2010).

The steps of wine acidification process by EDBM are described as follows: when the electric current is applied, the K^+ ions contained in the must or wine are drawn to the cathode (the negative pole), they pass through the CEM and are stopped by the BPM. The electric current that is applied between the two electrodes splits water molecules into OH^- and H^+ inside the BPM, that is in contact with must or wine.

The OH^- ions migrate to the anode (the positive pole) into the concentrate stream, while the H^+ ions migrate to the cathode and replace the K^+ ions that are extracted from the must or wine in order to conserve the ion equilibrium. EDBM causes acidification (pH decrease) by lowering the potassium content in the wines. For a reduction of pH values, there is a concomitant enhancement in titratable acidity (El Rayess and Mietton-Peuchot 2016). As suggested by the OIV, the total acidity must not exceed 54 meq/L (4 g/L expressed as tartaric acid) when musts and wines are acidified (Castelluci 2010).

On the other hand, the process when the titratable acidity of musts and wines is reduced is called de-acidification process. Yeasts (e.g. *Schizosaccharomyces pombe*) or bacteria (e.g. lactic acid bacteria) lead to de-acidification in wine during the fermentation process. However, the physico-chemical de-acidification implies acid precipitation or ion-exchange processes in a fixed-bed configuration. Calcium carbonate or potassium bicarbonate can be de-acidification agents that involve tartaric acid precipitation as insoluble salts (El Rayess and Mietton-Peuchot 2016). For all, in 2012 it was accepted, by the OIV, the de-acidification of musts and wines using ED with bipolar membranes (Castelluci 2012). The principle of must or wine de-acidification by EDBM is similar to the conventional acidification one, but the anions (e.g. TH^- and T^{2-}) are concerned in this process. The application of the electric current drives the anions to the anode; they pass through the AEMs and are stopped by the BPMs. The anion forms of organic acids are transferred from the feed compartment to the concentrate compartment where they are associated with H^+ ions, missing their ionic form. Thus, the wine is poorer in organic acids, reducing the titratable acidity, and in consequence the must or wine is de-acidified (Mondor et al. 2012). The OIV proposed that the wine from a de-acidified process should contain at least 1 g/L of tartaric acid (Castelluci 2012).

3 Concluding Remarks

In this chapter, the potential of electrodialysis membrane technology for cost-effectively separation process in agro-food industries has been examined. ED is not only used for agro-food streams processing, but also it is applied for agricultural wastes and by-products valorisation, generated from agro-food industries. The reduction, treatment and recycling of agro-food streams is a matter of utter importance nowadays. Society and governments in industrialized countries, as well as social and environmental organizations, businesses and academics have developed an environmental awareness, demanding cleaner production systems from companies as electrodialysis. Among them, ED applications, with monopolar and bipolar membranes, in this chapter are focused on diary and winery industry sectors. In the case of dairy industry, ED is mostly applied as a demineralization step of milk whey, however ED can be used for production of protein fractions, lactose recovery or lactic acid removal. Concerning winery sector, the main application of ED is in the tartaric acid stabilization of wine; but also, it can be used for tartaric acid and potassium recovery from vinasses.

All in all, ED is proposed as an alternative to traditional processes, having a more sustainable and eco-friendly approach following the frame of circular economy and in line with the industrial symbiosis. ED is a technology with several highlights such as modular design, automatic, easy to operate, food safety, minimum waste production and competitiveness. Additionally, future research may be addressing in: (i) new membrane manufacturing: develop new ion-exchange membranes, improve the performance of conventional technologies by enhancing mass transfer and retarding fouling/scaling; (ii) water transport reduction through the membranes, (iii) membranes development with lower electrical resistance (iv) new membrane stack designs; (v) novel hybrid processes (traditional techniques with membranes); and (vi) economic analysis for agro-food industries.

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Chapter 6
Separation of Bioactive Peptides and Proteins from by-Products and Co-Products Through Membranes

Himan Nourbakhsh and Seid Mahdi Jafari

Abstract The world's population is quickly increasing, demanding more efficient use of current protein and derivative sources, as well as the development of new and sustainable food production. It is expected that the request for protein throughout the world will be doubled in the next 30 years. This is attributable to population increase as well as a growing awareness of the necessity of protein in a balanced diet in general, especially for youngsters and the elderly. Different operations in the food business create by- and co-products that, depending on the situation, might be value-add goods. The majority of these by- and co-products are released by fish and meat industry, dairy industry, and plant-based sources. Heads, skins, frames, and shellfish of fish, whey, nuts, peels, stones, and oilseed meals are large amounts of by- and co-products from the mentioned industries that are great source of protein and bioactive peptides that it is necessary to be recovered and reused; otherwise can cause environmental issues. Membrane technology has received huge attention for recovery of protein and peptides rather than selective precipitation, crystallization, and chromatography techniques and it is quickly becoming a popular food processing trend. Ultrafiltration (UF), nanofiltration (NF), and electrodialysis ultrafiltration (EDUF) are membrane processes with great and special potential for the separation and purification protein and peptides with various molecular weights. The successful recovery and fractionation of proteins and small peptides with a diverse range of functional, nutritional, and biological properties from food-based co- and by-products have been reported and this technique is still introduced as the first optimal choice for the selective separation of the mentioned compounds from the food industry wastes.

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1 Importance of Membrane Technique in the Separation of Proteins and Peptides

The world population is rapidly growing, urbanizing, and prospering, necessitating better utilization of existing protein and its derivative sources and creating new and maintainable food production. By 2050, global protein demand is estimated to have doubled. This is due to population growth and an increasing understanding of the importance of protein in a healthy diet in general, particularly for children and the aging population (Boland et al. 2013; Aspevik et al. 2017). Therefore, the finding and exploration of new protein bases are of attention. In addition to their nutritious value, proteins have a lot of potential as functional food additives with useful properties when added to foods. Also, it should be noted that in nature, only a few substances exist in their purest form. Most of them need separation before they can be eaten or used as components in several processed foods and nutraceuticals.

"Materials produced by a production chain or during the main products" are described as by-products and co-products; respectively. In the food industry, different activities (animal slaughtering, preparing the animal tissue, fish processing, dairy processing, etc.) generate by- and co-products that can be value-add products depending on the case (Bechaux et al. 2019). Scientists are looking for technologies to convert industrial by- and co-products into substances with additional value as public interest in the supportable use and controlling of natural resources grows (Lynch et al. 2016). The majority of by-products get to waste dumps, causing environmental issues, and others end up in low-cost products like compost, animal feeds, and aquaculture (Torres et al. 2007; Suwal et al. 2018). However, several food industry residues, which are usually underutilized or improperly disposed of, have the ability to be processed into high-quality ingredients. Failure to use or misuse by-products result in a reduction of future sales as well as increased waste costs and health issues. The main origin of these compounds can be divided into three chief groups in the food industry; fish and meat industry, dairy industry, and plant-based processing industry.

1.1 Fish and Meat Industry

Each year, large amounts of by- and co-products from the marine processing industry are produced, including inferior muscles, heads, viscera, fins, skins, frames, shellfish, trimmings, and crustacean shell leftover (Harnedy and FitzGerald 2012). Indeed, the primary aim of industrial fish and meat processing is to produce key products like fillets, chops, and mince. The preparation methods provide a large amount of protein-rich residual raw materials. Residues account for around 40–60% of the animal's total weight and fish. Depending on the species, this involves heads, carcasses, bones, viscera, blood, hooves, skin, and feathers. Most of this material has the ability to be used in higher-value food and feed applications (Aspevik et al. 2017). The gathered data show the tremendous value of these products; raw fish flesh has a crude protein content that ranges from 17% to 22% (w/w). Also, protein levels in crustaceans and mollusks can range from 7% to 23% (w/w) (Murray and Burt 2001). On the other hand, essential amino acids, minerals, and vitamins are found in fish and meat products, which are significant sources of protein in the human diet (Venugopal 2009). Discarding such compounds can result in produce a substantial amount of waste by food companies. In France, for example, 900,000 tons of organic waste are produced each year (e.g., discarded preparations and stale food) (Bechaux et al. 2019). Developing high-value functional components from marine debris, discard, and by-products may be a viable alternative to the legal constraints, high costs, and environmental issues that come with disposing of such waste (Harnedy and FitzGerald 2012).

One of the other greatest sources of protein and hydrolysate is also fish industry by- and co-products. According to many reports, the amount of crude protein in fish by-products ranges from 8% to 35% (Roslan et al. 2014). Fish by-products, on the other hand, are high in industrially important compounds like protein, oils, and minerals. From a sustainability aspect, it is critical to assess fish protein by-products in terms of environmental implications as well as economic benefits of the fish processing sectors. Moreover, peptides of fish protein have several functions, such as antimicrobial, antioxidant, antihypertensive, and anti-diabetic properties, making them a possible source for the manufacture of functional foods, biopharmaceuticals, and nutraceuticals (Jung et al. 2006). The molecular mass and amino acid composition of the peptide fractions differ, which determines their biological activities (Suwal et al. 2018).

1.2 Dairy Industry

The fluid gained after the elimination of casein protein in milk is known as whey. Whey has long been regarded as a challenging co-product of the dairy industry because it is processed in large quantities and has a high polluting potential (Smithers 2008; Arrutia et al. 2016). The main whey proteins are distributed differently, with

β-lactoglobulin being the most plentiful (about 58%) protein with an 18.4 kDa molecular weight, followed by α-lactalbumin (about 12%) with a 14.2 kDa molecular weight, bovine serum albumin (about 1.5%), and immunoglobulins (IgG) being the least plentiful (about 1%) (Kaur et al. 2020). The only problem with using whey is that it has a lower concentration of these important proteins. Due to the high content of essential amino acids, particularly those encompassing sulfur, whey protein has a high nutritional value (Wen-qiong et al. 2019). Moreover, whey protein has functional properties that impart beneficial physical properties when used as a food ingredient, owing to its high solubility, water absorption, gelatinization, and emulsifying capacities, among other things (Baldasso et al. 2011). Whey production in the world is estimated to be between 180 and 190 million tons each year, while half of that is processed and the residue is discarded in the environment (Leite et al. 2000). Since whey is a powerful organic contaminant with a high chemical oxygen demand, it causes significant pollution issues (Wen-qiong et al. 2019). Therefore, it is critical to recommend appropriate methods for recovering useful items, such as lactose or proteins, while still reducing environmental issues.

1.3 Plant-Based Sources

High volumes of waste resources such as nuts, peels, stones, and oilseed meals are produced during the processing of oilseeds, fruits, and vegetables. Disposal of these products is typically a challenge that is exacerbated by regulatory constraints. Plant waste is susceptible to microbial spoilage, so it must be dried before being used. Thus, these waste materials mostly used as fertilizer and animal feed. In addition, their essential nutrients are lost. Hence, new possibilities of the usage of these wastes as by-products for more application in the making of high-demand food additives or supplements with high nutritional worth have gained interest, as these are high-value products and their recovery can be economically enticing.

1.4 Protein and Bioactive Peptides Separation

The protein and peptide mainly acquired from animal protein sources like milk, fish, chicken and, egg, as well as plant protein such as soy, corn, peanut, and rice. However, by-products and co-products obtained during the processing of these sources contain large amounts of protein and peptides (Martinez-Maqueda et al. 2012; Aluko 2015). As discussed above, the mentioned by- and co-products are a great source of proteins that it is necessary to be recovered and reused. One of the great resources for the separation and recovery of protein is marine co-products. For instance, the wastewater of the marine industry is rich in protein compounds and isolation of these compounds is valuable in two ways; first, the valuable bioactive

compounds would be recovered, second, the organic and biological load in the wastewater would be reduced. Fish diets usually contain 20–55% crude protein, making daily protein intake critical for both humans and animals (Ayadi et al. 2012). The separated protein also can be subjected to bioactive peptide mining. A bioactive peptide is a small piece of 2–20 amino acids that can positively moderate human physiological functions and is derived from a parent protein (Aluko 2012). It is originally inactive within its host protein, but once released, it becomes active. Bioactive peptides can function as controlling compounds with hormone-like action once they are released in the body (Van der Ven et al. 2002). Two groups of peptides are existing; endogenous peptides are released naturally from the parent protein during food curing or digestion; exogenous peptides are released "artificially" by enzymatic hydrolysis or artificial synthesis. The exogenous types can be given to people and have the same biological effects as endogenous peptides (Abdelkarim et al. 2014; Bechaux et al. 2019). Bioactive peptides are mostly produced by enzymatical hydrolysis of the proteins. The molecular weight and amino acid arrangement of bioactive peptides, as well as their biological activities, were greatly affected by the specificity of the enzyme applied for proteolysis, the nature of the protein substrate, the time and temperature conditions used during hydrolysis, and the enzyme to substrate ratio (Van der Ven et al. 2002; Sila and Bougatef 2016). As a result, new bioactive molecules derived from numerous food sources, especially those gotten and extracted after enzymatic hydrolysis, are being investigated to meet consumer demand. However, since protein hydrolysates are complex mixtures of peptides of identical molecular weights, it's critical to use the right fractionation method to get distilled peptide segments with higher bioactivity and functionality (Doyen et al. 2014).

The most studied bioactive peptides are those extracted from milk, eggs, whey, soybeans, fish, and rice (Xie et al. 2008; Lee et al. 2010; Nagpal et al. 2011; You and Wu 2011; Roblet et al. 2012; Bechaux et al. 2019; Phongthai and Rawdkuen 2020). Despite the numerous documented profits of food-derived bioactive peptides, such as anticancer, antioxidant, antihypertensive, antimicrobial, immunomodulatory, and antiobesity properties, their recovery and purification processes are crucial at an industrial level production system (Suwal et al. 2014a; Roslan et al. 2018; Phongthai and Rawdkuen 2020). To be used as a protein source, a by- and co- products must have a high protein content as well as a high protein value (quality), which is focused on well-balanced essential amino acids. The lack of allergic or poisonous substances, or the application of a suitable pretreatment for their efficient elimination, is another prerequisite for using the material for food purposes.

1.5 Membrane Separation of Protein and Peptides

Selective precipitation, crystallization, and some chromatography techniques such as size exclusion, ion exchange, hydrophobic interaction, and affinity binding have all been investigated for protein separation. Because of their low throughput and

high expense, all of these techniques have significant drawbacks for large-scale applications. Membrane separations for protein recovery, on the other hand, have a wide range of applications and are becoming popular as one of the latest food processing trends (Mate and Krochta 1994; Berot et al. 2005; Butylina et al. 2006; Akin et al. 2012).

Reverse osmosis (RO), nanofiltration (NF), ultrafiltration (UF), and microfiltration (MF) are membrane technologies used in protein and peptide separation (Fig. 6.1). They vary in the size of the membrane pores. Membrane separation technology, which combines the functions of separation, concentration, and purification, is commonly used in fields such as food, biology, environmental protection, and water treatment (Nourbakhsh et al. 2015). MF membrane is not suitable for the recovery of protein and peptides by membrane processing. Indeed, high molecular weight materials (fat globules and microorganisms), suspended particles, and solids are clearly removed by membranes in the MF range (Castro-Muñoza and Fíla 2018). On the other hand, owing to the accumulation of low molecular weight organic matter and inorganic salts in the ending product, the RO membrane is not suitable for recovering high-purity proteins (Strætkvern and Schwarz 2012). While the UF membrane can separate most protein molecules with 10 kDa molecular weight. Nevertheless, the UF membrane cannot efficiently reject the lower molecular weight peptides and during the long-term filtration process, it is prone to serious protein contamination. Nanofiltration membranes, in comparison to UF and MF membranes, can selectively distinguish monovalent and polyvalent salts, as well as effectively separate organic solutes with molecular weights greater than 200 Da. It is predicted that the NF membrane will recover bioactive peptides with a lower molecular weight, while the salts in solution will also pass through the NF membrane and into the permeate (Li et al. 2020). Therefore, by combining UF and NF membrane separation technology, proteins and peptides can be separated and purified effectively. These traditional membrane technologies offer many benefits, including (1)

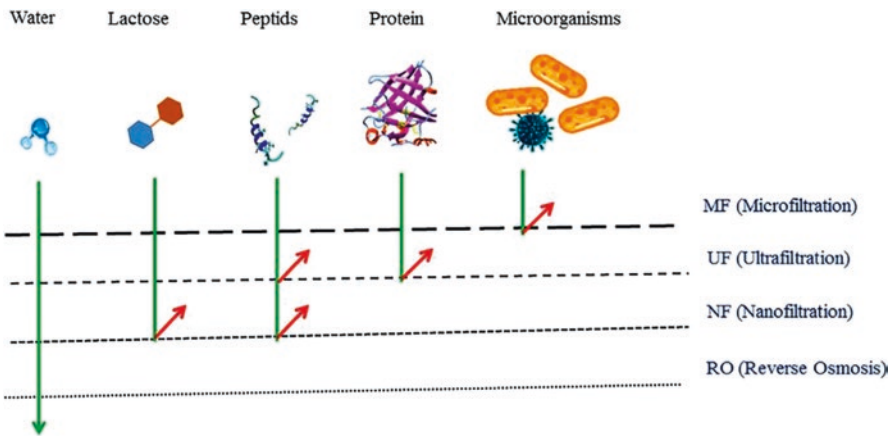

Fig. 6.1 Schematic diagram of a membrane separation and approximate particle size separation process

low energy demands, (2) high separation performance, (3) easy scale-up, (4) ease of operation, (5) high productivity, (6) no phase transition, and (7) no need for additional solvents (Drioli et al. 2011; Castro-Muñoza and Fíla 2018; Wen-qiong et al. 2019). Finally, membrane separation is a successful substitute separation for attaining an environmentally sustainable and a low-cost method.

2 Factors Affecting Membrane Separation of Proteins and Peptides

The most important influencing factors in the membrane separation of proteins and peptides are membrane materials, fouling, proteins solution properties (pH, ionic strength, and electrostatics situation), and the operating parameters of the membrane processing (temperature, transmembrane pressure, and pore size) (Søtoft et al. 2015; Birrenbach et al. 2021). Frequently, inorganic (ceramic) or organic (polymeric) materials membrane are used for protein and peptide filtration. Polymeric membranes include cellulose acetate, polyamide, polysulfone, and polyvinylidene fluoride appeared to be the most suitable for use in protein recovery due to their characteristics (Wen-qiong et al. 2019). The membrane mostly accommodated in hollow fiber and spiral-wound cartridges models. For whey protein recovery, hollow fiber and spiral membranes both provided with polysulfone (MWCO: 10 kDa) were used (Castro and Gerla 2005). Over the last few years, researchers have put a lot of time and money into creating new materials for various membrane applications. Because of their special properties, cellulosic and poly-(aryl sulfones) are commonly used in a variety of applications (Macedo et al. 2011). Ceramic membranes have the well-known benefits of reusability and the ability to be washed with common sanitizing agents used in the food industry, such as HNO_3, NaOH, NaOCl, and even H_2O_2. With a comparatively high protein retention or concentration potential of about 80% and relatively low lactose retention of about 7%, the ceramic membrane had good protein and lactose recovery properties (Wen-qiong et al. 2019).

Proteins are amphoteric compounds. The number and pKa values of amino groups with positively charge and carboxylic acid groups with negatively charge decide a protein's net charge (Reis and Zydney 2007). Proteins are positively charged at pH levels below their isoelectric point (pI) and negatively charged at pH levels above the pI and it is called net neutral at the isoelectric stage (Emin et al. 2018). Electrostatic repulsion between a charged membrane and a protein can thus be used to modulate the membrane separation selectivity. Electrostatic connections between proteins and the membrane are also favored at low salt concentrations (Liu et al. 2012). Although simple models can describe the interactions between membrane surface and protein, the effects of transmembrane pressure and thus flux on selectivity can be more complicated, requiring assessment of various degrees of concentration polarization for proteins of different sizes or differences in deformability due to specific protein structures. Earlier research by the Zydney's group

established that by applying differences in charges between the target substances and the membrane, it is conceivable to separate efficiently two kinds of proteins with similar molecular weight (Reis et al. 1999; Emin et al. 2018).

Membrane fouling is a significant problem in membrane separation. While membrane technologies have the potential for high separation speed, fouling, the accumulation of solute molecules on the membrane surface, is a major stumbling block that has restricted their use which decreases permeation flux and improves hydraulic resistance, lowering the overall process efficiency (Nourbakhsh et al. 2014a). Membrane fouling can certainly lead to solute retention in some way; in pressure-driven membrane processes, there are typically four types of fouling mechanisms: (i) partial pore blocking, (ii) full pore blocking, (iii) cake forming, and (iv) internal pore blocking (Razi et al. 2012; Nourbakhsh et al. 2014b). These fouling processes that can occur during the membrane filtration of natural extracts are depicted in detail in Fig. 6.2. Membrane fouling can be reduced by using the right membrane material and pH, resulting in higher flux and selectivity (Akin et al. 2012).

The use of membrane separations in complex food-based feed solutions raises concerns about fouling (Rajendran et al. 2021). Many attempts have been made to investigate this phenomenon and eliminate output losses caused by fouling (Tripathi et al. 2018). Regarding the purpose of this study, membrane fouling is caused by proteins, which are the most common substances during their separation from the by- and co-products. This phenomenon is caused by protein-protein and protein-membrane interaction forces and is affected by a variety of factors including pH, temperature, feed solution composition, membrane characteristics like material and pore size, and operating conditions like velocity and transmembrane pressure. The physicochemical properties of the protein and peptides and their transmission through membranes filtration were also significantly influenced by transmembrane pressure, pH, ionic strength, and temperature. To optimize the difference in effective hydrodynamic volume between the elements, the pH values should be similar to the pI values of the impurities (pH = pI ±1) and further away from the pI of the commodity protein as possible. Moreover, if the membrane charge be similar with

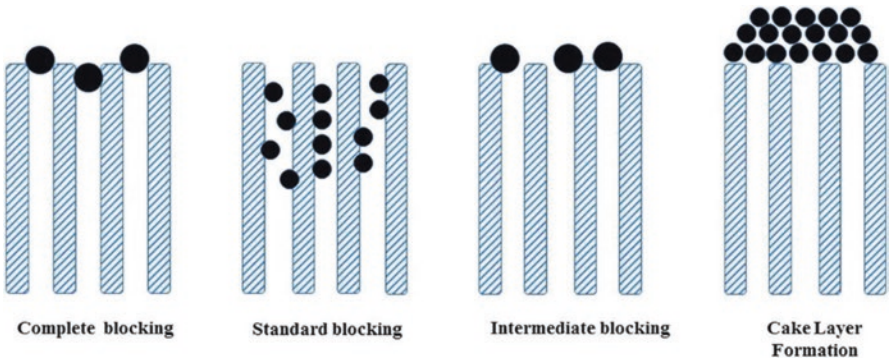

Fig. 6.2 Different types of membrane pore blocking during membrane filtration

the charge of the product protein, it is possible to improve the electrostatic repulsion of the product from the membrane pores at the chosen pH value. Indeed, the permeate flux is the lowest at the pI and the highest far from the pI (Das et al. 2009; Van et al. 2015; Wen-qiong et al. 2019). Because of the reduced isoelectric repulsion between proteins, adsorption and accumulation on the membrane surface occur at their peak at the pI, and thus aggregates pointedly on the membrane surface, making a substantial drop in permeate flux.

The composition of the deposit layer is influenced by temperature in an indirect way. Since the hydrophobic protein core is unfolded because of increasing temperature, thick deposit layer buildings form when either repulsive forces are low or enticing van-der-Waals forces increase (Steinhauer et al. 2015). Protein adsorption to rigid materials, such as membranes, is increased when protein hydrophobicity increases. The effect of temperature on the membrane fouling has been studied during UF and MF of whey and whey protein suspensions. During MF, membrane fouling due to adsorption processes was simplified at temperatures of $\leq$10 °C and > 35 °C (full whey protein infusion). At temperatures over 40 °C, an increase in temperature during membrane processing of sweet whey caused a dramatic increase in membrane fouling. The greater fouling reaction in the neutral pH range may be due to both the enhancement of thiol or disulfide response speed and calcium-based protein cross-linking when the temperature was raised (Steinhauer et al. 2015; Wen-qiong et al. 2019).

It can be said that fouling occurs as a result of protein deposition. The effect of temperature on non-covalent links engaged in secondary and tertiary structure stability, such as hydrophobic, electrostatic, and hydrogen bonding, causes denaturation in proteins. The hydrophobic groups interact while the secondary and tertiary structures of a protein are unfolded, reducing water binding. As a consequence of these hydrophobic reactions, aggregation occurs, which is accompanied by coagulation and precipitation. Denaturation reduces protein solubility relative to native protein, causing aggregation and making cooling impossible to reverse, resulting in fouling or mechanical deposition, which is often referred to as fouling (Pelegrine and Gasparetto 2006). In addition, ionic strength influences the interactions between protein molecules that cause membrane fouling. Since electrostatic repulsion decreases as ionic strength rises, the rate of membrane fouling rises. Protein gathering on the surface of membrane was aided by the bridging action of divalent cations such as Ca^{2+} (She et al. 2009). The effects of pH and ionic strength on membrane separation of peptides have been published in various studies (Cheang and Zydney 2003; Akin et al. 2012).

It is well understood that the molecule adsorption on the membrane surface is related to the membrane material (Beier et al. 2007). During the separation of protein and fat from surimi wastewater by Dumay et al. (2008), less membrane fouling was observed for a hydrophilic membrane rather than some more hydrophobic membranes (polyacrylonitrile, polyvinylidene fluoride, and polyethersulfone). During 5 h of wastewater filtration, the flux was also higher for the hydrophilic membrane. Clean water washing was adequate to restore the primary flux for the renewed hydrophilic membranes, but neither caustic nor acidic cleaning could

restore the flux of the hydrophobic membrane. It also appears that a hydrophilic UF membrane is less vulnerable to fouling in this case than more hydrophobic membranes, but proper pretreatment is still needed (Dumay et al. 2008; Søtoft et al. 2015).

Brewer's spent grain, spent brewer's yeast (SBY), and hot trub are examples of by-products produced by the brewing industry. SBY is the second-largest brewer's by-product, and it has a lot of promise as a source of protein and bioactive peptides (Marson et al. 2021). Marson et al. (2021) filtrated SBY through the UF membrane and examined membrane selectivity and fouling. At various pH levels (5 and 8), UF experiments were conducted with renewed cellulose (RC) and polyethersulfone (PES) membranes with a MWCO of 30 kDa. PES and a feed pH of 5 resulted in higher peptide rejection (60% of total solids and 83% of peptides). The peptide-rich fraction was successfully isolated from ribonucleic acids. At pH 8, the protein hydrolysate was less susceptible to protein adsorption and had less resistance to mass transfer. The UF efficiency of SBY hydrolysate was improved by using hydrophilic membranes and feeding it at pH 8. The ultrafiltration of SBY protein hydrolysate using the regenerated cellulose membrane had a successful result since this type of membrane has a more hydrophilic futures and a smoother surface. When the result under the same conditions compared with the polyethersulfone membranes, the regenerated cellulose membrane has shown sufficient protein compound and solids rejection as well as low protein adsorption. The creation of fouling on the membranes surface appears to be mainly caused by peptides and protein segments, which are the key elements in the SBY hydrolysate. They stated that physical adsorption, rather than electrostatic interactions, is the preferred method of protein deposition (Marson et al. 2021).

3 Application of UF Membranes in the Separation of Proteins and Peptides

Ultrafiltration (UF) membranes have gained a lot of attention in the last few years for protein fractionation because it has been shown that high selectivity can be achieved while maintaining high throughput (Emin et al. 2018; Rajendran et al. 2021). Indeed, the selectivity of solute separation during protein UF is a function of not only the membrane pore size, but also the operating situations; ionic strength, pH, and transmembrane pressure (Mahlicli et al. 2012; Emin et al. 2018). Proteins and other macromolecules are well retained by UF membranes. On the other hand, to isolate different bioactive peptides with the desired molecular weights and functional properties from protein hydrolysates, UF membrane systems with various cut-off sizes (100, 20, 10, 5, 3, and 1 kDa) were proposed (Sila and Bougatef 2016). The design of the UF system for proteins and peptides recovery from the main discussed sources of by- and co-products and protein hydrolysate is reviewed below. It is noteworthy to mention that UF membrane technology is a common technique in the dairy industry because it does not involve any heat-induced phase change

(evaporation), making it a more cost-effective method. This technique concentrates species with molecular weights of 10–1000 kDa (Kaur et al. 2020).The citations Sila et al. (2016), Damar et al. (2020), Roblet et al. (2013) and Roblet et al. (2016) are given in the text but reference details are not provided in the list. Please provide. The situation of **Sila et al. 2016** was changed to Sila and Bougatef 2016**.**

Fish by-products are a great source of proteins and they subjected to generate bioactive peptides. Fish protein hydrolysate (FPH) is a mixture of peptides of different sizes generated by enzymatic hydrolysis. Since the functional characteristics of peptides are related to their size, and the right molecular size, the control of degree of hydrolysis (DH) during hydrolysis to produce peptides with the anticipated molecular sizes (5–10 kDa) should be considered (Wan et al. 2005). As a consequence, it is a difficult process and almost impossible to achieve. Accordingly, it is important to have a better knowledge of the separation process, especially for the wide generation of these unique peptides. Column chromatography is widely used in advanced peptide purification methods, owing to its high selectivity. However, scaling up this approach is expensive. Due to its capability to isolate FPH efficiently, easily monitor, and enrich a tiny peptide fraction with strong biological activity, UF membrane may supply a less expensive alternative and the most practical equipment for peptide separation (Rajapakse et al. 2005; Raghavan and Kristinsson 2009; Roslan et al. 2018).

Tilapia is a common freshwater processed fish due to its nutritional value and widespread accessibility. In Asia, exhaustive tilapia farming has grown steadily in recent years, becoming a significant source of fish (Murthy et al. 2011). Significant amounts of by-products have been produced as a result of the increasing demand for tilapia fillets in the manufacture of fish-based food products. The majority of these by-products are thrown away, resulting in various environmental issues (Arvanitoyannis and Kassaveti 2008). They also contain significant quantities of proteins, which are considered to have high nutritional value in terms of essential amino acid composition and rich protein content ranging from 15% to 60% (Valdimarson and James 2001; Arnesen and Gildberg 2006). Protein recovery from these by-products and alteration to high-priced products like bioactive peptides is an interesting and talented option. Bioactive peptide extraction from fish by-products has gotten a lot of consideration in recent years because of their physiological functions including antihypertensive and antioxidative activities, which are useful in public health care and medicinal products (Jung et al. 2006; Roslan et al. 2014). The protein hydrolysate of tilapia by-products (TB) is made up of peptide mixtures of different sizes. Small-sized peptide recovery is becoming more important as a result of their unique properties, which can have excellent physiological functions. The separation of such small bioactive peptides has been carried out by UF membrane (10 and 5 kDa) (Roslan et al. 2018). In this work, the membrane's performance was assessed using permeate flux and peptide separation. For this purpose, the effect of stirring speed (0–600 rpm), pH (3, 5, 7, 8 and 9), and salt concentration (NaCl; 0 M, 0.2 M, 0.4 M, and 0.6 M) at different pressures (1.0, 1.5, 2.0, 2.5 and 3.0 bar) were considered through the membrane filtration of tilapia protein hydrolysate. The best parameters were found to be 2.5 bar transmembrane pressure, 600 rpm stirring

speed, pH 8, and no addition of NaCl, which produced permeate flux of 53 L/m^{2}h (10 kDa) and 27 L/m^{2}h (5 kDa), and peptide transmission of 87.33% (10 kDa) and 36.11% (5 kDa). According to this research, adding salt reduced permeate flux and peptide transmission. Finally, peptides with sizes less than 1000 Da were generated using a well-managed set of functional and physicochemical factors. Søtoft et al. (2015) applied several UF MWCOs (50, 20, 10 and 1 kDa) in order to recovery value-added compounds such as proteins, peptides and amino acids from fish industry waste since the protein/peptide has a very wide range of molecular masses compared to free amino acids. Finally, they have successfully separated the protein and peptide molecules by applying 50 kDa UF systems. A protein concentrate (>17 kDa) is generated at the 50 kDa level. 42% of waste is recycled and used to replace fresh water and chemicals. The amount of wastewater has been decreased by 62.5%. Amino acids and smaller peptides are concentrated 11 times, whereas proteins are concentrated 30 times.

Whey is a great source of proteins with nutritional, functional, and biological properties. Several recent research used UF, and NF membranes to concentrate whey proteins during cheese production and re-incorporate them to increase cheese yield (Akin et al. 2012, Wen-qiong et al. 2019; Damar et al. 2020). Their hydrolysates, in addition to whey proteins, have been also separated as useful bioactive peptides. Antihypertensive, antimicrobial, and immunomodulatory operations are among their possible therapeutic applications (Nourbakhsh et al. 2017). Separation of β-lg from whey was investigated by Bhattacharjee et al. (2006). They used flat disk membranes with MWCO concentrations of 5, 10, and 30 kg/mol, succeeded by ion-exchange membrane chromatography (IEMC). Firstly, lactose was eliminated by 5 kg/mol membrane and then 30 kg/mol membrane was applied to recover lactoferrin, Ig, and BSA. α-LA and β-LG were separated in the second stage using a 10 kg/mol membrane. The retentate was then loaded into the IEMC. On a total protein basis, a purity of 87% was reached. UF is also used to make whey protein concentrate because it enables minerals, water, lactose, and other low molecular weight compounds to move through while retaining proteins.

Damar et al. (2020) investigated permeate flux, membrane fouling, solute rejection, and permeate flux separation in UF of cheese whey using commercial UF membranes with 10 kDa MWCO. The reported results were interesting; membrane resistance, whey permeate flux, and hydraulic permeability were all affected by the polymeric composition, pore morphology of the membranes, and surface charge/hydrophobicity. Actually, water permeability was primarily influenced by pore morphology, while intrinsic membrane resistance was influenced by active layer porosity. Due to the strong antifouling propensity and sufficient solute rejection, a membrane with a hydrophilic surface character, low roughness, smooth surface morphology with high porosity, and sponge-like pore structure was shown to be the best suited for the concentration of acid whey proteins (Damar et al. 2020).

Different plant-based sources and by-and-co-products of them have been studied for the separation and recovey of protein and bioactive peptides like pea, soy, rice, corn, wheat, rapeseed, and sesame. Pea protein readily is available in the marketplace and used as useful functional components in a variety of food formulations.

During the traditional processing of pea protein isolates, a large percentage of protein remains in the pea whey, possibly requiring the development of modern technologies to recover it. Gao et al. (2001) examined two different MWCO UF membrane systems (10 and 30 kDa) together with the following bag-filtration or centrifugation pretreatments prior to UF for separation of whey pea protein. The designed UF system was able to increase recovering of protein content from 38.1 g/100 g to 84.4 g/100 g. Moreover, albumin proteins were recovered using the 10 kDa UF membrane, which could not be recovered using the 30 kDa membrane due to their low molecular weight (17.5 kDa). Gao et al. (2001) also found that proteins extracted from pea whey had better functional characteristics than commercially available proteins.

Researchers looked into the isolation of soy proteins from waste liquor, as well as the antioxidant properties of various protein and peptide fractions. Moure et al. (2006) analyzed 10, 30, and 50 kDa UF membranes for such separation. Peptide fractions of 10 kDa, 10–30 kDa, 30–50 kDa, and > 50 kDa were obtained. The antioxidant activity of the 10 kDa retentate was the highest, while the hydroxyl radical scavenging potential of the 30–50 kDa fraction was the highest.

Wheat germ has a high protein content of 30%, making it a potential plant-based protein and enzymatically derived peptides from wheat germ protein. Defatted wheat germ protein (DWGP) has been shown to have a high potential for producing ACE-inhibitory peptides through enzymatic means (Matsui et al. 2000; Qu et al. 2015). Qu et al. (2015) developed an effective method for generating ACE-inhibitory peptides from DWGP using continuous coupling of enzymatic hydrolysis and membrane separation (CEH-MS). The enzyme activity is completely utilized in this system. The mentioned-above research team investigated the combined use of enzymatic hydrolysis and a membrane separation method in order to reduce peptide production costs and increase operational performance during the separation of peptides from *Porphyra yezoensis* protein hydrolysate. To produce a successful separation of the target product from the substrate, the CEH-MS reactor system should be able to fully use the benefits of biochemical engineering and membrane separation techniques. They designed a batch, continuous with water feeding, and continuous with substrate feeding for the separation of peptides. The batch operation of the CEH-MS reactor improved the protein conversion degree, yield of peptides, production of peptides per unit of enzyme, and antihypertensive activity of peptides by 43.6%, 43.6%, 7.7%, and 3.9%, respectively, as compared to the conventional process. These figures were increased by 62.7%, 62.7%, 22.1%, and 4.4%, respectively, for continuous service with water feeding. The continuous activity with substrate feeding resulted in a 216.9% increase in peptide production. The CEH-MS reactor was shown to be more efficient than the conventional approach in terms of high raw material utilization rate and peptide yield.

Sesame seeds (*Sesamum indicum* L.) are a good source of protein. Because of its balanced amino acid composition, the defatted sesame seed is an essential source of protein for human consumption (Das et al. 2009). Its protein hydrolysates can be used in dairy, personal care products, coffee whitener, confectionaries, cosmetics, and the fortification of soft drinks and juices as dietary supplements, functional

ingredients, and flavor enhancers. Soups, meat products, sauces, snacks, gravies, and other savory applications use the hydrolysates. The processing of sesame protein hydrolysate was investigated by membrane technology. Das et al. (2009) used a UF membrane to separate protein from sesame seed hydrolysate. This research used a polyethersulfone (PES) membrane with a MCWO of 5 kDa. They also studied the operating parameters such as pressure, feed concentration, and pH on the permeate flux and rejection. Furthermore, the fouling aspect of the membrane caused by sesame protein hydrolysate was evaluated, and a cleaning method was suggested. The rejection of solute with a 5 kDa PES membrane was found to be between 50% and 70% depending on the operating conditions, which is consistent with the molecular weight distribution findings obtained by capillary electrophoresis. The minimal flow and maximum permeate concentration (i.e., minimum rejection) were achieved at the isoelectric point of the sesame protein hydrolysate. They discovered that as TMP rises, the permeate concentration rises, indicating that rejection decreases. This is most likely due to increased TMP allowing more small molecules to move through the membrane, resulting in an increase in permeate concentration. Additionally, decreasing the feed concentration from 400 ppm to 100 ppm resulted in a rise in permeate flux, according to the findings. The supply of solute molecules to be deposited on the membrane surface decreases as the feed is diluted, resulting in less hindrance to passage solute molecules and higher permeate flux. After a careful selection of operating conditions, the investigation clearly demonstrated that UF could be used to concentrate sesame protein hydrolysate Das et al. (2009).

Because of its high-quality hypoallergenic protein and low cost, rice bran, a by-product of the rice milling process, is progressively being utilized as a preliminary material for the making of protein concentrate and hydrolysate (Phongthai and Rawdkuen 2020). They exposed and released from a variety of protein sources using enzymatic hydrolyzing. Phongthai and Rawdkuen (2020) used pepsin–pancreatin to prepare and hydrolyze rice bran protein. After that, the bioactive peptides were recovered by filtration through 5-kDa UF membranes. They were successful to produce and separate bioactive peptides with great antioxidant properties.

It can be concluded that to guarantee UF's fitness and financial viability for a particular application, studies on membrane efficiency (water and hydrolysate fluxes) and fouling resistance (membrane surface examination, hydrophilicity, and membrane-material interactions) must be performed (Xu et al. 2018; Marson et al. 2021). Despite the fact that membrane filtration for protein recovery has been used in different industries such as whey recovery in the dairy industry, protein ultrafiltration still has issues. The following are the primary drawbacks: membrane fouling is caused by membrane pore blockage and the formation of a protein cake coating on the membrane surface, which appears as the membrane activity time is extended. Secondly, the high-cost membrane materials for whey filtration should be exchanged annually or so, and the high cost of cleaning materials for steady membrane washing has driven up the cost of the concentration and purification of whey protein. Third, for whey ultrafiltration during the ultrafiltration process, certain peptides, such as proteases, peptones (PP) and amino acids, from whey join the permeating

liquid. Indeed, some low molecular weight peptides and amino acids are present in the UF permeate, which cannot be recovered fully. The explanation for this is that peptides and amino acids with molecular weights less than MWCO of the UF can permeate through the membrane pore. Fourth, including the multiple stages of diafiltration as a next step for the recovery of the permeate increase the amount of pure water consumed (Wen-qiong et al. 2019).

4 Application of NF Membranes in the Separation of Proteins and Peptides

Nanofiltration (NF) is a technique for separating solvent, monovalent salts, and small organic molecules from divalent ions and larger organisms (Li et al. 2020). The creation of NF membranes, which have high potential in the separation of components with divers molecular mass ranging from 300 to 1000 Da, is one of the most significant recent developments in the recovery of small charged biomolecules, such as peptides and amino acids (Martin-Orue et al. 1998). The NF membrane process has been reported for application in the separation, purification, and fractionation of bioactive peptides from the hydrolysate. It can be due to that most peptides have similar physicochemical properties and only a separation technology that can differentiate between minor variations in charge, hydropathicity, size, or solubility is useful (Arrutia et al. 2016). Protein hydrolysates are a complex blend of amino acids and peptides that are apply in the practical food industry as ingredients. The molecular weight of peptides influences their biological behavior (Berot et al. 2001). Membrane separations also benefited from the use of charged NF membranes for the fractionation of certain molecules. Because of the molecular MWCO used (within the spectrum of bioactive peptides) and the importance of charge effects, NF is considered to be one of the best membrane processes for peptide separation (as peptides are charged molecules) (Butylina et al. 2006; Arrutia et al. 2016). As well, inorganic NF membrane prototypes display a significant increase in separation properties since their amphoteric activity is a function of pH. For example, during the NF of a mix of amino acids, basic amino acids (cations) are detached at a pH > 9 and acidic amino acids (anions) are recovered at a pH below 3 and. Likewise, a choosy separation between acid and basic peptides was gained at pH 9 for a mixture of peptides (Ghosh and Cui 1998; Doyen et al. 2011a). The size and charge of solutes also influence the selectivity of nanofiltration membranes. The solute transfer is essentially understood as the product of two steps: first, a charge-based spreading of ionic species at the selective boundary, and second, transfer through the membrane using a combination of diffusion, convection, and electrophoretic mobility (Martin-Orue et al. 1998; Zydney 1998).

Arriuta et al. (2016) developed a membrane process in order to separate peptides with the potential to become functional ingredients. They digested WPC by trypsin and the resulting hydrolysate for separation of peptides was subjected to UF/NF

membrane at different pH values in order to compare separation performances. Without the need for a pre-filtration stage, multifunctional peptides free of intact proteins were obtained. The separation factors were influenced by pH, with basic pH values being stronger. Membranes were also very good at distinguishing acidic peptides from other groups.

In the following, some applications of UF membrane in the separation and recovery of amino acid-based molecules from protein-based by- and co-products are discussed. Potato starch wastewater has a high chemical oxygen demand (COD) and contains high concentration of potassium, starch, proteins, and other organic materials (Zhu et al. 2016; Li et al. 2020). Despite the fact that effluent of potato starch during the production and processing phase only is about 10–20% of total wastewater generated, release of this portion without treatment is certain to result in significant environmental damage and the loss lots of valuable components such as proteins. Potato proteins usually used as animal feed and fertilizer while it can be processed into valuable food components due to their high nutritional content, antioxidant, and functional properties (Li et al. 2020). Hence, the separation of such value proteins from potato starch waste, as well as the safe treatment of this form of waste, become the most important aspects of potato starch wastewater treatment. Li et al. (2020) designed a new membrane processing for the recovery of potato protein. They tried to find a better method than Expanded Bed Absorption (EBA) that has been used for preparing potato protein powders with high molecular weight for food and low molecular weight protease inhibitor for medicine by the industry. They have argued that these methods not only fail to recover high yields of potato proteins, but they also consume a lot of energy and result in the complete loss of protein functionality, limiting their use (Li et al. 2020). They extracted and purified potato proteins from potato starch waste by the membrane technology process. Using a self-made hollow fiber (HF) UF and NF separation membrane integrated method, potato proteins were recovered and purified from simulated potato starch wastewater in a laboratory-scale research. The UF membrane was able to maintain 85.62% of the high-molecular-weight potato proteins in the potato starch wastewater, while the NF membrane rejected 92.1% of low-molecular-weight potato proteins.

Defatted corn germ (DCG) is a by-product of the corn oil extraction process. Minerals, calcium, and dietary fiber abound in DCG. DCG is currently primarily used as animal feed due to its nutritional content. The exploitation of DCG for human consumption has become necessary due to a rise in DCG demand around the world. Because of its high protein content, DCG is thought to be a good source of peptides with antihypertensive activity. Enzymatic hydrolysis is used to make peptides, and it is advantageous in terms of production rate and energy (Jang et al. 2008; Musa et al. 2020). Most of the time, the enzymatic hydrolysis and membrane separation methods are done separately, resulting in a lower peptide yield and a slow rate of protein conversion. Musa et al. (2020) designed a new continuous system of enzymatic hydrolysis coupled with membrane separation for isolation of peptides to improve peptide yield and operational capability. They separated peptides with ACE-inhibitory capacity obtained from ultrasonically pretreated defatted

corn germ protein (DCGP) by using a new continuous system of enzymatic hydrolysis coupled with membrane separation. The researchers noted that this method is a promising method for peptide creation with high ACE-inhibitory capacity from DCGP.

5 Electrodialysis with Ultrafiltration Membranes for the Separation of Proteins and Peptides

Bazinet et al. (2005) successfully developed and patented electrodialysis with ultrafiltration (EDUF), which contains of ultrafiltration and ion-exchange membranes packed in a traditional electrodialysis cell. The MWCO of a UF membrane allows for the concentration and filtration of solutes based on their sizes, whereas the electrodialysis (ED) method allows for the specific separation of molecules based on their electrical charges. Applying electrical field as only driven force is the great advantage of this technology which means no pressure is used in separation. Indeed, due to the lack of pressure, no substantial fouling at the membrane interface was observed. EDUF permits molecules to be separated based on their electric charges and molecular weights (Aider et al. 2008; Doyen et al. 2011a, 2014).

A traditional electrodialysis cell is applied in this procedure, but some ion-exchange membranes are replaced with UF membranes, allowing compounds with higher molecular weights than the membrane cut-off to be separated, extending the field of application of electrodialysis to biologically charged molecules. The simultaneous separation and concentration of migrating molecules will be another benefit of this method. In fact, if the recovery compartment has a smaller volume than the circulating feed solution, the migration molecule will be concentrated (Firdaous et al. 2009).

As mentioned in the previous section, the separation of bioactive peptides from their parent source is faced with some challenges. The most commonly used technologies for isolating bioactive peptides fractions or molecules are pressure-driven (UF and NF systems) and chromatographic processes. The use of column chromatography for the separation of bioactive peptides needs several modern column chromatography which can be time-consuming. In addition, peptide column yields can be low that making operation expensive (Wan et al. 2005; He et al. 2016). Also, it should be mentioned that this technique needs an expensive setup and skillful operators. Moreover, membrane separation techniques can separate bioactive peptides in a wide range based on molecular weight. However, low selectivity of usual membrane technologies like UF and MF for peptides with parallel molecular sizes and membrane fouling, the creation of novel and alternative separation processes is essential. Indeed, the hydrolysate's complexity and their peptides near molecular weight render it difficult to distinguish using traditional pressure-driven methods. Furthermore, after repeated usage, high-yield membrane separation may become

routinely obstructed, resulting in reduced recovering efficiency due to membrane fouling (Bazinet and Firdaous 2009; He et al. 2016).

The separation and recovery of bioactive compounds from a variety of food hydrolysates have already been demonstrated using EDUF technology. Since a number of bioactive peptides have been discovered in marine food processing by-products, there has been a growing interest in them (Harnedy and FitzGerald 2012; Suwal et al. 2014b). In the EDUF, the rate of peptide separation has been linked to UF membrane properties (MWCO and structure) as well as the electric field power used during treatment. However, pH was the most important factor in peptide separation selectivity and migration. Indeed, peptides are primarily positively charged at the pH < pI, whereas they are primarily negatively charged at pH > pI. The anode attracts negatively charged peptides, which migrate to the anionic compartment (KCl 1), while the cathode attracts positively charged peptides, which migrate to the cationic compartment (KCl 2), and neutral peptides remain in the hydrolysate compartment (Firdaous et al. 2010). Because the electric field is the driving force in EDUF, pH affects both the global charge of the peptides and their possible selective migration (as anionic or cationic molecules) (Fig. 6.3). pH is also reported to affect the surface charge of UF membranes. Thus, pH affects the selectivity and efficiency of UF membranes, as well as peptide membrane interactions and fouling (Roblet et al. 2013).

Within less than a decade, the EDUF technique has been widely hired to overcome the previously mentioned challenges during separation and purification of small healthy peptides from a complex solution. UF membrane characteristics, pH, electric field power, KCl concentration, and feed flow rate are all involved parameters in the EDUF process to improve peptide passage rate and selectivity (Doyen et al. 2011b; Suwal et al. 2014a).

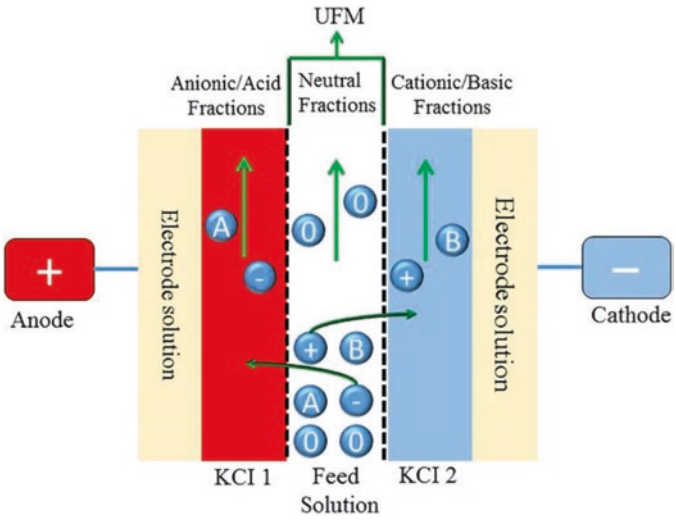

Fig. 6.3 Configuration of EDUF cell. UFM: ultrafiltration membrane

Firdaous et al. (2009) defined the EDUF process applied to the separation and concentration of bioactive peptides from the Alfalfa protein hydrolysate. In this project, they evaluated the possibility of EDUF to concurrently separate and concentrate basic and acid peptides from hydrolysate and discovered the experimental conditions that made it easier for target peptides, especially the antihypertensive peptide, to migrate. Alfalfa (*Medicago sativa*), a common crop in Europe and North America, yields around 2600 kilograms of protein per hectare. White hydrophilic proteins make up half of the proteins in alfalfa leaves, while green lipophilic proteins make up the other half. Because of their high digestibility, great functional properties, and equilibrated aminogram, white proteins are extremely useful in human nutrition. In an electrodialysis cell, two ultrafiltration membranes were loaded to create a configuration with two recovery compartments (KCl 1 and KCl 2). In these conditions, the impact of pH (3 and 9) on the migration of cationic and anionic peptides was investigated. It was discovered that EDUF can separate and concentrate charged peptides at the same time, with a transport rate of up to 7.3 g/m^2 h. Aside from selective separation, they showed that EDUF could solve some of the fouling issues that plague traditional pressure-driven processes. Actually, Firdaous et al. (2009) were able to separate bioactive peptides from Alfala hydrolysate using EDUF. However, they faced a lower transport rate of peptides. It seems that additional optimization is required in terms of pH control of the recovery compartment, longer operation times, enhancement in membrane area, and increase in the applied electric field strength.

Doyen et al. (2011a) investigated the selective isolation of peptides from a snow crab by-product hydrolysate using electrodialysis and ultrafiltration membranes, as well as the impact of the UF membrane material (polyethersulfone and cellulose acetate) on possible fouling. They reported that peptides with molecular weights ranging from 300 to 700 Da were successfully separated after a 6 h separation process. The success of EDUF to separate low molecular weight peptides is intriguing since the lowest molecular weight peptides have biological properties such as antihypertensive activity and antimicrobial properties. However, during the EDUF treatment, peptides with molecular weights ranging from 700 to 900 Da did not migrate. Furthermore, only the cellulose acetate UF membrane permitted the recovery of molecules with a high molecular weight (900–20,000 Da). They also represented that the low molecular peptides were the most adsorbed types at the UF membrane surface. Actually, electrostatic connections between the UF membrane material and the peptides do occur even when no pressure is applied in the system, opposing pressure-driven technologies. Furthermore, compared to pressure-driven technologies, where the formation of a solid gel layer was commonly observed, fouling during EDUF separation was very low.

Snow crab by-products were also subjected to the EDUF system for the separation of anticancer bioactive peptides by Doyen et al. (2011b). The authors´ findings demonstrated that peptides could travel in desired directions across ultrafiltration membranes when an electrical field was used between the electrodes. The chief yield was gained with a concentration of 285.1 μg/mL in the KCl 1 compartment at pH 9. In contrast to conventional separation pressure-driven processes, where

membrane fouling as a function of time is anticipated, EDUF ultrafiltration membranes showed no fouling. They also claimed that separated peptides at pH 6 showed anticancer activities.

Roblet et al. (2013), in comparative work, have investigated the effect of pH values on EDUF parameters and selective separation of peptides from soybean hydrolysate. During this work, they also examined changes in in-situ membrane electrical resistance during EDUF, changes in conductivity and peptide concentration of feed and recovery sections, and composition of final EDUF separated fractions. The pH value was found to have an impact on the composition of recovery compartments, but not on the rate of peptide migration, according to the findings. However, contrary to popular belief, even when the pH was raised, the migration rate in the anionic peptides recovery compartment (KCl 1) remained constant (no significant effect of pH was reported). Modifications in membrane selectivity could be caused by electrostatic repulsive/attractive interactions between membrane and peptides, as well as soft aggregation of high molecular weight peptides, which could be caused by pH changes. Furthermore, using EDUF technology at pH 9 appears to be an effective way to isolate cationic peptides with molecular weights less than 400 Da in the KCl 2 compartment while limiting the variety of anionic peptides in the KCl 1 compartment (Roblet et al. 2013).

Comprehension study of involving parameters in EDUF have been done during several types of research. Suwal et al. (2014a) considered the effect of ionic strength in the recovery of peptide and selectivity during EDUF of snow crab by-product hydrolysate. For the first time, they claimed that the cell configuration generated the greatest amount of peptide migration of about 14 g/m^{2}h with the lowest energy consumption. Furthermore, the researchers confirmed that in an EDUF configuration with 2 feeds and only 1 recovery compartment, KCl concentrations had no impact on peptide migration rate or energy consumption. Though, it has a huge effect on the selectivity of the EDUF system. In fact, higher KCl concentrations accelerated the migration of lower MW peptides (300–400 Da) (Suwal et al. 2014a).

In another work by Suwal et al. 2014b, the effect of cell configuration and local electric field in the EDUF process during peptide separation from snow crab hydrolysate were studied. They compared the effects of two EDUF cell configurations that used ultrafiltration membranes (20 and 50 kDa MWCO) on electrodialytic parameters including membrane resistance, electrical conductivity, peptide migration, and energy consumption. They firstly did the experiment with one feed and two recovery compartments and then with two feed and one recovery compartments. The peptide migration rate and selectivity, as well as the amino acid composition and peptide molecular weight summaries of the permeate segments found after 6 h of EDUF treatment, were significantly affected by the EDUF cell configurations. Configuration 1 resulted in a higher overall peptide migration rate of 6.00 g/m^{2}h than configuration 2, which was 4.41 g/m^{2}h. In configuration 1, on the other hand, the local electric field in the hydrolysate compartment decreased linearly during the EDUF phase, limiting peptide migration after about 2 h of EDUF treatment. The electric field in the hydrolysate compartment was found to be a rate-limiting

factor for peptide electromigration in this research. For the first time, the influence of local electric field evolution during EDUF separation was discovered in this research. Furthermore, cell structure has a major impact on the selectivity of the process, i.e., the composition of peptides (amino acids and molecular size), without influencing the amount of energy consumed. Consequently, this research clearly demonstrated that the EDUF cell configuration used in the separation of unique peptides from snow crab hydrolysate is critical (Suwal et al. 2014b).

Doyen et al. (2014) used electrodialysis to separate flaxseed protein bioactive peptides with two UF membranes (20 and 50 kDa) packed in the device to recover two distinct cationic peptide fractions (KCl-F1 and KCl-F2). They also characterized the recovered peptides to analyze the bioactivity of protein hydrolysate in terms of anti-diabetic activity and ACE inhibitory activity. In KCl compartments, peptide migration increased as a function of time after 6 h of treatment. Furthermore, when compared to the initial hydrolysate, the use of two different ultrafiltration membranes enabled recovering of the 300–400 and 400–500 Da molecular weight range peptides in the KCl-F1 and KCl-F2 fractions, respectively. Finally, the researchers reported that stacking two UF membranes with different MWCOs in the EDUF system adds another parameter to the separation of complex polypeptide mixtures and could open up a new path for the simultaneous processing of peptide fractions with different biological activities while avoiding membrane fouling (versus pressure-driven filtration technologies) (Doyen et al. 2014).

Rapeseed protein hydrolysate was subjected to the EDUF for separation and concentration of the antihypertensive peptides (He et al. 2016). The EDUF was able to concentrate cationic and anionic peptide chains in two different compartments after 6 h running. Protein hydrolysates with positively charged peptides could be better antihypertensive agents than negatively charged counterparts, based on in vitro enzyme inhibitory effects.

Suwal et al. (2018) also applied the EDUF technique for the separation of the bioactive peptides from rainbow trout fish protein hydrolysates to define their antioxidant properties. They also studied the possible separation of anionic and cationic peptides. They observed much better the peptide migration rate rather than other research with 19.55 ± 2.19 and 10.94 ± 0.39 g/m^2 h for the cationic and anionic separation, respectively. The antioxidant activity of the cationic and anionic peptide fractions recovered from hydrolysate using EDUF was more than twofold higher. As a result of this research, EDUF has been shown to be an efficient method for recovering antioxidant peptides from enzymatic hydrolysates of fish protein by-products (Suwal et al. 2018). Finally, the separation of protein and peptide by EDUF is based on their sizes using filtration membrane with sieving effect, and also the peptides' net charge using electric potential difference as a driving force for migration. Although the efficacy (i.e. peptide migration rate) of this technique is lower than that of traditional membranes, and it is still not commercially available, it is very selective, and the separated peptides have significantly improved bioactivity (Doyen et al. 2011a; Roblet et al. 2016; Suwal et al. 2018).

6 Conclusions

Peptides, especially small peptides with a molecular weight lower than 1000 g/mol, are small molecules with a diverse range of functional, nutritional, and biological properties. Hence, the pharmaceutical, food, and cosmetic industries are all very interested in them. However, the industrial processing of small peptides contained in food-based protein is slowed by two blockages. To begin, small peptides coexist with amino acids, oligopeptides, and a variety of other compounds in an extremely complex mixture. Second, active peptides normally have unique physicochemical property, such as charge, that is critical to their function. Separation and fractionation are thus essential for the effecient use of peptide sources. Membrane technology can effectively apply for this purpose. In this regard, UF and NF membrane technologies represented great results in purification and recovery of protein and peptides from different animal or plant sources. Also, the food industry could benefit from EDUF membrane technology, especially for the separation and recovery of bioactive compounds from a variety of by- and co- products.

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Chapter 7
Separation of Polyphenols and Carotenoids Using Nanofiltration

Senem Kamiloglu, Tugba Ozdal, Gizem Catalkaya, and Esra Capanoglu

Abstract Nowadays, the application of membrane technologies in the food industry attracted attention due to increasing interest towards environmentally friendly processing procedures as well as the production of foods with higher nutritional value. Nanofiltration, a pressure-driven membrane operation, became an economically appealing technology in the food industry for the concentration, fractionation and purification of several different compounds. In particular, the nanofiltration process showed to be efficient for the recovery of polyphenols and carotenoids. As polyphenols and carotenoids are sensitive to high temperatures, the application of nanofiltration procedure at relatively low temperatures is advantageous for their stability. In this chapter, an overview of the recent developments and future potentials of nanofiltration processes used for the separation of polyphenols and carotenoids are highlighted. The studies in this regard suggested that nanofiltration, although still evolving, established a high separation efficiency of polyphenols and carotenoids and is a promising technology to achieve a cost-effective process.

Keywords Nanofiltration · Membrane · Polyphenols · Flavonoids · Carotenoids · Carotenes

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1 Introduction

Membrane separation technologies stand out as alternatives to traditional processes for the chemical, medicinal, biotechnological and food industries. In some of these cases, the main attractions of these systems are reduced energy consumption, reducing of the number of manufacturing phases, better reliability of separation and increased consistency of the finished product (Strathmann 1990). The application of hydraulic pressure as the driving factor for mass transport is the factor which separates the more common membrane separation processes-microfiltration, ultrafiltration, nanofiltration and reverse osmosis. Nevertheless, since they are specifically extracted due to their molar masses or particle size, the structure of the membrane determines which compounds will permeate and which will be maintained (Cheryan 1998).

The fluid flow, whether liquid or gaseous, is perpendicular to the membrane surface in a traditional filtration system, so that solids settle on it, causing frequent disruption of the filter cleaning or replacement process. The fluid flow is perpendicular to the surface of the membrane in tangential membrane filtration, and due to its high velocity, the solutes that appear to settle on the membrane are removed away, making the process more effective (Paulson et al. 1984).

Microfiltration utilizes pressures under 0.2 MPa and distinguishes molecules between 0.025 and 10 μm, ultrafiltration needs pressures exceeding 1 MPa and distinguishes particles with molecular masses between 1 and 300 kDa, nanofiltration requires pressures within 1 and 4 MPa and distinguishes particles with molecular masses within 350 and 1000 Da, while reverse osmosis requires pressures between 1 and 4 MPa (Nakao 1994). The pore size of a membrane is usually suggested in the literature and primarily by the producers, by means of the molecular weight cut-off (MWCO), which specifies the molar mass of the tiniest fraction that will be maintained with an efficiency of at least 95 per cent. Nanofiltration has been used successfully to concentrate bioactive compounds derived from food products (Chiu et al. 2009).

In this chapter, nanofiltration applications for the recovery of polyphenols and carotenoids from various food matrices will be reviewed in detail.

2 Nanofiltration Applications for the Recovery of Polyphenols

2.1 Flavonoids

Flavonoids are compounds of low molecular weight, consisting of 15 carbon atoms organized in a $C_6{-}C_3{-}C_6$ configuration. The structure of flavonoids consists of two aromatic rings, linked through a three-carbon bridge, usually in a heterocyclic ring form. Alterations in this heterocyclic ring's substitution pattern generate six distinct

subclasses, i.e., flavonols, flavanols, flavones, flavanones, isoflavones and anthocyanidins (Balasundram et al. 2006). Epidemiological studies reported that diets rich in flavonoids provide several benefits associated with health-promoting effects by reducing the risk of development of chronic diseases such as cardiovascular diseases, diabetes type II and certain types of cancers (Domínguez-Avila et al. 2017). Considering that the research on the extraction of flavonoids from natural sources attracted great attention in the last several decades. Conventional extraction methods may cause the degradation of flavonoids due to high temperature and long extraction times or they may cause health risks (Azmir et al. 2013). On the other hand, pressure-driven membrane processes such as nanofiltration is reported to be an effective alternative for the concentration of flavonoids from natural sources (Table 7.1).

Grape (*Vitis vinifera* L.) is one of the major fruit crops in the world, which can be consumed raw or processed into other products. Although several grape-based food products are present in the market, studies have shown that approximately 75% of the world grape production is utilized in the wine industry. Grape pomace, representing 25% of total grape weight, is an abundant by-product from the wine industry, which is comprised of the skin, seeds and stalks (Beres et al. 2017). The by-products of the wine processing industry are reported to be rich in flavonoids, particularly in monomeric flavan-3-ols and oligomeric proanthocyanidins (De la Cerda-Carrasco et al. 2015). Membrane separation processes such as nanofiltration is an alternative approach to conventional methods for the separation of these bioactive compounds from the by-products of the wine processing industry. In one of the earliest reports on this topic (Santamaría et al. 2002), polyphenolic extract from defatted milled grape seeds was nanofiltered using AFC40 membrane to remove the low molecular weight acids and aldehydes, followed by ultrafiltration using PU608 and PU120 membranes. The retentate obtained from ultrafiltration was then microfiltered with FP200 membrane to obtain a purified solution of oligomeric proanthocyanidins. Finally, a PU608 ultrafiltration membrane was used for the fractionation of proanthocyanidins into two fractions: (i) a pure solution composed of dimers and trimers and (ii) a solution enriched in oligomeric proanthocyanidins (Santamaría et al. 2002). In another study (Díaz-Reinoso et al. 2009), aqueous extracts from distilled fermented grape pomace were purified using different commercial ultrafiltration and nanofiltration membranes made of composite polyamide, polymeric, and ceramic materials to obtain fractions enriched in polyphenols. Although Inside Céram membrane resulted in extracts with the highest polyphenol content (52%), all other tested membranes were also reported to have similar rejections for the polyphenols and hence were found to be suitable for concentration applications (Díaz-Reinoso et al. 2009). Giacobbo et al. (2013) evaluated three laboratory-made cellulose acetate membranes (CA400-22, CA400-26 and CA400-28) and two commercial nanofiltration membranes (NF270 and ETNA01PP) for the separation of polyphenols from winery effluents. Among the tested membranes, NF270 showed the highest rejection for polyphenols (93.8%), whereas ETNA01PP membrane displayed the lowest rejection (27%) (Giacobbo et al. 2013). The same research group (Giacobbo et al. 2017) also applied ultrafiltration and nanofiltration techniques

Table 7.1 Nanofiltration applications for the recovery of flavonoids

Material	Tested membranes				Selected membrane(s)	Polyphenol rejection	Reference
	Membrane	Supplier	Polymer	MWCO (Da)			
Grape by-products	AFC40	n/a	Polyamide	60% $CaCl_2$	Used in sequence	100%	Santamaría et al. (2002)
	PU608		Polysulphone	8000			
	PU120		Polysulphone	20,000			
	FP200		Polyvinilidene fluoride	20,0000			
	Nanomax 95	Millipore	Polyamide/ Polysulphone	250	Inside Céram	52%	Díaz-Reinoso et al. (2009)
	Nanomax 50	Millipore	Polyamide/ Polysulphone	350			
	DL2540	Osmonics	Thin film	150–300			
	GE2540	Osmonics	Thin film	1000			
	Inside Céram	Tami	Titania	1000			
	CA400–22	Laboratory made	Cellulose acetate	n/a	NF270	93.8%	Giacobbo et al. (2013)
	CA400–26	Laboratory made	Cellulose acetate				
	CA400–28	Laboratory made	Cellulose acetate				
	NF270	Filmtec Corp., Minneapolis, MN, USA	Polypiperazine				
	ETNA01PP	Alfa Laval, Nakskov, Denmark	Fluoropolymer				

	NF270	Filmtec Corp., Minneapolis, MN, USA	Polypiperazine fluoropolymer	200–300	Used in sequence	ACN: 100%	Giacobbo et al. (2017)
	ETNA01PP	Alfa Laval, Nakskov, Denmark	Fluoropolymer	1000		TPC: >90%	
	ETNA10PP	Alfa Laval, Nakskov, Denmark		10,000			
	M-U2540	AMI membranes	Polyacrylonitrile	20,000	HYDRACoRe 70pHT	91.9%	Kontogiannopoulos et al. (2017)
	HYDRACoRe 70pHT	Hydranautics	Sulfonated polyethersulfone	720			
	NF270	Dow Filmtec	Polypiperazine	97% $MgSO_4$			
	NF90	Dow Filmtec	Polyamide	97% $MgSO_4$			
	ESP04	PCI membranes	Modified polyethersulfone	4000			
	HFW1000	Pentair	Modified polyethersulfone	1000			
	NF270	Filmtec Corp., Minneapolis, MN, USA	Polypiperazine	300	NF270	>90%	Giacobbo et al. (2018)
	ETNA01PP	Alfa Laval, Nakskov, Denmark	Fluoropolymer	1000			

(continued)

Table 7.1 (continued)

Material	Tested membranes				Selected membrane(s)	Polyphenol rejection	Reference
	Membrane	Supplier	Polymer	MWCO (Da)			
	MS19	GE Osmonics, Minnetonka, MN, USA	Polyamide	125–200	MWCO of 150–400 Da for FLV and ACN	FLV: 95.4%	Yammine et al. (2019)
	DL	GE Osmonics, Minnetonka, MN, USA	Thin film	150–300		ACN: 95.9%	
	HL	GE Osmonics, Minnetonka, MN, USA	Thin film	150–300			
	NF	Alfa Laval	Polyamide	200–400			
	DK	GE Osmonics, Minnetonka, MN, USA	Polyamide	300–600			
	MX-07	GE Osmonics, Minnetonka, MN, USA	Polyamide	500–1000			
	BQ-01	GE Osmonics, Minnetonka, MN, USA	Polyamide	1000			
	ETNA01PP	Alfa Laval	Fluoropolymer	1000			
Citrus by-products	DCQ-III	China blue star mem. Technology	Polysulphone	100,000	Inopor® nano	91–99%	Conidi et al. (2011)
	Etna 01PP	Alfa Laval	Fluoropolymer	1000			
	Inopor® nano	Inopor	TiO_2	750			
	Inopor® nano	Inopor	TiO_2	450			

	NF-70	Dow Filmtec	Polyamide/ Polysulphone	180	NFPES10	ACN: 89.2%	Conidi et al. (2012)
	NF-200	Dow Filmtec	Polypiperazine	300		FLV: 70%	
	N30F	Microdyn Nadir	Polyethersulfone	400			
	NFPES10	Microdyn Nadir	Polyethersulfone	1000			
	NF270	Dow Filmtec	Polypiperazine	150–250	NFPES10	88.4–90.1%	Conidi and Cassano (2014)
	N30F	Microdyn Nadir	Polyethersulfone	400			
	NFPES10	Microdyn Nadir	Polyethersulfone	1000			
Aronia	SEPA ST	Osmonics	n/a	n/a	SEPA ST	>99%	Gilewicz-Łukasik et al. (2007)
Strawberry juice	n/a	PAM selective membranes	Polyamide	n/a	Used in sequence	P3G: 95%	Arend et al. (2017)
	n/a	GE Osmonics	Polyvinylidene difluoride	150–300			
Blackberry juice	NF270	Dow Filmtec	Polypiperazine, composite	150–300	NF270	ACN: >94%	Acosta et al. (2017)
	UTC60	Toray	Polyamide, composite	n/a		ET: 100%	
	MPF36	Koch membrane systems	Composite	n/a			
	DL	GE Osmonics	Polyamide, polysulphone	150–300			
	DK	GE Osmonics	Polypiperazine, polysulphone	150–300			
	NP010	Microdyn Nadir	Polyethersulphone	n/a			
	NP030	Microdyn Nadir	Polyethersulphone	n/a			

(continued)

Table 7.1 (continued)

Material	Tested membranes				Selected membrane(s)	Polyphenol rejection	Reference
	Membrane	Supplier	Polymer	MWCO (Da)			
Blueberry pomace	NF270	Filmtec Corp., Minneapolis, MN, USA	Polyamide	200–400	Both	>97%	Avram et al. (2017)
	NF245	Filmtec Corp., Minneapolis, MN, USA	Polyamide	200–400			
Elderberry juice	Etna 01 PP	Alfa Laval	Fluoropolymer	1000	NP030	>75%	Tundis et al. (2018)
	NP010	Microdyn Nadir	Polyethersulphone	1000			
	NP030	Microdyn Nadir	Polyethersulphone	400			
Pomegranate by-products	Etna 01PP	Alfa Laval	Fluoropolymer	1000	Desal GK	ACN: 90.7%	Conidi et al. (2017)
	PES 004H	Microdyn Nadir	Polyethersulphone	4000		TPC: 84.8%	
	SelRO MPF-36	Koch	Thin film	1000			
	Desal GK	GE	Thin film	2000			
	NF270	Dow Filmtec	Polyamide	155–200	NF270	≥98%	Papaioannou et al. (2020)
Pequi	NF-90	Dow Filmtec, São Paulo, SP, Brazil	Polyamide	200–300	NF-90	97%	Machado et al. (2013)
Watermelon juice	HL2521TF	GE Osmonics, Minnetonka, USA	Polyvinylidene difluoride	150–300	HL2521TF	96%	Arriola et al. (2014)
Jamun seeds	n/a	Alfa Laval Pvt. ltd., India	Polyethersulphone	25, 50, 100	Used in sequence	79.8–84.6%	Balyan and Sarkar (2016)
	n/a	Permionics membranes Pvt. ltd., India	Polyethersulphone	250,400, 1000			

Apple pomace	DuraMem200	Evonik, Germany	Polyamide	200	NFX	98–99%	Uyttebroek et al. (2018)
	Desal-5 DK	GE Osmonics, USA	Polyamide	150–350		Catechin: 83%	
	NFX	Synder filtration, USA	Polyamide	150–300		Epicatechin: 93%	
	NF90	Dow Filmtec, USA	Polyamide	n/a			
	DuraMem300	Evonik, Germany	Polyamide	300			
	NF030306	SolSep, Netherlands)	Polyamide	n/a			
	NanoPro AS3012	AMS technologies, Israel	Polyamide	180			
Jussara	NP010	Microdyn Nadir	Polyethersulfone	1000	Desal 5-DK	ACN: 98%	Vieira et al. (2018)
	NP030	Microdyn Nadir	Polyethersulfone	400			
	NF90	Dow Filmtec	Polyamide, composite	180			
	NF270	Dow Filmtec	Polyamide, composite	340			
	Desal 5-DK	GE Osmonics	Polyamide, composite	150–300			
	Desal 5-DL	GE Osmonics	Polyamide, composite	150–300			
Artichoke by-products	DCQ III-006C	China blue star membrane technology	Polysulphone	50,000	Desal DL	A7G: 100%	Conidi et al. (2014)
	NP030	Microdyn Nadir	Polyethersulfone	400			
	Desal DL	GE Water & Process Technologies	Polyamide	150–300			
	NP030	Microdyn Nadir	Polyethersulfone	400	Used in sequence	Apigenin: >85%	Cassano et al. (2015)
	Desal DL	GE Water & Process Technologies	Polyamide	150–300			
	Inside ceram	Tami Industries	TiO_2	15,000	Used in sequence	A7G: 100%	Conidi et al. (2015)
	NF 270	Dow-Filmtec	Polyamide	200–300			

(continued)

Table 7.1 (continued)

Material	Tested membranes				Selected membrane(s)	Polyphenol rejection	Reference
	Membrane	Supplier	Polymer	MWCO (Da)			
	NP010	Microdyn Nadir	Polyethersulfone	1000	MWCO of 200 Da	>92%	Cassano et al. (2016)
	NP030	Microdyn Nadir	Polyethersulfone	400			
	NF200	Filmtec-Dow	Piperazineamide	300			
	Desal DL	GE	Polyamide	150–300			
	Desal DK	GE	Polyamide	150–300			
	NF270	Dow FilmTec	Polyamide	200–400	All	80–90%	Rabelo et al. (2016)
	DK	GE Osmonics	Polyamide	200			
	DL	GE Osmonics	Polyamide	150–300			
Mate	HL2521TF	Osmonics membranes Minnetonka, USA	Polyvinylidene difluoride	150–300	HL2521TF	99%	Prudêncio et al. (2012)
Roselle	NF 90	Dow FilmTec	Polyamide	200–400	All	93–100%	Cissé et al. (2011)
	NF 200	Dow FilmTec	Polyamide	200–400			
	NF270	Dow FilmTec	Polyamide	200–400			
	UTC60	Toray	Polyamide	n/a			
	MPF36	Koch membrane	Composite	n/a			
	MPF34	Koch membrane	Composite	n/a			
	DL	GE Osmonics	Polyamide polysulfone	150–300			
	DK	GE Osmonics	Polyamide polysulfone	150–300			
	NP010	Microdyn Nadir	Polyethersulphone	n/a			
	NP030	Microdyn Nadir	Polyethersulphone	n/a			

Sideritis ssp. L.	Starmem™ 240	Membrane extraction technology ltd., UK	Polyimide	400	Duramem™ 300	100%	Tylkowski et al. (2011)
	Duramem™ 300	Membrane extraction technology ltd., UK	Modified polyimide	300			
	Duramem™ 500	Membrane extraction technology ltd., UK	Modified polyimide	500			
Eucalyptus bark	JW	GE Osmonics	Polyvinylidene fluoride	30,000	JW	FCT: 17%	Pinto et al. (2014)
	PLEAIDE	Orelis Environnement	Polyethersulfone	5000		PCA: 28%	
	90,801	SolSep	Polyamide	350			
Cocoa seeds	DL	GE Osmonics	n/a	n/a	All	80–95%	Sarmento et al. (2008)
	HL	GE Osmonics					
	NF	Dow FilmTec					
	NF-90	Dow FilmTec					
Propolis	NF90	Osmonics, Minnetonka, USA	Polyamide, polysulphone	n/a	NF90	AE: 99%	Mello et al. (2010)
						EE: 90%	
	Starmem™ 122	Membrane extraction technology ltd., UK	Polyimide	220	Used in sequence	>95%	Tylkowski et al. (2010)
	Duramem™ 200	Membrane extraction technology ltd., UK	Modified polyimide	200			
	Duramem™ 900	Evonik mem. Extraction technology ltd., UK	Modified polyimide	900	Used in sequence	30–94%	Tsibranska et al. (2011)
	Duramem™ 500	Evonik mem. Extraction technology ltd., UK	Modified polyimide	500			
	Duramem™ 300	Evonik mem. Extraction technology ltd., UK	Modified polyimide	300			

ACN Anthocyanins, *AE* Aqueous extract, *A7G* Apigenin 7-*O*-glucoside, *EE* Ethanolic extract, *ET* Ellagitannins, *FCT* Formaldehyde-condensable tannins, *FLV* Flavonoids, *MWCO* Molecular weight cut-off, *PCA* Proanthocyanidins, *P3G* Pelargonidin 3-*O*-glycoside, *TPC* Total phenolic content, *n/a* not available

using a series of membranes with decreasing MWCO to fractionate and purify polyphenols from wine lees. Ultrafiltration membrane with MWCO of 10,000 Da was more advantageous in terms of separation of the polyphenols from the polysaccharides. Moreover, nanofiltration membrane retained all the anthocyanins and more than 90% of the total polyphenols (Giacobbo et al. 2017). In another study by the same researchers (Giacobbo et al. 2018), ultrafiltration/nanofiltration of the winery wastewaters was performed with ETNA01PP and NF270 membranes under a wide range of cross-flow velocities and transmembrane pressures up to 15 bar. The results highlighted that concentration polarization increases with the increased transmembrane pressure and under low cross-flow velocities (Giacobbo et al. 2018). Another study on the recovery of polyphenols from winery waste lees (Kontogiannopoulos et al. 2017) assessed several ultrafiltration and nanofiltration membranes for their efficiency in separating tartaric acid and polyphenols. The 70pHT membrane displayed good separation of polyphenols (91.9%) and low-fouling filtration performance (Kontogiannopoulos et al. 2017). A recent study (Yammine et al. 2019) investigated nine commercial nanofiltration membranes with MWCO of 150–1000 Da for the separation of polyphenols from grape pomace extracts. The membranes having MWCO of 500–1000 were able to recover polymeric proanthocyanidins, whereas membranes with MWCO of 300–600 were found to be useful for the fractionation of monomeric compounds. The rejections towards polymeric flavan-3-ols were high (59.3–100%), whereas for catechin the range was rather variable (23.0–99.4%). Furthermore, the membranes with the lower MWCO range (150–400 Da) showed high average rejection towards flavonoids and anthocyanins (95.9%) (Yammine et al. 2019).

Besides the grape by-products, other flavonoid-rich fruits such as citrus fruits, berries, pomegranate and several others are also examined for extraction of polyphenols using membrane separation processes. Conidi et al. (2012) investigated the potential of a nanofiltration process for the separation and concentration of flavonoids from orange press liquor obtained after blood orange peel processing. Four different spiral-wound nanofiltration membranes with different MWCO (250–1000 Da) and polymeric material (polyamide, polypiperazine amide, polyethersulphone) were evaluated. The results revealed that among the tested membranes, NFPES10 membrane showed the highest rejections towards anthocyanins (89.2%) and other flavonoids (70%) (Conidi et al. 2012). Bergamot (*Citrus Bergamia Risso*) is another member of the citrus family that is widely used in the cosmetic and perfume industry for essential oil production. On the other hand, the juice containing a high amount and variety of flavonoids is regarded as a waste material. Considering that Conidi et al. (2011) investigated the recovery of polyphenols from bergamot juice using membrane-based processes including ultrafiltration and nanofiltration. Initially, bergamot juice was ultrafiltrated to remove suspended solids, followed by different ultrafiltration and nanofiltration treatments for the evaluation of MWCO on the rejection of polyphenols as well as sugars and organic acids. The best polyphenol separation was achieved with the nanofiltration membrane with a MWCO of 450 Da (91–99%) (Conidi et al. 2011). In another study by the same researchers (Conidi and Cassano 2014), three commercial nanofiltration membranes

with different MWCO and polymeric material (NFPES10, N30F and NF270) were studied for the recovery of flavonoids from bergamot juice. Among the tested membranes, NFPES10 showed high rejections towards flavonoids (88.4–90.1%) (Conidi and Cassano 2014). Aronia, a violet-black fruit-berry native to North America, contains a significant amount of anthocyanins (Wu et al. 2017). According to the study by Gilewicz-Łukasik et al. (2007), Aronia anthocyanins were almost completely rejected (more than 99%) by the tested nanofiltration membrane in the presence of sodium sulfate (IV). In a study by (Arend et al. 2017), anthocyanin-rich strawberry (*Fragaria X ananassa Duch*) juice was concentrated with microfiltration followed by nanofiltration. As a result, the major anthocyanin compound, i.e., pelargonidin 3-*O*-glycoside, presented retention up to 95% (Arend et al. 2017). Blackberry (*Rubus adenotrichos* Schltdl.) juice, which is rich in anthocyanins and ellagitannins, was also concentrated using various nanofiltration membranes. Each tested membrane presented 100% of total ellagitannin retention, whereas, at a volumetric reduction ratio of 1, more than 94% of the total anthocyanins were retained. Overall, NF270 membrane at 3 MPa demonstrated the highest potential for concentration of blackberry polyphenols (Acosta et al. 2017). Blueberry (*Vaccinium corymbosum*) pomace, the remaining solid residue of juice processing, is a fruit by-product that includes a high content of monomeric and polymeric anthocyanins. Avram et al. (2017) used two different nanofiltration membranes to extract anthocyanins, flavonols and other phenolics from blueberry pomace. Both membranes (NF270 and NF245) exhibited good retention of total polyphenols (more than 97%), while the cross-flow mode of filtration was found to reduce membrane fouling considerably (Avram et al. 2017). Similarly, concentration of the polyphenols from elderberry (*Sambucus nigra* L.) juice was investigated using three commercial nanofiltration membranes with different MWCO (400 and 1000 Da) and polymeric material (composite fluoro-polymer and polyethersulphone). All selected membranes exhibited good rejections towards anthocyanins (cyanidin 3-*O*-sambubioside and cyanidin 3-*O*-glucoside), rutin and astragalin (more than 75%) and lower rejections towards catechin and protocatechuic acid (25–42%). The NP030 membrane, a polyethersulphone membrane with a MWCO of 400 Da, showed the highest rejection towards polyphenols compared to the other two nanofiltration membranes (Tundis et al. 2018). Another study on the separation of polyphenols, including anthocyanins, ellagic acid, phytoestrogenic flavonoids and tannins, from pomegranate juice tested different ultrafiltration and nanofiltration membranes with nominal MWCO ranging from 1000 to 4000 Da. Among the investigated membranes the Desal GK, with a MWCO of 2000 Da, showed higher productivity, lower fouling index and good cleaning efficiency compared to other membranes. The yields of polyphenols and anthocyanins in the retentate stream were 84.8% and 90.7%, respectively (Conidi et al. 2017). A recent study by Papaioannou et al. (2020) also used nanofiltration process to concentrate the polyphenols from pomegranate husk. The results revealed an optimum membrane performance at 10 bar pressure and pH 6, with high polyphenol retention (≥98%) (Papaioannou et al. 2020). Concentration of polyphenols from pequi (*Caryocar brasiliense* Camb.), a typical Brazilian fruit, is studied by Machado et al. (2013). The authors showed that 97% of polyphenols were

retained from aqueous pequi extract, whereas only 15% retention was observed in the case of a 95% ethanol extract using a NF90 membrane. This big difference in retention between aqueous and ethanol extracts was explained by the hydrophilic nature of the NF90 membrane (Machado et al. 2013). Arriola et al. (2014) evaluated the potential of nanofiltration for the concentration of bioactive compounds from watermelon (*Citrullus lanatus*) juice and reported good recovery of flavonoids (96%). Similarly, the phenolic compounds from the seeds of jamun (*Syzygium cumini* L.) fruit, native to India, were purified and concentrated successfully using integrated ultrafiltration and nanofiltration membranes (Balyan and Sarkar 2016). In another study (Uyttebroek et al. 2018), a commercial nanofiltration membrane NFX was utilized to concentrate polyphenols from apple pomace. The results showed that for the aqueous ethanolic extract of apple pomace, the average retention of the polyphenols was 98–99%, except for catechin (83%) and epicatechin (93%), due to their relatively low molecular weight (290 Da). These observations were explained by the MWCO of the NFX membrane of 150–300 Da (Uyttebroek et al. 2018). Extracts of anthocyanin-rich jussara (*Euterpe edulis*) fruits, native to Brazil, were concentrated by nanofiltration using six commercial flat-sheet membranes with nominal MWCO ranging from 150 to 1000 (NF270, NF90, NP010, NP030, Desal 5-DK and Desal 5-DL). NF270, NF90, Desal 5-DK and Desal 5-DL membranes were effective in retaining cyanidin 3-*O*-rutinoside and cyanidin 3-*O*-glucoside equally, whereas NP010 and NP030 membranes performed high selectivity only for cyanidin 3-*O*-rutinoside. Overall, Desal 5-DK membrane displayed the highest anthocyanin retention capacity (98%) (Vieira et al. 2018).

Artichoke (*Cynara scolymus* L.) is a rich source of polyphenols including flavonoids such as apigenin and luteolin as well as their 7-*O*-glucosides. By-products from the artichoke processing industry including leaves, external bracts and stems comprise approximately 80–85% of the total biomass of the plant. Blanching waters also represent an additional residue of the artichoke processing industry. These by-products are generally used as animal feed or discarded; however, they could be used as a source of polyphenols (Lattanzio et al. 2009). Conidi et al. (2014) investigated an integrated membrane process based on the utilization of ultrafiltration and nanofiltration to separate polyphenols from artichoke wastewaters. First, ultrafiltration process was applied using a hollow fibre membrane (DCQ III-006C) to remove suspended solids. Subsequently, two different nanofiltration membranes, NP030 and Desal DL, were used for the separation of polyphenols from sugars. Compared to the initial juice (61 mg/L), a higher amount of apigenin 7-*O*-glucoside was found in the ultrafiltration feed (100 mg/L). The permeate stream of the Desal DL membrane did not contain apigenin 7-*O*-glucoside, whereas NP030 membrane displayed a lower rejection towards this compound (82%). This process allowed the production of a retentate with high polyphenol content, which could be utilized in the food, nutraceutical, or cosmeceutical industry (Conidi et al. 2014). The same researchers (Cassano et al. 2015) also used two nanofiltration membranes (NP030 and Desal DK) in a sequential design to separate polyphenols from aqueous artichoke extracts. In optimized operating conditions (4 bar, 25 °C), NP030 membrane exhibited high rejections of apigenin (more than 85%). After the permeate from the NP030

membrane was processed with the Desal DK membrane, a stream free of both polyphenols and sugars was obtained, which can be reused for irrigation or recycled in the artichoke processing industry (Cassano et al. 2015). In another study by the same research group (Conidi et al. 2015), the combination of membrane processes (ultrafiltration as a pre-treatment followed by nanofiltration) and polymeric resins was applied for the selective purification of polyphenols from artichoke wastewaters. The content of apigenin 7-*O*-glucoside in the permeate after ultrafiltration was 6% lower than the feed solution, whereas no polyphenols were detected after nanofiltration process. Among the three different tested macroporous resins, S7968 presented the highest adsorption ratio for apigenin 7-*O*-glucoside (100%), followed by S6328 (99.88%) and S2328 (85.70%). The authors reported that the low adsorption ratio of the S2328 resin may be related to the low affinity of the analyzed compounds with cation exchangers (Conidi et al. 2015). Cassano et al. (2016) further examined the recovery of flavonoids from artichoke brines using five commercial spiral-wound nanofiltration membranes (NP010, NP030, NF200, Desal DL and Desal DK) with different polymeric materials (polyethersulphone, polyamide) and MWCO (200–1000 Da). The results showed that the majority of flavonoids (more than 92%) were recovered with nanofiltration membranes of 200 Da (Cassano et al. 2016). Another study Rabelo et al. (2016) evaluated the sequential process based on the use of ultrasound extraction and membrane technology for the recovery of polyphenols from artichoke solid wastes. Different solvent compositions (0–75% ethanol), ultrasound power (0–720 W) and nanofiltration membranes (NF270, DK and DL) were evaluated and the results revealed that the most suitable conditions to obtain the highest polyphenol recovery was 50% ethanol, 240 W ultrasound power and nanofiltration using DK membrane (Rabelo et al. 2016).

In addition to fruits and vegetables, some other plants are also utilized for polyphenol extraction using nanofiltration process. For example, mate (*Ilex paraguariensis* A. St. Hil), an important plant from the subtropical region of South America, is rich in different biologically active compounds including flavonoids (Murakami et al. 2011). Accordingly, Prudêncio et al. (2012) investigated the concentration of major polyphenols from aqueous extract of mate bark using nanofiltration technology and concluded that 99% of the polyphenols were retained in concentrates. Another study tested ten nanofiltration flat-sheet membranes and eight tight ultrafiltration membranes with various nominal MWCOs (0.2–150 kDa) to concentrate anthocyanin extract from roselle (*Hibiscus sabdariffa* L.). For all the tested nanofiltration membranes, retention of total anthocyanins ranged between 93–100% (Cissé et al. 2011). Tylkowski et al. (2011) used three nanofiltration membranes (Starmem™ 240, Duramem™ 300, Duramem™ 500) to concentrate flavonoids from *Sideritis ssp*. L, an endemic plant for the Balkan Peninsula. The authors demonstrated that Duramem™ 300 membrane performed complete rejection of polyphenols including flavonoids. Moreover, separation of flavonoids from low molecular compounds was possible at MWCO more than 400 Da (Tylkowski et al. 2011). Another plant that is utilized for the concentration of polyphenols was *Eucalyptus* bark, which is evaluated using two ultrafiltration (JW and PLEAIDE) and one nanofiltration (SolSep 90801) membranes. All the tested membranes displayed selective retention of

polyphenols, however, JW membrane promoted the highest enrichment of formaldehyde-condensable tannins (17%) and proanthocyanidins (28%) (Pinto et al. 2014). Cocoa and propolis are among other products that are studied for flavonoid concentration using nanofiltration membranes. Sarmento et al. (2008) concentrated the polyphenols from cocoa seeds using commercial nanofiltration polymeric membranes, (DL, HL, NF and NF-90). The results of the study revealed that the tested membranes showed polyphenol rejections of 80–95% (Sarmento et al. 2008). Flavonoids and other phenolic compounds from aqueous and ethanolic extract of propolis were concentrated through nanofiltration using NF90 membrane. For aqueous solution, the membrane retained approximately 99% of the flavonoids, whereas for the ethanolic solution this value was 90% (Mello et al. 2010). Similarly, Tylkowski et al. (2010) reported the sequential concentration of the propolis extract by nanofiltration using two membranes (Starmem™ 122 and Duramem™ 200) and achieved rejections of more than 95% with the Duramem™ 200 membrane. In another study by the same researchers (Tsibranska et al. 2011), membranes with different MWCO (300–900 Da) were used to fractionate flavonoids from propolis extract. Rejections for total polyphenols and flavonoids ranged from 30% (900 Da) up to 94% (300 Da membrane).

2.2 Non-flavonoids

Non-flavonoid compounds include phenolic acids, tannins, stilbenes, lignans and other polar compounds such as tyrosol and hydroxytyrosol. Phenolic acids are divided into two subgroups: (i) hydroxybenzoic acids having C_6–C_1 structure, and hydroxycinnamic acids with a three-carbon side chain (C_6–C_3) (Balasundram et al. 2006; Bohn 2014). Similarly, tannins are also classified into two groups: (i) hydrolyzable tannins and (ii) condensed tannins, also called catechin tannins or proanthocyanidins. Hydrolyzable tannins are further divided into two groups: (i) gallotannins, providing sugar and gallic acid on hydrolysis, and (ii) ellagitannins, which yield not only sugar and gallic acid but also ellagic acid upon hydrolysis (Smeriglio et al. 2017). As in flavonoids, extraction of non-flavonoid compounds also received attention. In this context, nanofiltration is used for the concentration of non-flavonoid compounds from different natural sources (Table 7.2).

Olive (*Olea europaea*) mill wastewater is a phenolic-rich wastewater liquid stream that is obtained after the extraction of olive oil. Garcia-Castello et al. (2010) concentrated polyphenols from olive mill wastewaters using an integrated membrane system. Olive mill wastewater was initially submitted to a microfiltration operation, which recovered 78% of the polyphenols. Following that, microfiltration permeate was submitted to nanofiltration and this procedure resulted in recovery of almost all polyphenols including hydroxytyrosol, procatechuic acid, tyrosol, caffeic acid, *p*-coumaric acid, and oleuropein (Garcia-Castello et al. 2010). Similarly, Dammak et al. (2014) examined the retention of oleuropein by the nanofiltration membranes. The authors reported that the highest rejection rate was observed with

Table 7.2 Nanofiltration applications for the recovery of non-flavonoids

Material	Tested membranes				Selected membrane(s)	Polyphenol rejection	Reference
	Membrane	Supplier	Polymer	MWCO (Da)			
Olive products	n/a	Verind SpA Milano, Italy	n/a	n/a	Used in sequence	≈100%	Garcia-Castello et al. (2010)
	Nadir N30F	Microdyn-Nadir GmbH, Venlo, Netherlands	Polyethersulphone	578			
	DK	Osmonics Desal, USA Osmonics Desal, USA	Polyamide/ Polysulfone	150	MPF44	OLP: 96%	Dammak et al. (2014)
	DL	Osmonics Desal, USA Osmonics Desal, USA	Polyamide/ Polysulfone	300			
	G10	Osmonics Desal, USA Osmonics Desal, USA	Polyethylene glycine	2500			
	G5	Osmonics Desal, USA Osmonics Desal, USA	Polyethylene glycine	1000			
	MPF34	KOCH, USA	Silicone/Polysulfone	200			
	MPF36	KOCH, USA	Silicone/Polysulfone	1000			
	MPF44	KOCH, USA	Silicone/Polysulfone	250			
	NTR7250	Nitto Denko co., JP	Polyvinyl alcohol	300–400			
	NTR7410	Nitto Denko co., JP	Sulfonated polyether sulfone	17,500			
	NTR7430	Nitto Denko co., JP	Sulfonated polyether sulfone	2000			
	NTR7450	Nitto Denko co., JP	Sulfonated polyether sulfone	700–800			

(continued)

Table 7.2 (continued)

Material	Tested membranes				Selected membrane(s)	Polyphenol rejection	Reference
	Membrane	Supplier	Polymer	MWCO (Da)			
	Isoflux	TAMI Industries	TiO_2	n/a	Used in sequence	85%	Bazzarelli et al. (2016)
	n/a	Membraflow	TiO_2	n/a			
	DL1812	GE	Polyamide	150–300			
	NF90	Filmtec-Dow	Polyamide	200			
	LiquiCells ExtraFlow	Membrana	Polypropylene	n/a			
	Shirasu porous glass	SPG technology	Al_2O_3 SiO_2 glass	n/a			
	n/a	n/a	Polypropylene	n/a	Used in sequence	78.3%	Jahangiri et al. (2016)
	UF(ARS)	Biocon	Polysulfonamide	20,000			
	NF-70	Filmtec	Polyamide	200			
	TOPER	Microporous membrane, CN	n/a	n/a	Used in sequence	HT: 100%	Khemakhem et al. (2017)
	ZeeWeed 1500	GE power & water, Minnetonka, MN	n/a	5000		SA: 100%	
	HL2540TF	GE Osmonics, Minnetonka, MN	n/a	300		OLP: 100%	
	MD 020 TP 2 N	Mycrodyn Nadir, Wuppertal, Germany	Polypropylene	n/a	Used in sequence	HCA: 100%	Conidi et al. (2019)
	GK	GE Osmonics	Polyamide	3500			
	GH	GE Osmonics	Polyamide	2500			
	GE	GE Osmonics	Polyamide	1000			
	NFA-12A	Parker	Polyamide	500			
	DK	GE Osmonics	Polyamide	150–300			
	NF270	Dow, EEUU	Polyamide	300 Da	NF270	≈100%	Sánchez-Arévalo et al. (2021)

Artichoke by-products	DCQ III-006C	China blue star membrane technology	Polysulphone	50,000	Desal DL	CLA: 100%	Conidi et al. (2014)
	NP030	Microdyn Nadir	Polyethersulfone	400		CYN: 100%	
	Desal DL	GE Water & Process Technologies	Polyamide	150–300			
	NP030	Microdyn Nadir	Polyethersulfone	400	Used in sequence	CLA: >85%	Cassano et al. (2015)
	Desal DL	GE Water & Process Technologies	Polyamide	150–300		CYN: >85%	
	Inside ceram	Tami Industries	TiO_2	15,000	Used in sequence	CLA: 100%	Conidi et al. (2015)
	NF 270	Dow-Filmtec	Polyamide	200–300		CYN: 100%	
	NP010	Microdyn Nadir	Polyethersulfone	1000	MWCO of 200 Da	THCA: >92%	Cassano et al. (2016)
	NP030	Microdyn Nadir	Polyethersulfone	400		CLA: >92%	
	NF200	Filmtec-Dow	Piperazineamide	300		CYN: >92%	
	Desal DL	GE	Polyamide	150–300			
	Desal DK	GE	Polyamide	150–300			
	NF270	Dow FilmTec	Polyamide	200–400	All	CLA: >95%	Rabelo et al. (2016)
	DK	GE Osmonics	Polyamide	200			
	DL	GE Osmonics	Polyamide	150–300			
Fruit juices	VNF1	Vontron, China	Polyamide	240	Both	GA: 18.91–86.34%	Cai et al. (2017)
	VNF2	Vontron, China	Polypiperazine amide	150		PCA: 26.20–79.97%	
						CA: 39.69–55.04%	
						FA: 39.69–45.82%	
						CLA: 96.80–98.23%	

(continued)

Table 7.2 (continued)

Material	Tested membranes				Selected membrane(s)	Polyphenol rejection	Reference
	Membrane	Supplier	Polymer	MWCO (Da)			
Pequi	Microfiltration	Millipore	Mixed cellulose esters	n/a	Used in sequence	EA: >80%	de Santana Magalhães et al. (2019)
	Ultrafiltration	Microdyn Nadir	Polyethersulfone	5000		*p*-coumaric acid: 95%	
	Nanofiltration	Microdyn Nadir	Polypropylene	500–600			
Mate	HL2521TF	Osmonics membranes, Minnetonka, USA	Polyvinylidene difluoride	150–300	HL2521TF	45DCQA: 100%	Murakami et al. (2011)
						GA: 95%	
						34DHBA: 99%	
						CLA: 98%	
Rosemary	Duramem™ 200	Membrane extraction technology, UK	Polyimide	200	Duramem™ 200	CA: 93.9–96.1%	Peshev et al. (2011)
	Duramem™ 300	Membrane extraction technology, UK	Polyimide	300		RA: 99.5–99.7%	
	Duramem™ 500	Membrane extraction technology, UK	Polyimide	500			

CA Caffeic acid, *CLA* Chlorogenic acid, *CYN* Cyanirin, *EA* Ellagic acid, *FA* Ferulic acid, *GA* Gallic acid, *HCA* Hydroxycinnamic acids, *HT* Hydroxytyrosol, *OLP* Oleuropein, *PCA* Protocatechuic acid, *RA* Rosmarinic acid, *SA* Syringic acid, *34DHBA* 3,4-dihydroxybenzoic acid, *45DCQA* 4,5-dicaffeoylquinic acid, *n/a* not available

MPF44 membrane at pH 8.0 (96%) (Dammak et al. 2014). Later, a process combining microfiltration, nanofiltration, osmotic distillation and membrane emulsification was investigated for the recovery of phenolics from olive mill wastewaters. This process enabled the recovery of 85% of the initial phenolic content present in the raw wastewater (Bazzarelli et al. 2016). Another study that sequentially used microfiltration, ultrafiltration and nanofiltration for the recovery of phenolic compounds from olive mill wastewaters, concluded that 78.3% of phenolic compounds were recovered after the nanofiltration step (Jahangiri et al. 2016). In a similar way, Khemakhem et al. (2017) combined microfiltration, ultrafiltration and nanofiltration for the concentration of phenolics from olive leaves extract. Results revealed that 100% of hydroxytyrosol, syringic acid and oleuropein were recovered after the nanofiltration step (Khemakhem et al. 2017). Conidi et al. (2019) also employed microfiltration, ultrafiltration and nanofiltration processes to examine the recovery of phenolic compounds from olive mill waste. Membranes having MWCO of 150–500 Da demonstrated rejection towards hydroxycinnamic acid derivatives of about 100%, whereas the rejection towards total polyphenols was 72% (Conidi et al. 2019). In another study, the efficiency of nanofiltration to purify the tyrosol in the olive mill wastewaters has been studied. The results demonstrated that almost all phenolics were separated after nanofiltration at optimized conditions (Sánchez-Arévalo et al. 2021).

As indicated above, artichoke (*C. scolymus* L.) is a rich source of polyphenols, especially flavonoids. Besides flavonoids, artichoke also contains phenolic acids, in particular chlorogenic acid and cynarin. Accordingly, Conidi et al. (2014), who used two different nanofiltration membranes (NP030 and Desal DL) to separate polyphenols from artichoke wastewaters reported that the permeate stream of the Desal DL membrane did not contain any phenolic acids, whereas NP030 membrane displayed a lower rejection towards chlorogenic acid (95%) and cynarin (90%) (Conidi et al. 2014). The same research group used the same two nanofiltration membranes (NP030 and Desal DK) sequentially for the separation of phenolics from aqueous artichoke extracts. As a result, high rejections were observed towards chlorogenic acid and cynarin (more than 85%) (Cassano et al. 2015). Similarly, Conidi et al. (2015) combined membrane processes and polymeric resins to purify phenolics from artichoke wastewaters. The authors reported that no phenolics were detected after nanofiltration and S7968 resin presented the highest adsorption ratio for chlorogenic acid (81.35%) (Conidi et al. 2015). Cassano et al. (2016) further investigated the recovery of phenolics from artichoke brines using various different nanofiltration membranes and demonstrated that more than 92% of total hydroxycinnamic acids, chlorogenic acid and cynarin were recovered when nanofiltration membranes of 200 Da were used (Cassano et al. 2016). Another study that also applied the nanofiltration process for the recovery of phenolics from artichoke wastes, obtained a retention of chlorogenic acid higher than 95% (Rabelo et al. 2016).

Besides olive and artichoke by-products, phenolic compounds from fruits and other plants were also concentrated using nanofiltration process. Cai et al. (2017) used two nanofiltration membranes (VNF1 and VNF2) with different polymeric materials (polyamide and polypiperazine amide) and MWCOs (240 and 150 Da) for

the recovery of phenolic compounds from fruit juices. The rejections of gallic, protocatechuic, caffeic, ferulic and chlorogenic acids were 18.91–96.80% and 39.69–98.23% for VNF1 and VNF2, respectively (Cai et al. 2017). In another study, pequi, a fruit native to Brazil, is used for the concentration of phenolic compounds. Processes of microfiltration, ultrafiltration and nanofiltration were applied sequentially and as a result more than 80% of ellagic acid and 95% of *p*-coumaric acid were recovered (de Santana Magalhães et al. 2019). Furthermore, Murakami et al. (2011) concentrated the phenolic compounds in mate extract using nanofiltration process, which recovered 100%, 95%, 99% and 98% of 4,5-dicaffeoylquinic, gallic, 3,4-dihydroxybenzoic and chlorogenic acids, respectively. Another study utilized three nanofiltration membranes (Duramem™ 200, Duramem™ 300 and Duramem™ 500) to concentrate phenolics from rosemary (*Rosmarinus officiallis* L.). Duramem™ 200 membrane showed the best performance with rejections of 93.9–96.1% and 99.5–99.7% for caffeic and rosmarinic acids, respectively (Peshev et al. 2011). Achour et al. (2012) concentrated phenolic compounds from *Thymus capitatus* using membrane processes. The results demonstrated that the synthetic nanofiltration membrane concentrated more phenolic compounds in the retentate than the commercial nanofiltration membrane and synthetic ultrafiltration membrane (Achour et al. 2012).

3 Nanofiltration Applications for the Recovery of Carotenoids

Carotenoids are generally tetraterpenoids with 40 carbon atoms, which are the red, yellow or orange pigments found in fruits and vegetables and grouped as carotenes or xanthophylls. Carotenoids are polyenic hydrocarbons with varying degrees of unsaturation, and xanthophylls are synthesized from carotenes by reactions of hydroxylation or epoxidation. Examples of carotenes are β-carotene and lycopene, while for xanthophylls, lutein and zeaxanthin (Ambrósio et al. 2006; Rodriguez-Amaya 2001).

The value of β-carotene in the human diet is well known and acts as a significant source of vitamin A as it can be converted *in vivo* into vitamin A (Chuang and Brunner 2006). It serves as a possible alternative way to tackle vitamin A deficiency, which is prevalent throughout the world (Barison 1996). Many researches have proven that carotenes can prevent certain types of cancer, such as stomach, lung, oral and pharyngeal cancers (Peto et al. 1981). Carotenoids may also boost the immune system and help to defend against influenza, bronchitis, infections, and toxins. In addition, carotenoids are potent dyes of which the desired properties can be imparted to foods at very low amounts as parts per million (Gordon et al. 1983). Carotenoids have grown in value and popularity due to the extensive use of natural compounds in the cosmetics, pharmaceuticals, and food industries. Therefore, their recovery from food or by-products is very important.

Various foods are good sources of carotenoids, such as squash, carrot, pineapple, sweet potatoes, lettuce, mustard and kale, among others. On the other hand, there are some local sources which are rich in β-carotene including Brazilian wine palm (Mauritia flexuosa) and palm fruit (Elaeis guineensis), tucuma (*Astrocaryum aculeatum*), macaúba (*Acrocomia aculeata*), pupunha (Bactris gasipaes) and pequi (*Caryocar brasiliense*) (Ambrósio et al. 2006). Carotenoids are also present in bacteria, fungi and algae (Rodriguez-Amaya 2001).

Carotenoids are susceptible to light, temperature and acidity, as well as to oxidation reactions regarding the presence of unsaturated bonds. They are lipophilic compounds, insoluble in water and soluble in solvents such as acetone, alcohol and chloroform (Ambrósio et al. 2006; Rodriguez-Amaya and Kimura 2004). Almost all carotenes are extracted and lost during traditional physical and chemical methods of palm oil processing. It is suggested that, prior to the chemical or physical processing of crude palm oil, carotenoids should first be extracted by introducing an extra membrane filtration stage to the process. Various techniques are used to retrieve carotene from crude palm oil and intensive research studies have been performed on the production and recovery of carotene. Within these, nanofiltration provides a good solution for extracting carotenes from crude palm oil owing to its low energy consumption, having the process at ambient temperatures and preserving heat-sensitive compounds. Numerous applications have recently been reported for organic solvent nanofiltration (OSN) including homogeneous catalytic recovery, solvent exchange, chiral isolation, concentration of natural extracts and peptide synthesis. There are only a few studies related to the membrane technologies for recovering carotenoids from palm oil, in which the oil was first trans esterified into methyl esters, and then the carotenes are extracted from methyl esters by nanofiltration (Chiu et al. 2009; Darnoko and Cheryan 2006).

3.1 Carotenes

Lycopene is one of the most important carotenes that has been increasingly studied due to its positive impacts on health and a potent lipophilic antioxidant in tomatoes (Li et al. 2020). Lycopene has been reported to have protective effects on the cardiovascular system (Costa-Rodrigues et al. 2018), lower the risk of myocardial infarction (Pereira et al. 2017), reduce blood pressure (Wolak et al. 2019), prevent LDL cholesterol oxidation (Wang et al. 2020), lower the risk of prostate cancer (Rowles et al. 2017), lung cancer (Cheng et al. 2020), ovarian cancer (Sahin et al. 2018) and breast cancer (Singh et al. 2017), and have positive effects on neurodegenerative diseases including Alzheimer and Parkinson diseases (Chen et al. 2019). The health effects attributed to lycopene are mostly derived from its antioxidant properties (Imran et al. 2020).

Nanofiltration provides new opportunities due to its advantages, which are also correlated with the preservation of lower particles compared to microfiltration and ultrafiltration methods. Arriola et al. (2014) have studied the effect of nanofiltration

on the concentration of bioactive compounds of watermelon juice. They have reported that lycopene showed the highest rejection coefficient (0.99). Therefore, nanofiltration was found to be an effective alternative for concentrating the main bioactive compounds in watermelon juice (Arriola et al. 2014).

Luo et al. (2013) have studied lycopene concentration from several extracts by solvent resistant nanofiltration membranes. They have used three membranes including Starmem 122, Starmem 240 and Duramem 300 and the performances of these membranes were determined by their rejection and permeation rates. Membrane characterization was performed by SEM and FTIR before and after nanofiltration. They have reported that Starmem 240 showed promising performance for concentrating lycopene while the concentration was 2–3 times higher than the feed. A drop in permeability was observed because of the corrosion that would have been overcome by ultrasonic dipping in petroleum. It is possible to reuse the permeate solvent, thus adding additional economic benefits and environmental protection. After the permeation, the Starmem 240 membrane was rather stable depending on the SEM and FTIR (Luo et al. 2013).

Arana Rodriguez (2009) have studied concentration and purification of lycopene from tomatoes and tomato juice using membrane technology and solvent extraction. In their nanofiltration analysis, five polymeric membranes were tested with hexane lycopene extracts. Initial design estimates suggest that a 5-step nanofiltration process can recover 90.2% of lycopene which could result in a final retentate stream of 157 mg/L lycopene or more and a permeate stream of 3.6 mg/L lycopene that can be recycled to the extraction stage. Financial calculations indicate that the industrial implementation of lycopene recovery membrane technology is cost effective and successful (Arana Rodriguez 2009).

β-Carotene (BC) is a natural lipophilic carotenoid mainly present in vegetables and fruits. It acts as provitamin A because it is metabolized into vitamin A *in vivo*. Therefore, BC intake is expected to exhibit the pharmacological actions of vitamin A, including maintenance of healthy skin and mucous membrane and improvement of visual acuity (Grune et al. 2010). In addition, BC is known to have a strong antioxidant activity, and it can remove excess active oxygen produced *in vivo*. It has been reported to be effective in preventing degenerative diseases such as cardiovascular diseases, diabetes, and some types of cancer (Fiedor and Burda 2014). Therefore, BC is used in various fields such as pharmaceuticals, food supplements, and cosmetics. Their recovery from food or by-products are very important.

The concept of integrating supercritical CO_2 extraction (SC CO_2) with nanofiltration separation (NF) to extract and purify low molecular weight compounds (up to 1500 g mol^{-1}) has already been suggested. The Commissariat a 'l'Energie Atomique (CEA) has developed two nanofiltration tubular membranes sufficiently resistant to withstand supercritical conditions and initially designed for liquid filtration for separating compounds of low molecular weight, in a range of 500–1000 g mol^{-1}. The first membrane is a multilayer composite nanofilter, composed of a macroporous aluminum substrate, a mesoporous titanium oxide substrate and an organic upper layer in NafionA. The organic/inorganic structure of the nanofilter incorporates the mechanical flexibility of the inorganic substrate and the selectivity of the organic

layer that is the active layer in nanofiltration. The other membrane is a strictly inorganic nanofilter. The same macroporous alumina substrate is coated with a titanium oxide layer. The layer is obtained using the sol–gel route. For this NF membrane, the TiO2 conception provides very good thermal and chemical resistances to the nanofilter. Owing to its appealing physico-chemical properties and its low critical point (7.38 MPa and 304.2 K), carbon dioxide was selected as the supercritical fluid used for extraction (Cassano et al. 2018).

Sarrade et al. (1998) conducted a study for the purification of β-carotene from either carrot oils or carrot seeds. This pigment, often used in the agro-food and cosmetic industries, is sensible towards temperature and oxidation, and therefore difficult to isolate. The coupled process leads us to obtain, in both cases, encouraging results in terms of separation and purification. For purification of β-carotene from carrot oil, the use of a T membrane increased the concentration of the pigment by 2.4 times in the permeate. When carrot seeds are treated, the main part of the purification was obtained with the CO_2 stage, but with TN membranes, a 30% profit acquired from the NF stage was observed (Sarrade et al. 1998).

Palm oil is one of the richest sources of α- and β-carotene (400–3500 mg/kg), which constitute more than 80% of the total carotenoids in palm oil (Schroeder et al. 2006). According to Darnoko and Cheryan (2006), palm oil contains elevated amounts of carotenoids and tocopherols that can be removed by transforming them to their methyl esters, accompanied by the use of membrane technology to isolate carotenoids from methyl esters. Various solvent-stable nanofiltration membranes have been tested for this purpose. The flow rate with a model solution of crude palm oil methyl esters was in the range from 0.5 to 10 L/m^2 h, and β-carotene retention was from 60% to 80% using a transmembrane pressure of 2.76 MPa at 40 C. A multiple stage membrane process for the continuous production of concentrated palm carotenoid methyl esters was planned. With a feed rate of 10 tons/h of palm oil methyl esters containing 0.5 g/L of β-carotene, the process was able to produce 3611 L/ h of a carotenoid concentrate containing 1.19 g/L of carotene and 7500 L/h of bleached methyl esters containing less than 0.1 g/L of b-carotene. Besides, Chiu et al. (2009) investigated the concentration of carotenoids from crude palm oil by nanofiltration with retention of 75% of β-carotene. However, the disadvantage of this process is that the edible oil is lost or rendered useless for further consumption.

Pequi (*Caryocar brasilense* Camb.) is a traditional Brazilian fruit, rich in polyphenols and carotenoids. Machado et al. (2013) have studied aqueous and alcoholic pequi extraction, in a bench scale, evaluating the influence of time and temperature variation on the recovery of polyphenols and carotenoids. For the best extraction conditions (25 °C within 1 h for aqueous extract and 40 °C within 24 h for alcoholic extract), a re-extraction of residues has been carried out which improved the recovery of compounds from the fruit. The final extract which was a combination of the first and second extracts was subjected to a concentration phase by nanofiltration in a stirred cell with a temperature of 25 °C and a pressure of 800 kPa. Rejection of bioactive compounds was limited for the alcoholic extract to about 10% for carotenoids and 15% for polyphenols. Nanofiltration demonstrated a high concentration efficiency of polyphenols and carotenoids for aqueous extract with a retention coefficient of about 100% and 97%, respectively (Machado et al. 2013).

3.2 Xanthophylls

Lutein and its stereoisomer zeaxanthin are two fat-soluble xanthophylls which are classified under the carotenoid family. Along with their conversion isomer meso-zeaxanthin, these xanthophylls are the primary components of macular pigment, upon ingestion a compound concentrated in the macula area of the retina that is responsible for fine-feature vision, that makes them unique among the other natural carotenoids (Eisenhauer et al. 2017). It has been shown that a decrease in the accumulated lutein and zeaxanthin in the macula and lens is associated with the development of cataracts and age-related macular degeneration which are causes of blindness (Fábryová et al. 2019). Xanthophylls, in other words oxo-carotenoids, involve at least one oxygen atom in their structure. Lutein (β,ε-carotene-3,3′-diol) and zeaxanthin (β,β-carotene-3,3′-diol) are dihydroxy derivatives of α- and β-carotene, respectively and 3 and 3′-position of the ionone rings of them are substituted with two hydroxyl groups (Fig. 7.1). Their polarity is greater than carotenoids since they contain hydroxyl groups. The antioxidant capacity of carotenoids is affected by the pattern of conjugated double bonds and it also determines the light-absorbing features of these compounds. Double bonds in the ring of lutein and zeaxanthin are partially conjugated, whereas nine C-C double bonds present in the polyene backbone are fully conjugated. Their maximum absorption wavelengths are approximately 445 and 450 nm, respectively and at these wavelengths their molar extinction coefficients (ε_{mol}) remain in between 140,000 and 145,000 cm^{-1} mol^{-1} (Stahl 2005). Associated with their polarity and conjugated double bonds they have; they have been shown to possess prominent free radical scavenging activity (Sindhu et al. 2010). Several studies have also pointed out their role in the prevention of certain types of cancer (such as lung, colorectal, ovarian and breast cancer) and coronary heart disease. In addition to these biological activities, they can also absorb and attenuate the blue light that leads to retinal damage upon excessive exposure activity (Ma and Lin 2010; Ribaya-Mercado and Blumberg 2004). It is no surprise that these xanthophylls have a critical role in maintaining better vision by accumulating in macula and lens that are highly vulnerable to oxidative damage due to exposure to intense light. However, despite their similarity to α- and β-carotene, they do not exhibit provitamin A activity (Ma and Lin 2010).

Many fruit and vegetables contain high amounts of lutein and zeaxanthin. In the global market, lutein is mainly extracted from marigold flowers, which is also known as the genus Tagetes. However, due to the fact that the processing of marigold flowers is dependent upon the periodic harvesting, which is a labor-intensive work, several microorganisms including microalgae are used as the potential sources for lutein and zeaxanthin extraction. *Flavobacterium* sp., *Synechocystis* sp., *Spirulina*, *Chlorella* fusca, *Chlorococcum* citroforme are some examples of microbial sources of lutein and zeaxanthin (Becerra et al. 2020; Sajilata et al. 2008). In particular, microalgae are gaining more attention in this field since they have high lutein and zeaxanthin content, 5–10 times faster growth rate compared to higher plants (Lin et al. 2015). Table 7.3 shows the lutein and zeaxanthin content of several

Table 7.3 Lutein and zeaxanthin contents of several foods

Food source	Form	Lutein + Zeaxanthin (μg/100 g)
Artichokes (globe)	Raw	464
Arugula	Raw	3555
Asparagus	Raw	710
	Canned	630
Avocado	Raw	271
Banana	Raw	22
Basil	Raw	5650
Broccoli	Raw	1403
Brussels sprouts	Raw	1590
	Boiled	1290
Cabbage (red)	Raw	329
	Pickled	168
Cabbage (white)	Raw	30
Cantaloupe	Raw	32
Carrot	100% juice	333
	Raw	256
Cilantro	Raw	865
Collard	Raw	4323
Corn	Raw	644
Edamame	Cooked	1619
Eggs	Pickled, whole	350
	Yolk	1158
	Whole	459
Grapefruits	Raw	6
Grapes (Muscadine)	Raw	64
Green peas	Raw	2477
Green pepper	Raw	341
Kale	Raw	39,550
	Boiled	4983
Leek	Raw	1900
	Boiled	925
Lemon	Raw	11
Lettuce	Raw	277
Mango	Raw	23
Mustard greens	Raw	3730
Onions (red)	Raw	4
Orange	Raw	129
Papaya	Raw	89
Parsley	Raw	5561
Peaches (yellow)	Raw	132
Pecans	Unroasted	17

(continued)

Table 7.3 (continued)

Food source	Form	Lutein + Zeaxanthin (μg/100 g)
Pepper (green, sweet)	Raw	341
Pepper (red, chili)	Raw	717
Pepper (red, sweet)	Raw	51
Persimmon	Raw	834
Pistachio	Raw	2903
Pumpkin	Raw	1500
Rhubarb	Raw	170
Spinach	Raw	12,198
	Cooked	11,308
Squash (green)	Raw	2125
Strawberries	Raw	26
Swiss chard	Raw	11,000
Tangerines	Raw	138
Tomatoes (grape)	Raw	104
Turnip greens	Raw	12,825

The data presented in this table is extracted from Agricultural Research Service of the US Department of Agriculture (USDA)

foods according to the database published by the Agricultural Research Service of the US Department of Agriculture (USDA 2020). Especially green leafy vegetables such as spinach or kale contain these compounds abundantly. In such vegetables, the yellow-orange color of these xanthophylls is concealed due to the high amount of chlorophyll (Nwachukwu et al. 2016). As it can be seen from the Fig. 7.1, lutein and zeaxanthin's structures are closely related. Only, the position of the double bond in one ionone end ring differs in each compound (Breithaupt and Schlatterer 2005). Analyzing and quantifying is one of the challenges in the determination of lutein and zeaxanthin content of foods. The separate determination of these compounds was not available until recently since the analytical methods did not measure up to quantify them individually. Therefore, in most literature data lutein and zeaxanthin contents of the foods are presented together (Eisenhauer et al. 2017).

In general, natural compounds of high value are present at low amounts in their natural sources. Therefore, after the extraction of these compounds with an appropriate solvent results in a very dilute extract and it needs further separation, concentration and purification. The purification step can be considered as the most challenging part of the production of natural compounds. For this reason, the development of selective, sustainable and energy-efficient separation and purification technologies for high-value natural products is being searched (Sereewatthanawut et al. 2018). Organic solvent nanofiltration is one of the new technologies that provide separation based on molecular weight or size of solutes between 50 and 2000 g mol^{-1}, solvent recovery or solvent exchange, basically by implementing a pressure gradient in the organic media (Szekely et al. 2014). To the best of our knowledge, there is only a

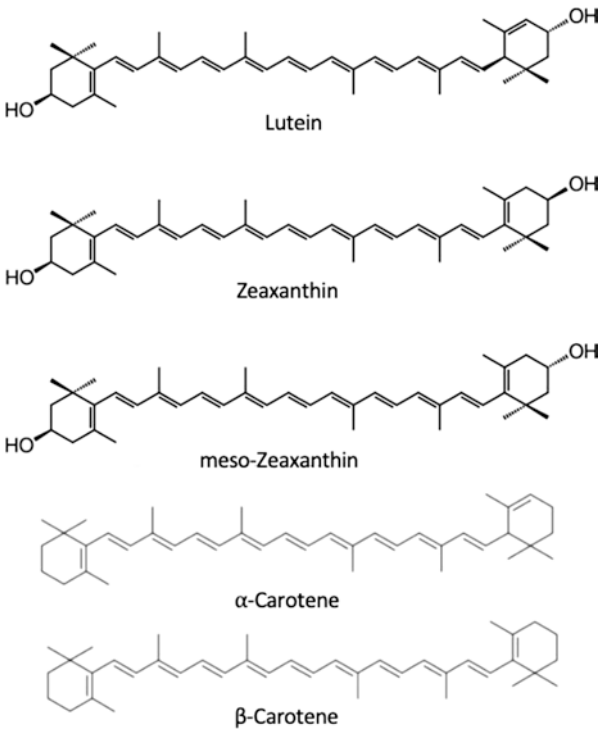

Fig. 7.1 Chemical structures of xanthopylls and some selected carotenoids

single study in the literature on the nanofiltration process of xanthophylls. Tsui and Cheryan (2007) investigated the purification of xanthophylls extracted from corn with 85% aqueous ethanol by organic solvent nanofiltration. According to their findings, ethanolic extract of xanthophylls was successfully purified and concentrated by implementing a series of filtration, ultrafiltration and nanofiltration. Additionally, the DK membrane (300 Da MWCO, GE-Osmonics, Minnetonka, MN) was found to be superior according to its flux, rejection and stability properties.

4 Conclusions and Future Perspectives

Recently, in relation to the major interest for natural compounds with biological activities, the pressure-driven membrane-based technologies have been used effectively for the recovery, separation and fractionation of bioactive compounds from food and by-products. In particular, nanofiltration membranes have been recognized for their capability to recover polyphenols and carotenoids from several types of food products.

Membrane processes have become potentially attractive tools in the processing of especially fruit juices as an alternative to the conventional methods used for

concentrating bioactive compounds because of their advantages in terms of high recovery and/or removal performance, mild operating conditions, lack of phase transition and low energy consumption. Nanofiltration provides beneficial opportunities, which are often correlated with the preservation of lower particles relative to microfiltration and ultrafiltration methods. The key benefit of using nanofiltration membranes for the concentration of bioactive compounds from the food matrix is the ability to pick membranes with sufficient molecular weight cut-off to fractionate molecules of equivalent molecular weight in a range of 100–1000 Da. It can be predicted that the use of nanofiltration processes, with the development of membrane science and technology, will become much more common due to their advantages. However, the number of studies needs to be increased to have a better idea about their advantages, limitations, and applications.

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Chapter 8
Recovery of Volatile Aroma Molecules from Agro-Food Systems by Means of Pervaporation

Francesco Galiano, Ilya L. Borisov, Vladimir Volkov, and Alberto Figoli

Abstract Pervaporation (PV) has been known a rapid growth in the last 20 years as a valid membrane process, over other conventional techniques, for the recovery of aroma compounds from agro-food systems. PV is based on the use of non-porous membranes which selectively regulate the transport of target molecules dissolved in a liquid feed mixture. PV is particularly appreciated thanks to its low energy consumption, no addition of chemicals for achieving the separation and preservation of the integrity of the aroma compounds. However, despite the large number of studies carried out, a full exploitation of PV in the aroma recovery industry is still limited. The first section of this chapter will provide an introductive overview on the PV process including the fundamentals, the transport mechanism and the fields of applications. The second part of the chapter will be dedicated on the use of PV in the recovery of aroma compounds from model mixtures and from real systems. A state-of-the-art will be provided including the most recent findings in the recovery of aroma by PV highlighting the principal breakthroughs achieved in this field, the main variables influencing the separation performance of the process and the future perspectives.

Keywords Aroma recovery · Pervaporation · Membrane processes · Hydrophobic pervaporation · Volatile organic compounds recovery

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1 Fundamentals

Pervaporation (PV) is a membrane process of liquid separation at the molecular level. In this process, the multi-component liquid mixture to be separated is brought into contact with one side of the selectively permeable non-porous membrane, and the vapor (permeate) that has penetrated through the membrane is removed from its other side and condensed in the cold trap. The term "pervaporation" (permeation + evaporation) was first introduced by Kober (1917). As it was kindly reported by Kober: "In the course of some experiments on dialyzation, my assistant, Mr. C.W. Eberlein, called my attention to the fact that a liquid in a collodion bag, which was suspended in the air, evaporated, although the bag was tightly closed". It was further concluded that the aqueous vapor is "given off" through the membrane. This phenomenon was named pervaporation (Kober 1917). As it was reported by Van der Bruggen and Luis (2014), a similar observation was made by Kahlenberg, who reported in 1906 on the separation of a mixture of a hydrocarbon and an alcohol through a rubber membrane (Kahlenberg 1906).

To perform PV separation, it is necessary to create and maintain the driving force of the process, which, in the general case, is the gradient of the chemical potential μ along the membrane thickness:

$$\frac{d\mu_i}{dx} = R\frac{d}{dx}\left(T \ln a_i\right) \tag{8.1}$$

where x is coordinate perpendicular to the surface of the membrane, a_i – thermodynamic activity of component i, T – temperature, R – universal gas constant.

The chemical potential can be expressed through the partial pressures of the components (following the Raoult's law for liquids and Dalton's law for ideal gases):

$$a_i = p_i / p_i^0 \tag{8.2}$$

where p_i and p_i^0 – equilibrium partial pressure above the liquid mixture and partial pressure of the pure component i at a temperature T, respectively. The mass flux of the component through the membrane is determined by the driving force of the process:

$$J_i = -L_i \frac{d\mu_i}{dx} \tag{8.3}$$

where L – coefficient (not necessarily constant).

In practice, the driving force of the process is the activity gradient, which is achieved by reducing the vapor pressure on permeate side of the membrane. Technically, this can be realized by vacuum (vacuum pervaporation Fig. 8.1a) (Néel et al. 1985; Feng and Huang 1997; Basile et al. 2015), by stripping the permeate vapor with an inert gas (Kujawski and Krajewski 2004; Brazinha et al. 2009) (sweep gas pervaporation Fig. 8.1b), or condensation on the cooled surface directly in the

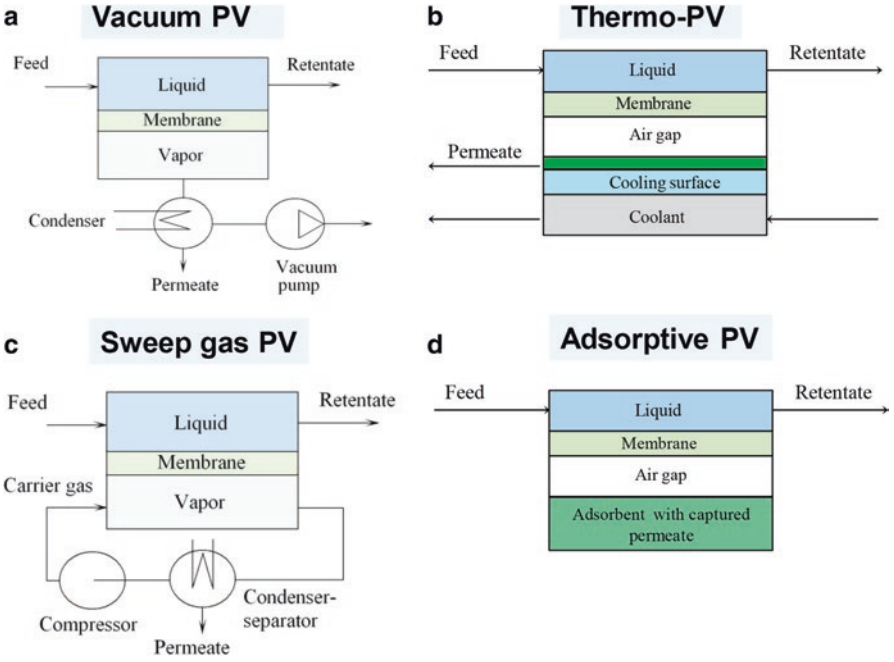

Fig. 8.1 Schemes of the PV process: vacuum (**a**), sweep gas (**b**), thermogradient (**c**), adsorptive (**d**)

membrane module (Aptel et al. 1976; Volkov et al. 2016, 2020; Kirsh et al. 2013; Koter et al. 2015) (thermo-pervaporation Fig. 8.1c).

There is also a new method of reducing vapour pressure on the permeate side due to the capture of the vapours by adsorbents, for example, activated carbon (Borisov 2018).

In the vacuum PV (Fig. 8.1a), the feed mixture (upstream) is fed to the one membrane surface. A vacuum pump provides reduced pressure behind the membrane. The permeate vapor (downstream) that has penetrated through the membrane is condensed in a cooler (condenser). Resulting liquid (or solid) permeate, enriched in preferentially penetrating components, is collected in a special container. The liquid mixture that has been depleted of penetrants that leaves the membrane modules without passing through the membrane to the downstream is called retentate. In industrial PV plants, only the vacuum mode of the process is currently used. Three other methods (Fig. 8.1b, c and d) are used so far only in laboratory studies.

Despite the difference in technical solutions, the very principle of PV separation of liquid mixtures remains unchanged. It is characterized by the following main features:

1. Unlike most membrane processes, during the transfer of the components to be separated from one side of the membrane to another, a liquid-vapor phase transition occurs. In this regard, in terms of energy consumption, the use of PV for the recovery of components present in small quantities from a liquid mixture is most effective. While the target product of the process can be both permeate and retentate;

2. Membrane has a non-porous separation layer that is in contact with the feed mixture;
3. Membrane, in general, has a high affinity for the selectively penetrating components of the mixture, which leads to its non-uniform (anisotropic) swelling in the direction from the liquid to the vapor-gas phase (refers to polymeric membranes).

Based on the compositions of the permeate and the feed, the efficiency of the PV separation of the liquid mixture of two components i and j can be characterized by the dimensionless separation factor α or enrichment factor β:

$$\alpha_{ij} = \frac{\left(C_i / C_j\right)''}{\left(C_i / C_j\right)'} = \frac{C_i'' / C_i'}{C_j'' / C_j'} = \frac{\left(P_i / P_j\right)''}{\left(P_i / P_j\right)'} \tag{8.4}$$

$$\beta = C_i'' / C_i' \tag{8.5}$$

where i is a preferentially penetrating component, indices ($''$) and ($'$) refer to the permeate and feed stream, respectively, C is the concentration of the component, P is the membrane permeability coefficient. Unlike the enrichment factor, the magnitude of the separation factor is independent of the way the concentration is expressed. As a rule, it is not possible to simultaneously ensure an increase in the flux of permeate and the separation factor. If the flux increases, then the separation factor decreases, and vice versa (Koops et al. 1994). To describe the trade-off between permeability and separation selectivity, a "quality criterion" of the membrane is introduced – the PV separation index *PSI* (Van der Bruggen and Luis 2014):

$$PSI = J_i\left(\alpha_{ij} - 1\right) \tag{8.6}$$

PV can be represented as a thermodynamically equivalent sequential process of the saturated vapour formation and its transfer through the membrane, as shown in Fig. 8.2. Thus, the PV separation factor can be represented as consisting of two contributions – the selectivity of evaporation α_{ev} and the selectivity of the membrane α_m (Böddeker 1990; Wijmans and Baker 1993):

$$\alpha_{pv} = \alpha_{ev} \cdot \alpha_m \tag{8.7}$$

In the distillation, the vapor phase can only be enriched with the more volatile component. However, in case of PV, depending on the membrane properties, permeate can be enriched with both a more and less volatile component. This is well illustrated by the so-called Thompson diagram (Böddeker 1990), which schematically depicts the relationship between the permeate pressure (set and maintained during PV) and the permeate composition for membranes with different selectivity α_m (Fig. 8.3). The diagram presents the process, schematically shown in Fig. 8.2.

In the step **1**, the components of the binary liquid mixture with concentrations c_i and c_j. are evaporated. In this case, an equilibrium vapor is formed, enriched in the highly volatile component i, in which the partial pressures of the components are

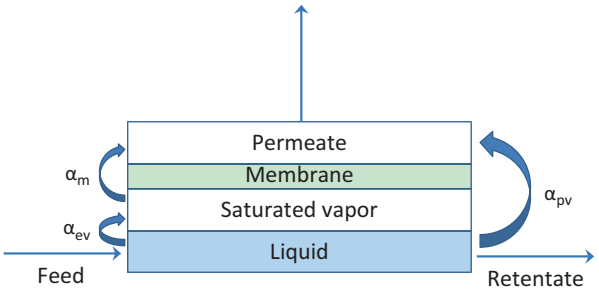

Fig. 8.2 A process thermodynamically equivalent to PV

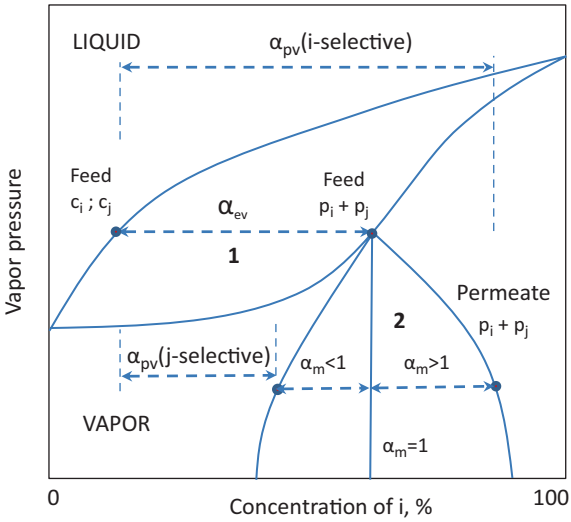

Fig. 8.3 Thompson diagram (Böddeker 1990). The effect of the permeate vapor pressure and the selectivity of membranes on the composition of the permeate (schematically)

equal to p_i and p_j. In the step **2**, the vapor passes through the membrane. While the partial pressures of the components are reduced, and the permeate is enriched in one of them. The permeate composition depends on both the selectivity of the liquid-vapor phase transition and the selectivity of the membrane used. If $\alpha_m > 1$, then PV is more selective for the volatile component i comparing to distillation. In case when $\alpha_m < 1$, PV has increased selectivity for the low-volatile component j. The composition of the permeate substantially depends on the pressure maintained in the downstream compartment of the module. Moreover, depending on the characteristics of the membrane, it can lead to additional enrichment ($\alpha_m > 1$) or depletion ($\alpha_m < 1$) of the vapor phase by the more volatile component i in comparison with the equilibrium evaporation (distillation) of the feed mixture. In case of $\alpha_m = 1$ or while maintaining the permeate pressure close to equilibrium, the selectivity of the separation process remains at the distillation level.

From Fig. 8.3 it follows that PV can have obvious advantages over distillation or evaporation in cases when it is not possible thermodynamically to separate the

components of the mixture. PV is promising for the separation of mixtures forming azeotropes in processes such as dehydration of solvents (Vane 2020), the separation of methanol from a mixture with MTBE (Castro-Muñoz et al. 2018) and ethanol with ETBE (Pulyalina et al. 2019). Other applications of PV can be the separation of liquids with close boiling points (separation of aromatic and aliphatic hydrocarbons (Pulyalina et al. 2016)), separation of azeotropic mixtures (Buonomenna et al. 2011; Li et al. 2018) or the selective removal of low boiling components from mixtures with volatile ones (purification of wastewater from phenols (Hao et al. 2009), the removal of aroma compounds from water (Figoli et al. 2018; Brazinha et al. 2011)). Due to the use of membranes with high selectivity, PV is indispensable for the removal of toxic volatile organic compounds from water (Peng et al. 2003; Castro-Muñoz and Fíla 2019). The maximum permissible concentration (MPC) of chlorinated organics and aromatic substances, as well as esters in water can be in parts per million. For this reason, removal by distillation is not economically feasible. Processes with increased selectivity, such as PV (Peng et al. 2003; Vane et al. 2001) are, therefore, required. An important feature of PV is that it can be carried out under mild conditions, below the boiling point of the mixture. This provides the opportunity of its application for the removal of thermally unstable compounds in the food, pharmaceutical and perfumery industries, for example, aroma compounds (Galiano et al. 2019a; Castro-Muñoz 2019a), as well as for the *in-situ* removal of reaction products directly during the synthesis process (Castro-Muñoz et al. 2019a). In the latter case, the membrane can perform not only the separation, but also the catalytic function (Qing et al. 2017; Galiano et al. 2019b). PV can be used both for chemical membrane reactors (recovery of esters from the reaction mixture during esterification (Castro-Munoz et al. 2018)) and membrane bioreactors (recovery of alcohols from fermentation broth in the process of biomass fermentation (Volkov et al. 2020; Zhu et al. 2019)). In the membrane bioreactor, PV allows not only to shift the equilibrium towards the formation of the target products, but also to reduce the inhibitory effect of alcohols on microorganisms, thus increasing the duration of fermentation, the productivity of the process, the yield of the target products, and reducing the cost of its recovery. For example, Vane (2008) reports that using PV, where the membrane has a separation factor of more than 30, it is possible to significantly reduce the energy consumption for the recovery of ethanol from the fermentation mixture as compared to distillation.

2 General Principles of Materials Choice for PV Membranes

Transport of low molecular weight substances through non-porous membranes during PV, as in gas separation, includes the following stages: sorption of the penetrant molecule on one side of the membrane, diffusion in the bulk of the membrane and desorption on the other side of the membrane (solution-diffusion mechanism, see Fig. 8.4a, b) (Wijmans and Baker 1995). Therefore, the selectivity of the PV process is determined by the differences in the transmembrane transfer rates of the components of the liquid mixture in the membrane material.

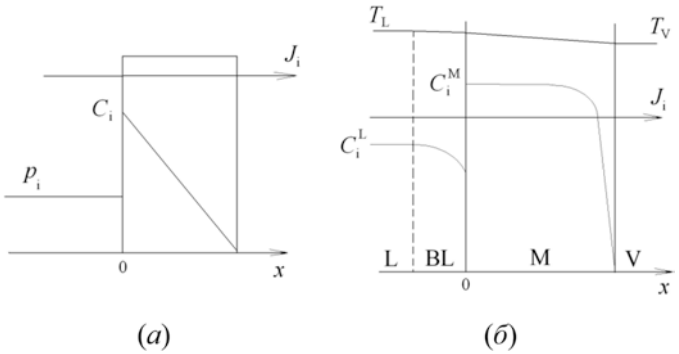

Fig. 8.4 The concentration profiles of the substance penetrating through the membrane: *a* gas separation, *b* pervaporation. p_i partial pressure of component *i*, *L* liquid, *BL* boundary layer, *M* membrane, *V* vapor

In case of permeability of non-condensable gases at moderate penetrant pressures, equilibrium sorption and diffusion obey, respectively, the laws of Henry and Fick. While, according to the solution-diffusion model, permeability selectivity can be represented as:

$$\alpha_P = \frac{P_i}{P_j} = \frac{S_i}{S_j}\frac{D_i}{D_j} = \alpha_S \alpha_D \tag{8.8}$$

where P is the permeability coefficient, S is the solubility coefficient, D is the diffusion coefficient. Thus, the permeability selectivity α_p of the components i and j is equal to the ratio of their permeability coefficients.

It follows from Eq. (8.8) that selectivity of permeability is determined by both the thermodynamic component (solubility selectivity α_s) and the kinetic component (diffusion selectivity α_D). A similar approach is also effective in considering the regularities of selective transport in the processes of PV (Volkov 1994; Bell et al. 1988). However, it should be remembered that in case of PV, in contrast to membrane gas separation, the prediction of the selectivity of the real separation process from the ratio of the characteristic permeability coefficients of individual substances can be considered only as a first approximation of the estimated separation efficiency (Wijmans and Baker 1993; Castro-Muñoz et al. 2020a).

Volkov (1994) proposed, as the most general quantitative criterion for the assessment of the solubility selectivity α_s and diffusion selectivity α_D, to use the slope angles of linear correlations of the solubility and diffusion coefficients of gases and vapors from, respectively, the Lennard-Jones force constant, ε/k, and the size of the penetrant molecule. For example, d^2, where d is the gas-kinetic diameter of the collision of the penetrant molecule (Fig. 8.5 a, b). Indeed, as can be seen from Fig. 8.5a, in the semi-logarithmic coordinates, the S_1/S_2 ratio corresponds to the difference between the logarithms of the solubility coefficients of components *1* and *2*. The value of lg α_s is determined by the slope of the linear correlation. The higher the

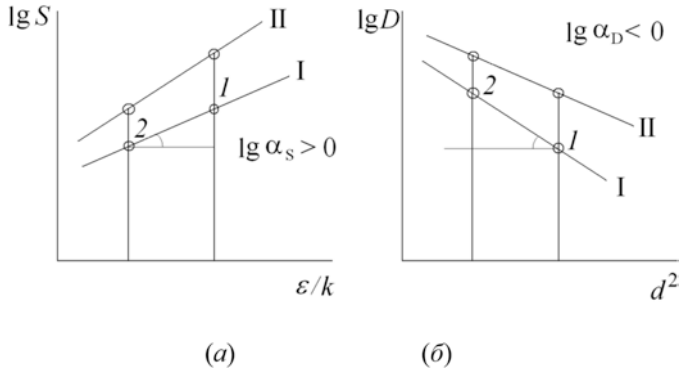

Fig. 8.5 Schematic representation of the correlation of the solubility coefficients (**a**) and diffusion (**b**) of the vapors of components *1* and *2* in polymers I and II

angle of the slope, the greater the selectivity of the dissolution of gases and vapors in this polymer. Similar reasoning is valid for the one shown in Fig. 8.5b linear correlation of the diffusion coefficient on the penetrant size.

It should be noted that the correlation dependence of ε/κ on d for gases and liquids is an increasing function. An increase in ε/κ during the transition from one type of molecule to another, as a rule, is accompanied by a simultaneous increase in d. In the absence of a strong specific interaction in the liquid – membrane system, the following regularity should be observed: the component of the binary mixture which molecules have increased affinity (component *1* in Fig. 8.5 a) compared to the second component to the membrane material, $(\varepsilon/\kappa)_1 > (\varepsilon/\kappa)_2$, it will be preferable to be sorbed by it in comparison with component *2*, $S_1/S_2 = \alpha_s > 1$.

At the same time, in accordance with Fig. 8.5b, due to the larger molecule size of component *1* compared to component *2*, it will diffuse more slowly than component *2* ($D_1/D_2 = \alpha_D < 1$). Thus, in the general case of the absence of a strong specific interaction, the thermodynamic (sorption) and kinetic (diffusion) components of the permeability selectivity tend to mutual compensation:

$$\lg \alpha_p = \left|\lg \alpha_S\right| - \left|\lg \alpha_D\right| \tag{8.9}$$

where $\alpha_p = P_1/P_2 = S_1D_1/S_2D_2$ (Fig. 8.6a, b).

The diffusion separation mechanism prevails in the system in accordance with inequality

$$\left|\lg \alpha_S\right| < \left|\lg \alpha_D\right| \tag{8.10}$$

In this case, during PV separation, the preferred penetration of a component with smaller molecular sizes is observed (component *2* in Fig. 8.5a, b). This regularity is characteristic, first of all, for low-permeability glassy polymers, and is used in the processes of dehydration of organic solvents by PV through, for example,

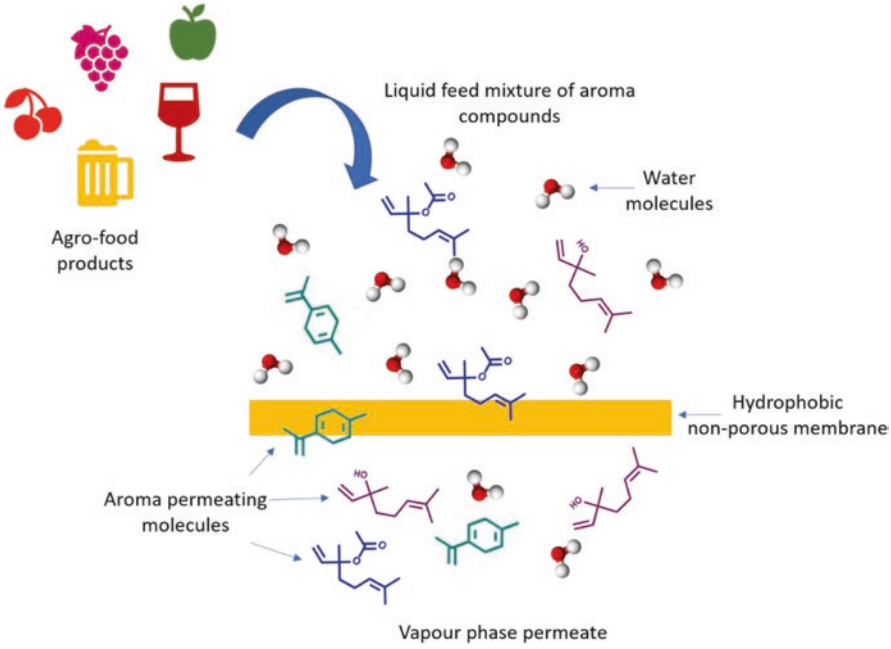

Fig. 8.6 Aroma recovery from agro-food products by PV

polyimides (Wang et al. 2009; Salehian and Chung 2017), polyacrylonitrile (PAN) and its copolymers (Otvagina et al. 2019).

When PV separation occurs by the diffusion mechanism, when inequality (8.10) is true, there is a clear pattern of the inverse mutual dependence of separation selectivity and flux. In other words, any changes in the structure of the membrane material, leading to an increase in its selectivity, are inevitably accompanied by a decrease in its permeability.

The sorption separation mechanism prevails in the system in accordance with inequality.

$$\left|\lg \alpha_S\right| > \left|\lg \alpha_D\right| \tag{8.11}$$

In this case, the separation is carried out according to the principle of thermodynamic affinity between the molecules of the components of the feed mixture and the polymer of the membrane. Such conditions can be realized both in the presence and in the absence of strong specific interactions in the liquid-membrane system.

In the absence of strong specific interactions of any of the components of the binary liquid mixture and the polymer of the membrane, inequality (8.11) can be satisfied only in the case of low diffusion selectivity values a_D. The latter is characteristic of rubbers (for example, polydimethylsiloxane (PDMS), polyalkylmethylsiloxanes) (Ohshima et al. 2005; Borisov et al. 2020), as well as for glassy polymers with a high free volume fraction (for example, polytrimethylsilyl propyne (PTMSP),

polymer of intrinsic microporosity (PIMs)) (Kirk et al. 2019; Ahmad et al. 2020). In all these cases, the preferred penetration during PV of a component with a large molecular size is observed (component *1* in Fig. 8.5a, b). In practice, according to this mechanism, separation is carried out in hydrophobic PV, where organic components are concentrated from their solutions in water (Golubev et al. 2020; Uragami et al. 2016).

If a component is present in a liquid binary mixture capable of experiences strong reversible specific interactions with the membrane material (for example, donor-acceptor interactions or the formation of hydrogen bonds), then inequality (8.11) will almost always be fulfilled for it. The component will primarily penetrate through the membrane. Examples of the practical use of such membranes are the processes of dehydration of organic solvents through hydrophilic membranes based on polyvinyl alcohol (Xia et al. 2016), polysaccharides (Uragami et al. 2015) and polyelectrolytes (Kononova et al. 2018).

3 Simulation Approaches

Simulation of PV is a complex multi-parameter task. PV depends on the process conditions, the hydrodynamic regime in the feed and its physicochemical properties, the membrane module geometry and membrane properties. Quantitative analysis of PV is also a very difficult task due to the nonlinear gradient of a large number of variables along the membrane thickness (Fig. 8.4b). The simulation of mass transfer through the membrane is mainly carried out using empirical and semi-empirical approaches. The most developed are approaches to the calculation of binary systems.

The mechanism of transport of low molecular weight substances through non-porous polymer membranes in PV is the same as in gas separation, and comprises the following stages: sorption of the penetrant molecule on one side of the membrane, diffusion in the bulk of the membrane and desorption on the other side of the membrane (Fig. 8.4a, b). This is the so-called sorption-diffusion mechanism or the solution-diffusion mechanism (Azimi et al. 2019).

Since the separation ability of PV membranes, as a rule, is determined by the selective sorption of the target component in the membrane material, anisotropic swelling of the selective membrane layer is observed in this case (Fig. 8.4b).

The concentration of the component i on the feed-side membrane surface $C_i^{\text{м}}$ is determined by the value of its equilibrium sorption from the liquid phase and, provided there is no effect of the concentration polarization, practically coincides with the equilibrium concentration between the membrane material and the mixture. An important condition for PV is to reduce the vapor pressure of permeate to a minimum. Therefore, the concentration of any component from the output side of the membrane, most often during simulation, is taken to be close to zero, since it is determined by the value of equilibrium sorption from the vapor phase. The transport of the components of the binary mixture i and j through the separation layer of the

membrane is determined by the values of the local diffusion coefficients (D_i and D_j) and distribution coefficients at the input and output boundaries of the membrane. Mass transfer of component *i* through the membrane is characterized by a mass flux through the membrane J_i. This value mainly determines the performance of the membrane, and its calculation is one of the main theoretical tasks. The flux of the component under steady state conditions in the general case is given by the integral form of the first Fick law:

$$J_i = \frac{1}{l_M} \int_0^{C_i^M} D_i\left(C_i, C_j\right) dC \tag{8.12}$$

where J_i is the flux of component *i* under steady state transport conditions (kg m^{-2} s^{-1}); C_i^M is the concentration of the component *i* on the feed side membrane surface; $D_i(C_i, C_j)$ is the local diffusion coefficient of the component *i* in the swollen polymer at the point where the concentrations of components *i* and *j* are equal to C_i and C_j, respectively, l_M is the membrane thickness. The concentration dependence of the diffusion coefficient varies for different membrane materials and penetrants. In case where the empirical dependence of the diffusion coefficient on concentration is not known, Fick's law is approximately written as

$$J_i = -\left\langle D_i \right\rangle dC_i / dx, \tag{8.13}$$

where $\langle D_i \rangle$ is average diffusion coefficient.

Assessment of Concentration Polarization Effect The efficiency of PV may depend on the resistance of the liquid-membrane boundary layer BL (Fig. 8.4b), which often leads to a strong decrease in the separation factor and flux. Consequently, the highest possible membrane performance cannot be always obtained, especially when a thin and a very selective membrane material is utilized (Raghunath and Hwang 1992; Baker et al. 1997). Such a phenomenon is caused by the occurrence of so-called concentration polarization (CP) effect (Baker et al. 1997; Wijmans et al. 1996). Species selectively transported through the membrane, such as organics in hydrophobic PV, are significantly faster removed from the feed solution adjacent to the membrane surface then non-selectively transported molecules. Therefore, the concentration of selectively transported components at the membrane surface is significantly smaller than in the bulk feed (Bhattacharya 1997). Due to that, a stagnant boundary layer is formed at the membrane surface, resulting in the necessity for the selectively transported species to pass the stagnant boundary layer prior to reach the membrane surface (Raghunath and Hwang 1992; Baker et al. 1997; She and Hwang 2004) (Fig. 8.4b). It should be underlined, that the boundary layer resistance is higher, and consequently the CP is more pronounced if membrane permeability and selectivity towards an organic component is higher. As it follows from the resistances-in-series model, the boundary layer resistance depends principally on the permeate flow rate; however, this correlation can be ignored in the most PV applications (Wijmans et al. 1996).

The most reliable way to increase the membrane selectivity (α) is to increase the boundary layer mass transfer coefficient value, for instance by selecting turbulence-promoting spacer materials and/or by operating the modules at high throughput rates. Wijmans et al. (1996) reported that the trichloroethylene enrichment factor increases six-fold to the value of 10,000 when the feed flow rate increased from 3.79 to 11.75 dm^3 min^{-1}.

To describe the extent of CP, so called concentration polarization modulus (C_m/C_f) can be determined. According to Feng and Huang (1997), the concentration polarization modulus can be written as follows (Eq. 8.14):

$$\frac{C_m}{C_f} = \left(E_0 - (E_0 - 1)\exp\left(-\frac{J_v \delta}{D} \right) \right)^{-1} \tag{8.14}$$

where: C_m is the component mole fraction in the feed solution at the membrane surface and C_f is the component mole fraction in the feed bulk solution, J_v is the component volume flux [m^3 m^{-2} h^{-1}]. Eq. (14) contains three unknown variables: the diffusion coefficient – D [m^2 s^{-1}], the boundary layer thickness - δ [m] and E_0 – intrinsic enrichment factor [−] calculated for PV conditions without occurrence of a boundary layer. The $\frac{\delta}{D}$ ratio is the boundary layer mass transfer coefficient.

Apparent enrichment factor (E) can be determined using Eq. (8.15):

$$E = \frac{C_p}{C_f} \tag{8.15}$$

where: C_p – is the component mole fraction in the permeate [mol mol^{-1}].

PV is usually focused on the selective removal of minor components from the bulk feed solution. Concentration polarization effect is more important when the target component concentration in the feed mixture is low and the membrane is highly selective (Feng and Huang 1997). According to Eq. (8.14) the concentration polarization significance depends exclusively on the parameters $\frac{J_v \delta}{D}$ and E_0. However, it must be remembered that both Peclet number and the intrinsic enrichment factor (E_0) depend also on the organic component concentration in the feed mixture (Feng and Huang 1997).

Concentration polarization occurs principally for the PV process of dilute solutions where the minor component is preferentially transferred through the membrane. In case of separation of concentrated solutions the effect of concentration polarization is practically negligible (Feng and Huang 1997).

Both, the Peclet number and the intrinsic enrichment factor are the parameters which cannot be directly measured experimentally. Parameters of Eq. (8.14) can be determined from PV experimental data in various ways (Feng and Huang 1997; Baker et al. 1997; Bhattacharya 1997; Neel 1991; Nijhuis et al. 1991). The common approach of $\frac{J_v \delta}{D}$ value determination involves the application of data for the over

all VOC mass transfer coefficient (Q_{ov} [mol^{-1} m^2 Pa s]), derived from PV experiments according to Eq. (8.16) (Wijmans et al. 1996):

$$\frac{1}{Q_{ov}} = \frac{1}{k_{bl}} + \frac{P}{l} \tag{8.16}$$

where $\frac{P}{l}$ is membrane permeance [mol m^{-2} Pa^{-1} s^{-1}], l is the membrane selective layer thickness [m] and k_{bl} is a boundary layer coefficient [mol^{-1} m^2 Pa s].

Plotting $\frac{1}{Q_{ov}}$ as a function of l, k_{bl} value can be obtained by extrapolation to $l = 0$ (Nijhuis et al. 1991; Gref et al. 1992). It must be underlined that the procedure requires experimental data points at a constant feed velocity under conditions in which the membrane resistance is a considerable fraction of the overall mass transfer resistance.

Several authors (Baker et al. 1997; Bhattacharya 1997) proposed an equation for determination of boundary layer coefficient:

$$k_{bl} = a v_f^c \tag{8.17}$$

where: v_f is the feed liquid velocity in the flow channel along the membrane surface [dm^3 h^{-1}].

In this approach, pervaporation data obtained with a given membrane are used for plotting $\frac{1}{Q_{ov}}$ *vs* $\frac{1}{v_f^c}$. The value of exponent c is chosen in such a way that the experimental data points fit a straight line, and a value is subsequently obtained from the line slope Eq. (8.17) (Bhattacharya 1997).

Another approach was proposed by Baker et al. (1997). Authors suggested that mass transfer coefficients can be determined from the concentration polarization equation (Eq. 8.18):

$$-\ln\left(1-\frac{1}{E}\right) = -\ln\left(1-\frac{1}{E_0}\right) + \frac{J_v \delta}{D} \tag{8.18}$$

In this methodology, determination of the mass-transfer coefficient (δ/D) and the intrinsic enrichment factor of the membrane (E_0) involves the use of Eq. (8.18) followed by plotting $-\ln\left(1-\frac{1}{E}\right)$ *vs* the permeate volume flux (J_v), measured at constant feed solution flow rates but at different permeate pressures or at various feed temperatures (Baker et al. 1997).

The correlation between the PV system performance and the concentration polarization can be also described using data obtained at various feed solution velocity values and applying Eq. (8.19) (Ahmad et al. 2020):

$$-\ln\left(1-\frac{1}{E}\right)=-\ln\left(1-\frac{1}{E_0}\right)+\frac{J_v}{av_f^c} \tag{8.19}$$

As discussed by Nagy and Kulcsar (2010), using mass transport parameters of both the membrane and the boundary layers (solubility, convective velocity, diffusion coefficients, the layer thicknesses), simple and clear expressions can be obtained to calculate the concentration distribution in the boundary layer and the membrane layer, as well as the mass transfer rate, the enrichment factor and the concentration polarization modulus. The coupled model developed provides an opportunity to predict the PV process separation efficiency and allows to choose the preferable membrane structure for reaching the desired separation factor values (Nagy 2010).

Borisov et al. (2018) studied various parameters (temperature, organic component concentration and feed mixture velocity in the membrane module) influencing the concentration polarization modulus value and the diffusional boundary layer width for the pervaporative separation of methyl acetate from diluted aqueous solutions. The separation process was carried out using the high-performance Pervatech PDMS membrane. The proposed model procedure enables discussion of CP effect based on intrinsic enrichment factor calculation, without the need of determination of overall mass transfer coefficient. The main advantage of the procedure proposed is the fact that the intrinsic enrichment factor is calculated based exclusively on the experimental data obtained at different feed mixture velocity values (Borisov et al. 2018).

Solution-Diffusion Model Mass transfer through a dense membrane occurs by the sorption-diffusion-desorption mechanism, i.e. transfer is limited by sorption equilibrium and diffusion through the selective layer of the membrane. The separation of components during passage through the membrane is based on the difference in their sorption and diffusion properties. The solution-diffusion model was first used to describe PV through a dense membrane in (Binning et al. 1961).

In this model, it is assumed that the pressure in the membrane is constant and that the boundaries of the membrane are in equilibrium with the surrounding phases (Castro-Muñoz et al. 2020b). Mass transfer through the membrane occurs in several stages (Fig. 8.4b):

1. Diffusion of the components in the boundary layer of the liquid mixture towards the membrane;
2. Sorption (solution) of the feed components on the surface of the membrane;
3. Diffusion in the bulk of membrane material along the gradient of chemical potential;
4. Desorption (evaporation) from the surface of the membrane from the permeate side;
5. Vapour diffusion in the boundary layer behind the membrane towards the permeate condensation surface;

It should be noted that diffusion in the boundary layer is often neglected in the turbulent mode of feed mixture flow. As for the desorption and diffusion processes of permeate vapor, in vacuum PV (as a rule, with a pressure behind the membrane <10 mm Hg), they occur very quickly, and therefore are not explicitly included in the model equations.

The concentration of the component in the mixture at the membrane surface C_f is not equal to the concentration of this component inside the membrane, undergoing a break at the boundary. In accordance with the law of distribution of Nernst concentrations (and for gases - with Henry's law) on different sides of the phase interface, the concentrations are interrelated through the partition ratios K^L and K^G:

$$C_M = K^L C_f, C_M = K^G p_f \tag{8.20}$$

To describe the sorption equilibrium, experimentally obtained sorption isotherms are needed. Sorption can be described in terms of the activity $a = \gamma x$ and the dimensionless molar fraction of the component in the membrane $x = C\rho^{-1} = cM\rho^{-1}$, that are associated with the sorption isotherm, $a_i \oplus p_i / p_i^0$, where γ is the dimensionless activity coefficient, ρ is the bulk density, M is the molecular weight of the component, c is the molar concentration, p^0 is the equilibrium saturated vapor pressure.

In a state of equilibrium, the activity of the components on both sides of the phase interface is equal. Given the definition of chemical potential, the mass flux through the membrane can be expressed in terms of the difference in activity a_i, concentration C_i or partial pressure of the component p_i at the inlet and outlet of the membrane.

$$J_i = \frac{D_{M,i} C_{M,i}}{a_{M,i}} \frac{\left(a_{f,i} - a_{p,i}\right)}{l_M} \tag{8.21}$$

$$J_i = D_i \frac{\left(C_{fM,i} - !_{Mp,i}\right)}{l_M} \tag{8.22}$$

$$J_i = D_i K_i^G \frac{\left(p_{f,i} - p_{p,i}\right)}{l_M} \tag{8.23}$$

Here D is the diffusion coefficient of the dissolved component, l_M is the thickness of the membrane. Since the independent determination of the quantities that form the expressions $D_{M,i} C_{M,i} / a_{M,i}$ and $D_i K_i^G$ is sometimes difficult, a phenomenological parameter is introduced – the permeability coefficient P_i,

$$P_i = D_{M,i} C_{M,i} / a_{M,i} \text{ or } P_i^G = D_i K_i^G, \tag{8.24}$$

which is in the experiment for each component. In vacuum PV at low permeate vapor pressures $C_{fM,i} > > C_{Mp,i}$ and $p_{f,i} > > p_{p,i}$,. Taking this into account, Eqs. (8.13), (8.14) and (8.15) are written in a simplified form:

$$J_i \oplus \frac{P_i}{l_M} a_{f,i}, J_i \oplus \frac{D_i}{l_M} C_{fM,i} \text{ and } J_i \oplus \frac{P_i^G}{l_M} p_{f,i} \tag{8.25}$$

The dependences of fluxes, permeability coefficients, diffusion, and sorption of components on temperature T are often described by Arrhenius law. In case of sorption described by the Henry isotherm, the concentration of the component in the membrane is associated with its partial pressure. Therefore, the formula for the flux can be represented as:

$$J_i = \frac{P_i}{l_M}\left(C_{f,i} - p_{p,i} H_i^{-1}\right) \tag{8.26}$$

where H is a Henry constant.

Resistance-in-Series Model In (Wijmans et al. 1996), the solution – diffusion model was combined with the model of mass transfer resistance in series of thin layers (a boundary layer in a mixture, a selective layer, and a substrate layer).

Consider the case of vacuum PV (Fig. 8.4b). We write the Fick equation for the component flux in a system of thin layers (omitting the index i):

$$k_0\left(C_0 - C_p\right) = J, \tag{8.27}$$

where the total mass transfer coefficient is related to the mass transfer coefficients across the boundary layer and the membrane.

$$\frac{1}{k_0} = \frac{1}{k_f} + \frac{1}{k_M} \tag{8.28}$$

In case of vacuum PV $J \approx k_0 C_0$. By definition, the coefficient k is related to the mass transfer resistance R in a layer of thickness l, $1/k = l/D = R$. The mass transfer coefficient (resistance) of the boundary layer determines the role of concentration polarization. To calculate the resistance of a diffusion boundary layer, its thickness can be estimated using the methods described above. The resistance of the membrane layer $1/k_M = l_M/P_M$ depends on the properties of the membrane, the physicochemical properties of the components, and the thickness of the membrane. There may be cases when the membrane resistance is small, and the resistance of the boundary layer is comparable or even dominates, being a limiting factor of PV. This occurs during the PV of highly diluted aqueous-organic mixtures (Peng et al. 2003; Gudernatsch et al. 1991).

Models Taking into Account the Dependence of Diffusion Coefficients on Concentration In non-ideal concentration-dependent systems, the diffusion coefficient and the permeability coefficient of a component are concentration functions. Various models have been proposed to describe the concentration dependence of

diffusion coefficients. For instance, Rautenbach and Albrecht (1980) proposed linear and exponential approximations. The fully empirical model (Brun et al. 1985) is based on the approximation of the data of a PV experiment under the assumption that the flux depends on temperature according to the Arrhenius law. This approach was used to create a number of commercial programs for computer simulation of PV.

The solution-diffusion model was supplemented by the free volume theory (Shieh and Huang 1998a) and developed in (Shieh and Huang 1998b). The free volume theory makes it possible to predict quantitatively the concentration dependence of the thermodynamic diffusion coefficient.

4 Main Separation Tasks

There are three main separation tasks that are solved by the method of PV:

1. Water removal from organic solvents and their mixtures (hydrophilic PV).

This area of PV is currently the most studied in practical terms. During the existence of the method, at least a large number of polymers and inorganic materials have been tested in these processes. However, today only a small number of materials satisfy the requirements necessary for the industrial application of water selective membranes. Membranes should combine high water selectivity with high permeance, they must have good chemical and mechanical stability at elevated temperatures (about 100 °C) (Vane 2019).

2. Separation of organic-organic mixtures (organophilic PV).

The selection of the most suitable membrane material for use in organic-organic separation is an important factor and it depends on the chemical nature of the components to be separated. Only a few membrane materials have a specific affinity for one of the organic compounds and high solvent stability. Most often, polymers are used as membrane materials for the separation of organic mixtures, because they are preferable because of their good film-forming properties, great variety and low cost (Vandezande 2015). In organophilic PV, polymers containing polar and nonpolar fragments can be used, depending on the separation task.

Polymers, containing polar groups, such as polyvinyl alcohol (PVA) (Penkova et al. 2018; Singha et al. 2009; Castro-Muñoz and González-Valdez 2019), polylactic acid (PLA) (Galiano et al. 2019c; Msahel et al. 2021), polyvinyl chloride (PVC) (Aouak et al. 2016), polyether ether ketone (PEEK) (Zereshki et al. 2011), polyimides (Dai et al. 2016; Castro-Muñoz et al. 2019b), cellulose acetate (Ma et al. 2008) and chitosan (Galiano et al. 2019a; Kononova et al. 2018; Patil and Aminabhavi 2008; Castro-Muñoz et al. 2020c) provide selective diffusion of polar and aromatic solvents through the membrane, while being stable in feed mixtures.

3. Recovery of organics from water (hydrophobic PV).

The term hydrophobic (organophilic in early publications) PV is used to define PV mode, in which volatile organics are recovered from aqueous solutions. Although the application of hydrophobic pervaporation for volatile organics recovery is feasible, it is still not economically viable (Jullok et al. 2011; Lipnizki et al. 1999). The possible applications of hydrophobic PV for organic components removal from aqueous solutions have been already recognized in waste-water treatment (Lipski and Cŏté 1990; Czerwiński et al. 2004). PV can be also applied during recovery of aroma compounds in the food industry, e.g. recovery of dairy aroma components (Baudot and Marin 1996), etheric oil aroma components (Mauz et al. 1996), apple juice aromas (Börjesson et al. 1996), pomegranate aroma compounds (Raisi and Aroujalian 2011), and bergamot essential oil (Galiano et al. 2019a). Nowadays, a promising application of hydrophobic PV is its use for the recovery of ABE fermentation process products (Vane 2005; Kujawska et al. 2015; García et al. 2011).

The most promising PV membrane materials with high permeability and separation factors for recovering organics from water are elastomeric polymers including PDMS (Kujawska et al. 2015), polyoctylmethylsiloxane (POMS) (Rom and Friedl 2016) and polyalkylmethylsiloxanes (Kirk et al. 2019), high free volume glassy polymers such as poly[1-(trimethylsilyl)-1-propyne] (PTMSP) (Volkov et al. 2020; Borisov et al. 2014) or PIMs (Golubev et al. 2020; Žák et al. 2015), and mixed matrix membranes, such as membranes filled with hydrophobic zeolites (Dobrak et al. 2010; Liu et al. 2013; Vane et al. 2008; Castro-Muñoz and Fíla 2018).

5 PV in Aroma Recovery

The flavor is responsible of the determination of the pleasantness of a given food which depends on different properties such as the taste, the text, the pungency and the aroma (Bomben et al. 1973).

Aroma compounds are a blend of organic and volatile molecules present at very low concentration, usually ppm or ppb levels, in many natural sources. Chemically they can be distinguished as esters, alcohols, aldehydes, terpens, amines, mercaptans, lactones (Aroujalian and Raisi 2007). They are the main responsible of the fragrance, the taste and the odour of many natural products from which they are usually isolated. Aroma compounds are widely used, for their properties, in the cosmetic and food industry. However, some industrial processes occurring during the production of beverages and juices, such as the concentration step and the thermal treatment (e.g. pasteurization), can cause the loss or the deterioration of many of these valuable components. Chemical modifications due to thermal degradation, Maillard reactions or oxidation can, in fact, occur. In order to maintain the original flavour of the product it is important to recover the aroma compounds and add them back to the concentrated original product (Pereira et al. 2006).

Common techniques for aroma recovery are distillation, partial condensation, solvent liquid extraction and adsorption. However, the degradation of the aroma compounds, the high energy consumption and aroma contamination represent some of the main disadvantages associated to these processes (Lipnizki et al. 2002a). In this regard, PV can be considered as a valid alternative to other common techniques for the recovery of natural aroma compounds in an efficient and competitive way. PV process, in fact, allows the recovery of volatile compounds at low temperatures preserving the molecular integrity of the aroma components operating with a low energy consumption and high selectivity. PV can concentrate the aroma compounds of more than 100 times respect to their concentration in the aqueous solution (Karlsson and Trägårdh 1993). Hydrophobic or organophilic PV represents one the main area of applications of this process for the recovery of aroma compounds from juices or from aqueous solutions through the use of organophilic membranes (Fig. 8.6). Organophilic membranes present higher affinity for organic compounds favouring their removal from diluted aqueous solutions. PV is particularly efficient when organic solutes are immiscible in water. In this case the permeate phase is enriched with the organic volatile molecules, while the aqueous feed stream is purified and can be recycled. PDMS is the most employed material in this type of application due to its high selectivity and permeability towards many of the aroma compounds. Silicalite fillers are often employed in combination with PDMS membranes. The higher potential selective role of silicalite-grafted membranes, however, has been under debate by many authors (Baudot and Marin 1997).

Most of the aroma compounds are represented by hydrophobic molecules such as linear and cyclic esters requiring hydrophobic membranes for their recovery. Alcohols and aldehydes, on the contrary, are typically hydrophilic molecules. However, the common presence, in their chemical structure, of apolar groups like the benzene nucleus (this is the case of benzyl alcohol, *o*-cresol, thymol, benzaldehyde) makes these molecules often recoverable with hydrophobic membranes (Castro-Muñoz 2019b). Table 8.1 summarizes some of the most diffused agro-food aroma compounds recovered by means of PV.

Due to the large number of compounds constituting an aroma, most of the researches have been carried out using aqueous solutions with model aroma compounds, while just a few studies have been conducted on real extracts. Moreover, many researches focus on binary model systems instead of multi-component mixtures. The difference in these two kinds of approaches is quite different and mainly related to the so-called “coupling phenomenon”. Coupling effect is related to the intermolecular interactions occurring in multicomponent mixtures and the interaction that each component can have with the membrane (Ren and Jiang 1998). Coupling phenomena can be related to kinetic or thermodynamic factors. The kinetic factor enters into play when a fast permeant drags a slower permeating molecule to diffuse along with it through the membrane giving higher permeability for the slower compounds. The thermodynamic factor is related to a change in the concentration of one component in the membrane as a consequence of the presence of other molecules. This is mainly caused by the intermolecular interactions between the different species constituting the multi-component mixture and their single

Table 8.1 Agro-food aroma compounds recovered by PV and their physicochemical properties

Chemical class	Compound	Chemical structure	Occurrence	MW (gr/mol)	BP (°C)
Esters	Methyl acetate		Cashew apple	74.08	57.1
	Ethyl acetate		Apple, orange, pineapple, beer, wine	88.11	77.1
	Methyl butanoate (methyl butyrate)		Kiwifruit	102.13	102.8
	Ethyl butanoate (ethyl butyrate)		Pineapple, orange, strawberry, kiwifruit, apple	116.16	120
	Ethyl hexanoate		Pineapple, cashew apple, wine	144.21	168
	Linalyl acetate		Bergamot	196.29	220
Alcohols	Ethanol		Wine, beer	46.07	78.37
	Propanol		Beer	60.09	97
	Butanol		Apple	74.12	117.7
	Hexanol		Bilberry, pomegranate, kiwifruit, apple, wine	102.16	157
	Linalool		Bilberry, orange, strawberry, bergamot, tea	154.25	198
	α-Terpineol		Orange	154.25	219
	3-hexen-1-ol		Bilberry	100.16	156.5
	1-octen-3-ol		Kiwifruit, cashew apple	128.21	84.5
	3-methyl-1-butanol (Isoamyl alcohol)		Wine	88.15	130
	2-Methylpropan-1-ol (Isobutanol)		Wine	74.12	107.89
Aldehydes	Acetaldehyde		Beer	44.05	20.2
	Hexanal		Orange, apple, cashew apple	116	129
	3-Methylbutanal		Pomegranate	86.13	94
Ketones	2,3- Butanedione		Coffee, diary products	86.08	88
	2,3 - Pentanedione		Coffee	100.11	108
Aromatic compounds	Limonene		Orange, bergamot, lemon, cashew apple	136.24	176
	5-methyl-furaldehyde		Wine	110.11	187
	Phenyl acetaldehyde		Bilberry	120.15	195

MW molecular weight, *BP* boiling point, p^s saturation pressure, γ^{∞} activity coefficient at infinite dilution, *H* Henry's constant

interaction with the membrane material (Raisi and Aroujalian 2011). The coupling effect is still difficult to be measured and it can greatly depend on the different types of mixtures used. She and Hwang (2006), for instance, did not detect any coupling phenomenon for the PV of mixtures of dilute multiple flavor organics. Raisi and Aroujalian (2011), on the contrary, observed that the coupling effect between aroma compounds cannot be ignored and increased as the concentration of some aroma compounds in the feed mixture increased. It has also been found that the concomitant presence of non-volatile compounds such as proteins, sugars and lipids do not greatly interfere with the transport of the aroma compounds through the membrane (Baudot and Marin 1997; Castro-Muñoz 2019c). However, it has been observed that, in some cases, proteins like casein or bovine serum albumin (BSA) can increase the retention of volatile permeating molecules (Sorrentino et al. 1986; Druaux et al. 1995; Pichardo-Romero et al. 2020).

PV operating parameters such as temperature, feed cross-flow velocity and vacuum pressure can also affect the membrane performance during the aroma recovery process. The temperature is generally kept low (between 20 and 50 °C) to preserve the molecular integrity of thermo-sensitive compounds. The increase of feed temperature is associated with an increase in membrane flux. In the work of Lipnizki et al. (2002a), it was demonstrated that compounds with low recovery rates (such as alcohols) benefits more of the temperature increase in comparison with aroma compounds with high recovery rates (such as esters). Temperature variations can be, therefore, responsible of changes in the aroma profile. The feed flow rate can also affect the recovery of aroma compounds in PV. A too much low feed flow rate is, in fact, associated to an increase in the concentration polarization phenomenon which results in a decrease in membrane flux and selectivity.

An increase in permeate pressure produces a decrease of membrane permeate flux. The decrease in the driving force is, therefore, associated to a decrease of aroma compounds recovery. In general, aroma compounds with low volatility are more affected by the changes in permeate pressure in comparison to aroma compounds with high volatility as a consequence of their lower driving force across the membrane (Trifunović et al. 2006).

5.1 Aroma Recovery from Fruits, Coffee and Tea

More than 6000 compounds participate to the aroma of different types of fruits. Fruit passion and orange juices, for instance, have more than 200 compounds responsible of their aroma (Pereira et al. 2005; Castro-Muñoz et al. 2020d). The processing of fruit juices, at industrial level, can cause a loss of aroma accompanied by a decrease in product quality. Fruit juices, in fact, are subjected to a concentration step with the aim of removing the excess of water for improving the stability of the product and reducing the storage and the transportation cost.

PV represents one of the most promising technology for the recovery of these aroma compounds that can be added back to the juice in order to restore their original properties.

Aroujalian and Raisi (2007) studied the recovery of volatile aroma compounds from orange juices evaluating different process parameters such as feed flow rate, feed temperature and permeate pressure on PV performance (flux and selectivity) of PDMS asymmetric membranes. The recovery of six aroma compounds (ethyl acetate, ethyl butyrate, hexanal, limonene, linalool, α-terpineol), as the most representative molecules of orange juice, was considered.

It was found that the effect of feed flow rate (where the Reynolds number was increased from 500 to 2500) caused a slight increase in membrane flux (from about 0.16 to 0.18 kg/m^2 h) without appreciable variations in membrane enrichment factor. The rise in feed temperature (from 25 to 50 °C), on the contrary, had a significant effect on membrane total flux which increased from about 0.16 to 0.4 kg/m^2 h (at a permeate pressure of 1 mmHg). This was mainly due to an increase of the thermal motion of polymer chains which promoted the formation of a higher free volume accessible by more permeating molecules. Temperature increase was beneficial also for the enrichment factor which improved for all the aroma compounds considered. The permeate pressure is another important parameter worth to be considered in PV. An increase in permeate pressure, in fact, is responsible of a decrease in the driving force through the membrane, resulting in a decline of permeate flux. The variation in permeate pressure from 1 to 40 mmHg was positive for the enrichment factor of some aroma compounds (such as ethyl acetate, ethyl butyrate, hexanal) while it was slightly deleterious for the others (limonene, linalool and α-terpineol). This was mainly related to the different chemo-physical properties of the different aroma compounds such as polarity, relative volatility and molecular size.

A mathematical model for the pervaporative recovery of a multi-component mixture of aroma compounds (E-2-hexen-1-ol, n-hexanol, E-2-hexen-1-al, linalool, phenyl acetaldehyde, benzyl alcohol and Z-3-hexen-1-ol), characteristic of bilberry juice, was studied by Diban et al. (2008). Four different PDMS membranes with different thicknesses were investigated. The theoretical results showed that the increase in membrane thickness is responsible of an increase in enrichment factor. n-hexanol was calculated to have the highest value of enrichment factor (236.9), followed by E-2-hexen-1-ol (120.6) and linalool (49.3).

The recovery of aroma from citrus peel oil has become of great interest for the cosmetic and perfume industries thanks to their freshness and fragrance. In particular, the oil extracted from bergamot fruit is also appreciated from the pharmaceutical industry for its antiseptic and antibacterial properties. However, the presence of bergapten, able to induce melanogenesis and thickening of the stratum corneum when in combination with UV light, poses serious risks for its full exploitation in this field. In this regard, Figoli et al. (2006) were able to perform, by means of PV, the recovery of the aroma flavour bouquet from bergamot peel oil without the presence of the photoactive molecule bergapten. A PDMS membrane containing ZSM-5 filler, was employed for the separation of bergamot peel oil from different water/ethanol solutions. The membrane was found to be permeable to many of the aroma compounds investigated such as linalool, linalyl acetate and limonene which mainly contribute to the essence degree of the bergamot oil. Bergapten, on the contrary, was successfully retained by the membrane. The total flux increased (from about 0.13 to

about 0.22 kg/m^2 h at 50 wt% ethanol) with the increase of feed temperature (from 20 to 40 °C) as a result of a higher thermal motion of the polymer chains, and also increased (from about 0.07 to 0.22 kg/m^2 h at 40 °C) with the increase of ethanol concentration in the feed as a consequence of a higher swelling degree of the membrane. The temperature increase had also a positive effect on the enrichment factor which increased by a factor of 1.2 for linalyl acetate and 2.7 for linalool.

In another work, Galiano et al. (2019a) studied the recovery of three aroma compounds (linalool, limonene and linalyl acetate) extracted from bergamot peel by means of an enzymatic pre-treatment in order to enhance the extraction yield. Two commercial asymmetric membranes with a selective layer made of PDMS and POMS were employed for the PV tests. Both membranes presented an increase in enrichment factor when the enzymatic pre-treatment was employed. Linalyl acetate presented the highest values on enrichment factor (about 47) probably as a consequence of its higher affinity with the two hydrophobic membrane materials.

PV of four aroma compounds (3-methylbutanal, isopentyl acetate, *n*-hexanol, α-ionone) representative of pomegranate juice was studied by Raisi et al. (2008) using two commercial PDMS and POMS membranes. Both membranes were found to be more selective for 3-methylbutanal and isopentyl acetate. The reason can be ascribed to the presence of the hydroxyl group in *n*-hexanol which reduced the activity coefficients of organics in water, and to the higher molecular size of α-ionone which slowed down its diffusion through the membrane. In general, PDMS membranes presented higher flux (between 0.1 and 0.27 kg/m^2 h) respect to POMS (between 0.06 and 0.09 kg/m^2 h) but higher enrichment factors. The reason can be related to the higher hydrophobicity of POMS membrane, due to the presence of the bulky octyl groups, which restricted the permeation of water molecules where the aroma compounds where dispersed. By comparing the results, in terms of flux and enrichment factor, of model aroma aqueous solutions with real pomegranate juice, no great differences were observed excluding the existence of possible coupling phenomena.

The use of PV for the recovery of aroma compounds from soluble coffee was investigated by Weschenfelder et al. (2015) employing a PDMS membrane and evaluating the effect of feed flow rate, temperature and permeate pressure. Coffee beverages are a blend of more than 800 aroma compounds with a great number of functional groups (Sarrazin et al. 2000). The production of industrial soluble coffee implies a series of steps which can cause the transformation or loss of some important aroma compounds. The addition of these natural aroma compounds on processed instant coffee can be, therefore, beneficial for improving its organoleptic properties. In this work, the permeation of eight selected aroma compounds typical of industrial coffee solutions (2,3-butanedione; 2,3-pentanedione; 3-methylbutanal; benzaldehyde, acetaldehyde, furfural, 2,5-dimethylpirazine and 5-methyl furfural) was evaluated. The change in feed flow rate (1 l/min and 3 l/min) did not affect the partial flux of any of the investigated aroma compounds. This result evidenced that the mass transfer resistance of the compounds was governed exclusively by the resistance exerted by the membrane. The permeation flux of all organic compounds increased, instead, when the feed temperature was increased from 10 to 40 °C. The lowest temperature investigated (10 °C) corresponded to the lowest values of

enrichment factor for all the aroma compounds considered. The increase of temperature, however, produced different results on the basis of the aroma considered. 2,3-butanedione and 2,5-dimethylpirazine, for instance, presented the highest enrichment factor at 20 °C (45 and 40, respectively). Furfural and 5-methyl furfural enrichment factors were not influenced by temperature variations and presented the lowest values (below five). The increase in permeate pressure (from 300 to 2200 Pa) caused a decrease of the partial fluxes for all the aroma compounds except that for 5-methyl furfural. In general, the enrichment factor improved as the permeate pressure increased (except for furfural and 5-methyl furfural which remained constant). The highest value of enrichment factor (about 70) was measured for 2,5-dimethylpirazine at the permeate pressure of 900 Pa.

The recovery of eight aroma compounds (trans-2-hexenal, 3-methylbutanal, 2-methylpropanal, phenylacetaldehyde, benzyl alcohol, linalool, cis-3-hexenol, and β-ionone) from tea was studied by Kanani et al. (2003) in binary, multi-component and real tea solutions using POMS and PDMS membranes. The behaviour of the different aromas was dependent on the membrane used and on the type of solution. In binary solutions, the aldehydes displayed the highest values of enrichment factors while alcohols showed the highest enrichment factors in the multi-component mixture. In case of real tea extract, many differences were observed in terms of permeability and enrichment factors towards the eight investigated compounds due to the complexity of the system (containing more than 600 compounds).

In Table 8.2, the PV data of different articles dealing with the recovery of aroma compounds from fruit, coffee and tea matrices are summarised.

5.2 Aroma Recovery from Alcoholic Beverages

The market of low-alcohol or free-alcohol beverages, such as beer and wine, is knowing an interesting expansion during the last years as a consequence of the new driving restrictions and religious reasons (Conidi et al. 2020; Castro-Muñoz 2020). However, the taste of alcohol-free beverages does not perfectly match the taste and flavour of their classic alcoholic counterpart. This is mainly due to the fact that during the dealcoholisation step some of the original aroma compounds can be lost (Catarino et al. 2007).

Del Olmo et al. (2014), for instance, studied the pervaporative recovery of aromas in two different beers: a Special beer (with an alcohol volume content of 5.5%) and a Reserve beer (with an alcohol volume content of 6.5%). The recovered aroma compounds (ethyl acetate, isobutyl alcohol and isoamyl acetate) were then added to a free-alcohol beer and a low-alcohol beer in order to improve their organoleptic properties. Both beers, as a consequence of their closer alcohol content, presented a similar total flux (about 3–4 kg/m^2 s) when tested through an asymmetric PDMS membrane which was employed for the PV test. Ethyl acetate showed the highest enrichment factor (about 40 after 2 h of test) for both beers, followed by isoamyl acetate and isobutyl alcohol. The addition of recovered aromas in the free-alcohol

Table 8.2 PV articles dealing with aroma recovery from fruits, coffee and tea

Fruit source	Aroma compounds recovered	Membrane selective layer material	Operating conditions (temperature (T), feed flow rate (FR), permeate pressure (P))	Total flux (kg/m^2 h)	Enrichment factor (β)	Reference
Orange juice (real solution)	Ethyl acetate Ethyl butyrate Hexanal Limonene Linalool α-Terpineol	Asymmetric PDMS	T: 25–50 °C FR: 500–2500 Reynolds P: 1–40 mmHg	0.054 (T = 25 °C, P = 40 mmHg)	Ethyl acetate: ~ 11 Ethyl butyrate: ~ 5.8 Hexanal: ~ 6 Limonene: ~ 12 Linalool: ~ 8 α-Terpineol: ~ 5.2	Aroujalian and Raisi (2007)
Bergamot essential oil (real solution)	β -Pinene β-Myrcene Limonene δ-3-Carene γ-Terpinene Linalool Linalyl acetate δ-4-CareneTraces Trans-caryophyllen α-Bergamotene β-Bisabolene Bergapten Neryl acetate	Asymmetric PDMS	T = 20–40 °C	0.07–0.22 (T = 40 °C)	Linalool: ~ 28 Linalyl acetate: ~ 55 (T = 40 °C)	Figoli et al. (2006)

(continued)

Table 8.2 (continued)

Fruit source	Aroma compounds recovered	Membrane selective layer material	Operating conditions (temperature (T), feed flow rate (FR), permeate pressure (P))	Total flux (kg/m^2 h)	Enrichment factor (β)	Reference
Bergamot essential oil (real solution)	Limonene Linalool Linalyl acetate	Asymmetric PDMS	T = 25–40 °C	0.5–1.1	Limonene: ~ 4 Linalool: ~ 9 Linalyl acetate: ~ 17 (T = 40 °C)	Galiano et al. (2019a)
		Asymmetric POMS		0.05–0.1	Limonene: ~ 36 Linalool: ~ 26 Linalyl acetate: ~ 47 (T = 40 °C)	
Pineapple juice (model solution)	Ethyl acetate Ethyl butanoate Ethyl hexanoate	Asymmetric ethylene-propylene-diene terpolymer (EPDM)	T: 25 °C FR: 30 l/h	0.033	Ethyl acetate: 125.3 Ethyl butanoate: 516 Ethyl hexanoate: 213.2	Pereira et al. (2005)
Pomegranate juice (model and real solution)	3-methylbutanal isopentyl acetate *n*-hexanol α-Ionone	POMS	T: 30 °C FR: 2000 Reynolds P: 1 mmHg	0.06–0.09	3-methylbutanal: ~ 28 Isopentyl acetate: ~ 25 *n*-hexanol: ~ 28 α-Ionone: ~ 10	Raisi et al. (2008)
		PDMS		0.1–0.27	3-methylbutanal: ~ 45 isopentyl acetate: ~ 50 *n*-hexanol: ~ 33 α-Ionone: ~ 26	

Kiwifruit juice (real solution)	Methyl butanoate ethyl butanoate (E)-2-hexenal 3-hexen-1-ol (E)-2-hexen-1-ol 1-hexanol 1-octen-3-ol Methyl benzoate Ethyl benzoate	Styrene–butadiene–co-styrene (SBS)	T: 25–50 °C P: 5 mmHg	$1 \cdot 10^{-4}$ - $3 \cdot 10^{-4}$	(E)-2-hexenal: ~ 65 (E)-2-hexen-1-ol: ~ 42 1-octen-3-ol: ~ 7 Methyl benzoate: ~ 18 Ethyl benzoate: ~ 5 (T = 50 °C)	Figoli et al. (2010)
Grape juice (model solution)	Methyl anthranilate	PDMS-polycarbonate	T: 33 °C P: 3 mmHg	0.056	9.3	Rajagopalan and Cheryan (1995)
		Polyether block amide (PEBA)		0.102	15.3	
Strawberry juice (model solution)	Methyl butyrate Ethyl butyrate Butyl butyrate methyl caproate ethyl caproate linalool	Asymmetric PDMS	T: 50 °C P: 4 mbar	0.175	Methyl butyrate: 53 Ethyl butyrate: 34 Butyl butyrate: 15 Methyl caproate: 17 Ethyl caproate: 12 Linalool: 11	Isci et al. (2006)

(continued)

Table 8.2 (continued)

Fruit source	Aroma compounds recovered	Membrane selective layer material	Operating conditions (temperature (T), feed flow rate (FR), permeate pressure (P))	Total flux (kg/m^2 h)	Enrichment factor (β)	Reference
Apple juice (model solution)	Trans-2-hexanal Ethyl acetate Hexyl acetate Ethyl butanoate Butanol Hexanol	Asymmetric PDMS	T: 20 °C FR: 22000 Reynolds	0.045	Trans-2-hexanal: ~ 400 Ethyl acetate: ~ 100 Hexyl acetate: ~ 3800 Ethyl butanoate: ~ 1100 Butanol: ~ 25 Hexanol: ~ 90	Börjesson et al. (1996)
		Asymmetric POMS		–	Trans-2-hexanal: ~ 700 Ethyl acetate: ~ 200 Hexyl acetate: ~ 3900 Ethyl butanoate: ~ 2100 Butanol: ~ 40 Hexanol: ~ 75	
		PEBA		–	Trans-2-hexanal: ~ 150 Ethyl acetate: ~ 10 Hexyl acetate: ~ 900 Ethyl butanoate: ~ 200 Butanol: ~ 20 Hexanol: ~ 125	

Coffee (real solution)	2,3-Butanedione 2,3-Pentanedione 3-Methylbutanal benzaldehyde acetaldehyde Furfural 2,5-Dimethylpirazine 5-methyl furfural	Asymmetric PDMS	T: 10–40 °C FR: 1–3 l/min P: 300–2200 pa	–	2,3-Butanedione: ~ 45 2,3-Pentanedione: ~ 6 3-Methylbutanal: ~ 8 benzaldehyde: ~ 3 acetaldehyde: ~ 5 Furfural: ~ 2 2,5-Dimethylpirazine: ~ 42 5-methyl furfural: ~ 2 (T = 20 °C; FR: 1.5 l/min; P: 300 pa)	Weschenfelder et al. (2015)
Tea extract (real solution)	Trans-2-hexenal 3-methylbutanal 2-methylpropanal Phenylacetaldehyde benzyl alcohol linalool Cis-3-hexenol β-Ionone	PDMS	T = 30 °C	–	Trans-2-hexenal: 23 3-methylbutanal: 65 2-methylpropanal: 7 Phenylacetaldehyde: 117 Benzyl alcohol: 74 Linalool: 173 Cis-3-hexenol: 1113 β-Ionone: 990	Kanani et al. (2003)
		POMS			Trans-2-hexenal: 22 3-methylbutanal: 7 2-methylpropanal: 69 Phenylacetaldehyde: 26 benzyl alcohol: 24 Linalool: 31 Cis-3-hexenol: 900 β-Ionone: 1787	

and a low-alcohol beers, showed an improvement in the sensorial properties of the brews. The enriched beers, in fact, were preferred by the 90% of the tasters respect to their not enriched versions.

The extraction of aroma compounds from beer, before dealcoholisation, was also studied by Catarino et al. (2009) through a response surface methodology (RSM) based on mathematical and statistical analyses where the effect of different PV parameters (temperature, pressure and feed velocity) was evaluated using a POMS membrane. Different compounds, typical of the aroma beer composition, were considered. From the results it was found that, in general, the temperature was the variable principally influencing the permeation flux. In particular, the increase in temperature led to an increase in the selectivity of alcohols (such as propanol, isobutanol and amyl alcohols), while negatively influenced the membrane selectivity for esters (such as ethyl acetate, isoamyl acetate) and acetaldehyde. The selectivity for alcohols decreased with the increase in permeate pressure, while the selectivity of esters evidenced the opposite trend. The results showed how difficult can be the optimization of a process with a multi-components mixture. Bearing in mind the objectives of maximizing the membrane permeate flux, maximizing the aroma selectivity and minimizing the ethanol concentration in the feed, the optimal conditions that have been found were: 12.4 °C of feed temperature, 0.45 m s^{-1} for the feed velocity and 1 mbar of permeate pressure.

The recovery of eight aroma compounds from muscat wine was studied by Karlsson et al. (1995) using a PDMS membrane evaluating the effect of the feed temperature (from 6 to 35 °C) on flux and selectivity. From the results obtained, it was observed that the water and ethanol fluxes (as the major components of the wine) increased with the increase of the temperature showing similar values (from about 0.04 to 0.2 k/m^2 h). The enrichment factor of the various aroma compounds was also dependent on the applied temperature. Ethyl acetate showed the highest enrichment factor (between 190 and 162) which decreased as the feed temperature was increased. On the contrary, the other aromas showed an opposite trend: the enrichment factor increased as the temperature increased. Hexanol presented the second highest enrichment factor (between 25 and 55), followed by isoamyl alcohol (between 17 and 29), isobutanol (between 13 and 18) and methyl lactate (between 1.7 and 2.9). Two of the aroma compounds characteristics of the muscat wine (2,3-butanediol and 5-methyl-furaldehyde) were not detected in the permeate probably due to the fact that their partial permeate pressures was higher than the equilibrium feed pressure of the components, as can be confirmed by their high boiling temperatures (above 175 °C). The authors calculated for the muscat wine and the pervaporated aromas the so-called aroma value (AV_i) defined as the ratio of the aroma concentration to the aroma threshold value (ATV_i). The ATV represents the lowest concentration of an aroma in an aqueous solution that is necessary to be perceived (Simpson 1979). High values of AV_i are related to a high influence of the aroma on the overall aroma of the beverage. Lower values of AV_i, however, does not necessarily imply a lower importance of an aroma since it may contribute to the amplification of other aroma compounds present in the beverage. The AV_i obtained through PV were compared with the ones of the original wine. Isoamyl alcohol showed the highest AV_i in the wine followed by 5-methyl-furaldehyde, furaldehyde,

2,3-butanediol and ethyl acetate. In the PV permeate, isoamyl alcohol presented, as the wine, the highest AV_i (between 500–900) but it was followed by ethyl acetate (between 400–500) and hexanol (between 1535).

The recovery of eight aroma compounds (ethyl acetate, isobutyl alcohol, isoamyl alcohol, 1-hexanol, isoamyl acetate, ethyl hexanoate and linalool) from wine-must fermentation was studied by Schäfer et al. (1999). PV experiments were carried out using a POMS membrane at different stages of the fermentation process corresponding to different ethanol and aroma concentrations. The ethanol and aroma concentrations, in fact, tend to increase as the fermentation process goes forward. Isoamyl alcohol and isobutyl alcohol, also called fusel oil alcohols, presented an increase in their partial fluxes as their concentration in the feed increased. The enrichment factor reached a maximum of 60 and 100 for isobutyl and isoamyl alcohol, respectively. The three esters considered (isoamyl acetate, ethyl hexanoate and ethyl acetate) presented a similar trend in partial fluxes which increased with the increase of their feed concentration reaching a maximum enrichment factor of 450 for isoamyl acetate, 800 for ethyl hexanoate and 350 for ethyl acetate. Respect to the fusel oil alcohols, for the three esters the enrichment factor increased with the increase of their concentration in the feed solution. This was explained considering that the ethanol concentration also increased with the advancing of the fermentation. The ethanol molecules were more prone to form hydrogen bonds with the esters molecules in comparison to fusel alcohol molecules resulting in the so-called coupling effect which enhanced the diffusivity of the esters trough the membrane. Finally, 1-hexanol and linalool presented just a slight change in concentration during the fermentation process with an enrichment factor between 140–180 for 1-hexanol and between 80–150 for linalool.

5.3 Aroma Recovery from Food

It is also possible to apply the PV process for the recovery of aroma compounds deriving from food matrices.

Wastewater coming from seafood industry processing, for instance, contains a large amount of flavour components representing a high value food product (Cha et al. 1993). In this regard, Martìnez et al. (2013) studied the recovery of aroma compounds from brown crab boiling juice comparing the PV performance of two membranes made of POMS and PDMS. Seven aroma compounds (1-octen-3-ol, 1-penten-3-ol, 3-methylbutanal, hexanal, benzaldehyde, 2,3-pentadione and ethyl acetate) were selected for the preparation of a model multicomponent solution. Both membranes were able to concentrate all the selected aroma compounds even if the POMS membrane operated with lower total flux. For most of the aromas, the PDMS membrane presented higher enrichment factors and it was the membrane that better preserved the original feed aroma profile. The highest enrichment factors were obtained for benzaldehyde (51 for the PDMS membrane) and for 1-octen-3-ol (120 for POMS membrane). Brown crab boiling juice contains also different non-volatile components like salts (sodium chloride). Therefore, the effect of salt concentration was evaluated with PDMS membrane. It was found that salt had a positive effect in

improving aromas enrichment factor but up to a certain concentration (0.51 mol/kg). The positive effect can be related to the fact that salt reduces the solubility of organic compounds in water decreasing their activity coefficient favouring their permeation through the membrane. The negative effect, when its concentration was too high, can be related to the formation of fouling at membrane surface.

Oysters represent some of the most renowned seafoods in the world. To facilitate the opening of their shells and to increase their safety for human consumption, oysters are often immersed in boiling water. The boiling water becomes then rich of many volatile organic compounds (VOCs) with high technological potential. Santos Soares et al. (2020) studied, for the first time, the possibility to recover these aroma compounds from oyster boiling juice for a possible reuse as "natural flavours" in the food industry. 1-octen-3-ol, benzaldehyde and hexanal were investigated as main oysters aroma compounds present in its boiling juice using an asymmetric PDMS membrane. While the feed flow rate did not affect the total flux, the increase in the feed temperature caused an increase both in the total flux and in the partial organic fluxes. The enrichment factors varied for the single aroma compounds on the basis of the temperature applied (from 20 to 50 °C). In particular, 1-octen-3-ol showed the highest enrichment factor (about 27) at 30 °C which decreased when the temperature was increased to 40 °C (about 10) and 50 °C (about 3). In general, a decrease in enrichment factor, when the temperature is increased, means that the effect of diffusivity overcomes the effect of solubility. Benzaldehyde showed its highest enrichment factor (about 17) at 40 °C, while hexanal at 50 °C (about 4).

Baudot and Marin (1996) applied PV for the recovery of two aroma compounds found in dairy products: 2,3-butanedione and methylthiobutanoate. The first aroma is a relatively hydrophilic molecule generally recurrent in pasteurized milk, butter and yoghurt. Methylthiobutanoate is a high hydrophobic molecule which can be found at the surface of some ripened French cheeses. Two membranes made of PDMS and PEBA were employed for the experiments. For the binary solution water- methylthiobutanoate, PDMS membrane displayed the higher total flux (from two to four-fold) in comparison to PEBA membrane at all the different permeate pressures investigated. However, PEBA membrane showed better values of enrichment factor (up to 1205) allowing the collected permeate to separate in two phases (one organic and one aqueous phase) which could be easily separated. Even in the case of water-2,3-butanedione solution, PDMS membranes presented higher total and partial fluxes but very similar enrichment factors (between 15 and 19) in comparison to PEBA membranes.

6 Outlook and Conclusions

The possibility to recover natural aroma compounds from fruit juices, beverages and food has received an increasing interest in the biotechnological, food and cosmetic industry. The natural extraction of natural aromas, as alternative to the chemical synthesis, is generally the preferred choice due to the wider acceptance of natural compounds from the consumers. During the last three decades, PV demonstrated its

huge potential in the recovery of organic aroma compounds from aqueous solutions being able to preserve their molecular integrity, to operate with a single step and with a low energy consumption. A large number of studies evidenced the feasibility of concentrating different types of aroma compounds, belonging to different chemical classes and deriving from different sources, by means of PV. However, most of the studies carried out so far deals with the separation of binary or model aqueous solutions at laboratory scale. The scale-up of PV at industrial level is already a reality in the field of solvent dehydration and in the separation of azeotropic mixtures. Therefore, more studies using real food systems should be carried out in the next future to pave the way for a full exploitation of PV on a larger industrial scale in the aroma recovery field. The isolation of natural aromas is still an energy intensive and costly process in comparison to their counterparts chemically synthesised. Podstawczyk et al. (2017) carried out, in this regard, an economic analyses on the separation of aroma compounds from the apple hydrolate by using a semi-pilot PV plant in two process configurations: batch and continuous. The evaluation of different economic (raw material cost, product price, labour demand, taxation rate) and process variables (degree of folding) led to the conclusion that PV can be effectively considered as a profitable solution for the separation of aroma compounds from hydrolates for their use in the food industry. Lipnizki et al. (2002a) developed a simulation approach for the analyses of PV performance for ten select aroma compounds for the potential application of this process in the food industry. The study carried out showed the importance of a process simulation for the different parameters acting in PV (such as permeate pressure, feed temperature or module design) which can be successfully applied for the design of a PV unit at industrial scale. The potential of PV in the food industry was also demonstrated, by the same authors in a second study (Lipnizki et al. 2002b), for the recovery of apple aromas using semi-batch and continuous processes with PDMS and POMS membranes.

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Part III
Separation of Biological Metabolites Through Membrane Technologies

Chapter 9
Separation of Bioactive Compounds from Fermentation Broths Using Membranes

Elsa Díaz-Montes and Roberto Castro-Muñoz

Abstract The genetic modification of microorganisms and the optimization of the culture conditions have allowed biosynthesizing specific components from improved fermentation. However, the production of components is not the only issue, since their recovery and extraction are a challenge when it comes to the conservation of component bioactivity and extraction performance. The downstream processes with organic solvents are the most used in the recovery of components of fermentation broths; however, these processes involve consecutive techniques based on a series of unit operations which generates an increase in operating time and production costs. For this reason, pressure-driven membrane processes (i.e. micro- (MF), ultra- (UF) and nanofiltration (NF)) have begun to be considered as a viable alternative for component recovery. Therefore, the objective of this chapter is to provide an overview of the current findings of the bioactive components extracted from fermentation broths through pressure-driven membrane processes.

Keywords Fermentation broths · Bioactive compounds · Extraction · Purification · Membrane processes

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1 Introduction

Fermentation is anaerobic process considered as a catabolic route due to various microorganisms (e.g. *Zymomonasmobilis, Saccharomyces cerevisiae*, *Bacillus* spp. and *Leuconostoc mesenteroides*) employ nutrients from the medium to generate energy efficiency (Steinkraus 2004). Since ancient times, fermentation processes have been used for food purposes (e.g. production of bread, beer, wine and cheese), the research community has recently initiated to produce specific compounds, such as primary and secondary metabolites (e.g. phenols, organic acids, alcohols, ketones, aldehydes and esters) (Garibay et al. 2004; Nout 2001). The production of these compounds can be carried out through the use of specific substrates, varying the culture conditions, or through the genetic modification of microorganisms (Chen and Jiang 2018; de Sá et al. 2014; Santos et al. 2000). Unfortunately, their separation and recovery are challenging tasks, therefore, most of research has been focused on using various methods and procedures (e.g. electrical, mechanical and thermal) that allow efficient separation; however, most of the methods have disadvantages that directly affect the stability of these compounds and thus reducing recovery efficiency (Castro-Muñoz and Fíla 2018; Galanakis et al. 2016).

Table 9.1 shows the most relevant characteristics and disadvantages of conventional techniques used for the separation of valuable compounds. It can be identified that organic solvent extraction is the most widely used technique due to its ease of execution, but it generates low recovery rates due to the degradation of the compounds because of high process temperatures (>60 °C) and long operating time (>2 h), whereby the global production cost increases abruptly (Cassano et al. 2004; Castro-Muñoz et al. 2018a; Khebizi et al. 2017).

The formation of toxic compounds, loss of nutrients, use of solvents, long processing time, low extraction yield and high production costs are among the main drawbacks of these techniques. In this regard, researchers are actively looking for other emerging technologies for the separation and recovery of compounds. Membrane-based technologies arise as a promising technology for the recovery compounds, and more importantly, able to separate gases, azeotropic solvents, water treatment and remediation (Castro-Muñoz et al. 2018c; Castro-Muñoz et al. 2019a, b, 2021).

Membrane-based technologies include processes governed by pressure, such as micro- (MF), ultra- (UF) and nanofiltration (NF), which offer several advantages in the recovery of compounds since they do not additional phases or solvents for the separation and extraction. The use of membrane technologies as purification methods has been mainly focused on compounds from food products (e.g. fruits and juices) or the treatment of agro-food by-products (Castro-Muñoz et al. 2016, 2020; Li and Chase 2010; Vladisavljević et al. 2003); however, its application is not only limited to such kind of extracts since membranes can also be applied in fractionating fermentation broths. Although, these processes have been rarely applied to the compounds extraction from microorganisms (Li and Chase 2010), there are enough literature proofs that may provide convincing insights of their usefulness. Therefore,

Table 9.1 Characteristics and disadvantages of traditional techniques used for the separation of high-added value compounds

Technique	Characteristics	Extracted compounds	Disadvantages	Reference
Accelerated solvent extraction	Technique based on the heating process of the solvent accompanied by a high pressure.	Polyphenols and carotenoids	Formation of toxic compounds (e.g. furfural)	Rajha et al. (2014) and Xie et al. (2019)
Column-chromatographic technique	Separation method based on a system of two phases.	Aromatic compounds and terpenoids	Small volume processing	Bilal et al. (2018) and Chatterjee et al. (2018)
Enzyme assisted extraction	Method that uses enzymes to break the cell wall and extract the intercellular compounds.	Intercellular compounds	Use of solvents	Zhang et al. (2018a)
Extraction assisted by hydrotropic solvents	Green extraction because used solvents are chemically inert, easily separable, reusable, and selective.	Polyphenols	Long processing time High concentration of solvent	Nagarajan et al. (2016) and Prakash et al. (2014)
High pressure processing	Non-thermal treatment that destroys microbial agents and gives stability to the product without affecting its sensory properties.	Anthocyanins and flavonoids	Loss of nutrients Loss of functional compounds	Corrales et al. (2009) and Escobedo-Avellaneda et al. (2011)
High voltage electrical discharges	Method that applies a high voltage electric field causing the propagation of shock waves of pressure in the surrounding media, while the cavitation of gas bubbles achieve an increase in the electrical conductivity and the permeability of the intracellular material.	Flavonols and polyphenols	High cost of initial investment High energy consumption	Brianceau et al. (2016) and Roselló-Soto et al. (2015)
Ion-exchange chromatography	Insoluble resin matrix with opposite charge that uses elution gradients and inclusion of organic solvents.	Charged or ionizable compounds	Use of solvents	Bruce (2013)
Pulsed electric fields	Non-thermal method that uses short pulses of electricity to increase the permeabilization.	Sugars and oils	High cost of initial investment High energy dissipation	Mohamed and Eissa (2012) and Sarkis et al. (2015)

(continued)

Table 9.1 (continued)

Technique	Characteristics	Extracted compounds	Disadvantages	Reference
Pulsed ohmic heating	Thermal technology that heat foods by means of electric current flowing through them.	Lipids and polyphenols	Toxicity because of electrodes	El Darra et al. (2013), Kim et al. (2018) and Samprovalaki et al. (2007)
Solid phase extraction	Column with sorbent material (solid phase) that allows the compounds to be washed with solvents.	Polyphenols	Use of solvents	
Solvent extraction	Use organic solvents (e.g. ethanol, methanol, hexane, and acetone) and reflux to compounds extraction.	Flavonoids and carotenoids	Low extraction yield Long processing time High energy consumption Destructive effect	Prommuak et al. (2008) and Yan et al. (2018)
Soxhlet extraction	Method employs a cellulose thimble in an extraction chamber, which is placed on top of a flask collector under a reflux condenser with solvent.	Lipids	Use of solvents Long processing time	Bruce (2013)
Subcritical fluid extraction	Technique based on a distillation that uses low pressures, suitable for the separation of substances of high boiling point, high viscosity, and sensitive to heat.	Anthocyanins and oils	The equipment is not commercially available	Bleve et al. (2008) and Hrnčič et al. (2018)
Supercritical fluid extraction	Technique that uses fluids (e.g. CO_2) with characteristics of solvents (high diffusion capacity and low viscosity), this accelerates the speed of transport and improves the separation of lipids at low temperatures.	Oils and flavonoids	High equipment cost Low processing capacity High production costs	Alvarez et al. (2019) and Sun et al. (2018)

(continued)

Table 9.1 (continued)

Technique	Characteristics	Extracted compounds	Disadvantages	Reference
Microwave assisted extraction	Irradiates samples (solids or semisolids) that are immerged in a solvent. The energy of the waves leads to the molecules vibration.	Anthocyanins and aromatic hydrocarbons	Use of solvents	Liazid et al. (2011) and Yuan et al. (2019)
Percolation	Procedure that uses a percolator that supplies solvent to the material and slowly filters drop by drop.	Polyphenols	Use of solvents Long processing time High temperatures	Bruce (2013)
Ultra sound-assisted extraction	Technique based on the propagation of ultrasound waves that cause the cavitation phenomenon, solvent infiltrates in the samples causing the extraction of compounds.	Polyphenols	Use of solvents	Malićanin et al. (2014) and Paz et al. (2015)

this chapter contains an updated literature review on pressure-driven membrane technology usage to recovering compounds from fermentation broths.

2 Pressure-Driven Membrane Processes

The operation of pressure-driven membrane processes is based on a feed solution (i.e. in bulk) that passes through a membrane (semipermeable barrier that allows the transport of solutes) to fractionate into two different streams, well-identified as retentate and permeate. The retained stream contains, together with the main solvent, compounds with higher molecular weight compared to the nominal molecular weight cut-off (MWCO) of the membrane and the permeate stream contains compounds with a lower molecular weight than the MWCO of the membrane (Castro-Muñoz et al. 2018a; Hernández et al. 1990; Marcano and Tsotsis 2002). The MWCO of the membranes (directly related to their pore size) classifies the types of membrane processes are governed by pressure in MF (100–10,000 nm), UF (2–100 nm) and NF (0.5–2 nm) (Castro-Muñoz 2020). In addition, the pressure requirements to carry out the separation depend on the dimensions of membrane; however, according to the commercial characteristics, these can vary between 0.1–2 bar for MF, 1–10 bar for UF, and 5–20 bar for NF (Bamforth 2016; Galanakis et al. 2016).

In these types of processes, the characteristics of the compounds (e.g. polarity, molecular mass and dimensions), the operational parameters (e.g. flux, pressure and temperature) and the membrane characteristics (e.g. material, configuration and

morphology) determine the success of the separation (Breite et al. 2019; Ulbricht 2006). Additionally, the yield and efficiency of the process is also affected by the characteristics of the membrane, for example, the morphological structure defines the selectivity of the process; however, it has been already demonstrated that this selectivity can be improved by varying the pH (functional groups can be loaded). Moreover, several interaction, such as hydrophobic and Coulombic, may also greatly influence the retention of specific molecules (Crespo and Brazinha 2010). Most of the polymers behave as cations in acidic medium and as anions in alkaline medium, so that they are able to separate compounds with similar charge by minimal interaction depending on the effect of electrostatic repulsion. To date, polymeric membranes are the most used and commercially implemented in several pressure-driven membrane techniques (Mulder 1995; Petsko and Ringe 2004; Ulbricht 2006). For instance, Table 9.2 enlists the main characteristics of the membranes used in MF, UF, and NF.

Unfortunately, the yield of the process is also gradually affected by the fouling phenomenon that is generated during the separation; which can be controlled by decreasing membrane-compound interaction (Astudillo-Castro 2015; Breite et al. 2019; Castro-Muñoz and Yañez-Fernandez 2015). To provide a clear overview and fundamentals on such phenomenon, the following section gives a clear description and factors influencing on membrane fouling and biofouling.

2.1 Membrane Fouling and Biofouling

The fouling is defined as the phenomenon occurred by the deposition of either organic or inorganic solutes on the membrane surface and into the pores; while, biofouling is generated by biological, organic matter and colloidal particles. Both phenomena may reduce or restrict the transport of compounds and it depends on the physicochemical composition of the extract and the nature of the compounds (Castro-Muñoz and Fíla 2018; Choi et al. 2005; Maddah and Chogle 2017; Mulder 1995).

Fundamentally, the fouling phenomenon can occur in four different ways, as shown in Fig. 9.1: (i) complete pore blockage (reversible), (ii) partial pore blockage (irreversible), (iii) internal pore blocking (adsorption) and (iv) cake formation (Castro-Muñoz and Fíla 2018).

The complete and incomplete blockage occur due to the MWCO, when the inorganic matter is larger than the MWCO, a complete obstruction takes place, but if the matter has a smaller size compared with membrane' MWCO, it is embedded in the membrane and an incomplete but irreversible obstruction occurs due to the effect of the morphology and orientation of the particles. Adsorption blockage is caused by ionic or hydrophobic interactions that occur between inorganic matter and membrane. Whereas, the blockage is due to the accumulation of particles generated by the system pressure on the membrane surface (Breite et al. 2019; Choi et al. 2005; Mulder 1995; Wahlgren and Arnebrant 1991).

Table 9.2 Membrane characteristics involved in pressure-driven membrane processes

Membrane process application	Material type	Configuration structure	Morphology structure
MF, UF and NF	Cellulose acetate	Flat sheet, hollow-fiber	Mesoporous and macroporous
	Polyimide	Flat sheet, hollow-fiber	Mesoporous and macroporous
	Polyethersulfone	Flat sheet, spiral-wound, tubular, plate and frame	Mesoporous and macroporous
	Polyetherimide	–	Mesoporous
	Polyamide, aromatic	Flat sheet, spiral-wound, hollow-fiber, tubular	Mesoporous
	Polyamide, aliphatic	Flat sheet, spiral-wound, hollow-fiber, tubular	Macroporous
	Ceramic	Tubular	Microporous
MF and UF	Polyvinylidenedifluoride	Flat sheet, hollow-fiber, tubular	Mesoporous, macroporous
	Polysulfone	Flat sheet, hollow-fiber, tubular, spiral-wound, plate and frame	Mesoporous
	Polyacrylonitrile	Hollow-fiber	Mesoporous
	Polytetrafluoroethylene	Hollow-fiber	Macroporous
	Polyethylene	–	Macroporous
	Polyvinylchloride	–	–
	Polyetheretherketone	Hollow-fiber, tubular	–
MF	Cellulose esters (mixed)	Flat sheet	Macroporous
	Polypropylene	Hollow-fiber, tubular	Macroporous
	Polyethylene terephthalate	–	Macroporous
	Polycarbonate, aromatic	–	Macroporous
	Polyester (track-etched)	–	–
UF	Cellulose nitrate	Flat sheet	Macroporous
	Cellulose regenerated	Flat sheet	Mesoporous

Modified from Cassano et al. (2017), Castro-Muñoz (2018), Castro-Muñoz et al. (2016, 2017, 2018a), Castro-Muñoz and Fíla (2018), Koros et al. (1988), Munari et al. (1990) and Ulbricht (2006)

Moreover, the phenomenon of biofouling can occur due to the adhesion of organic matter to the membrane surface, or by the interaction between the functional groups of both phases. Therefore, some studies have reported the interaction of the hydrophobicity of the membrane with the compounds, since both the hydrophobic (e.g. polyethylene, polypropylene and polytetrafluoroethylene) and hydrophilic materials (e.g. cellulose esters and aliphatic polyamides) interact with organic compounds; however hydrophobic ones with greater intensity than hydrophilic ones (Mulder 1995; Saxena et al. 2009; Walrant et al. 2012). Fig. 9.2 illustrates the interaction between the functional groups of a cellulose acetate membrane (carboxyl

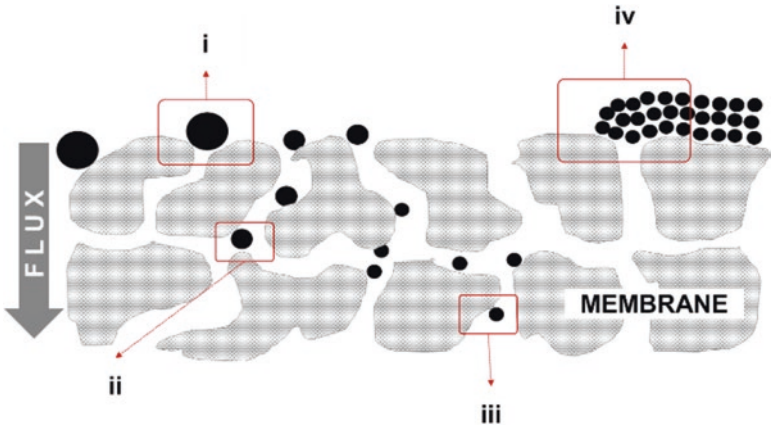

Fig. 9.1 Mechanism for membrane fouling: (i) reversible fouling, (ii) irreversible fouling, (iii) fouling by adsorption and (iv) polarization. (Adapted from Díaz-Montes and Castro-Muñoz 2019)

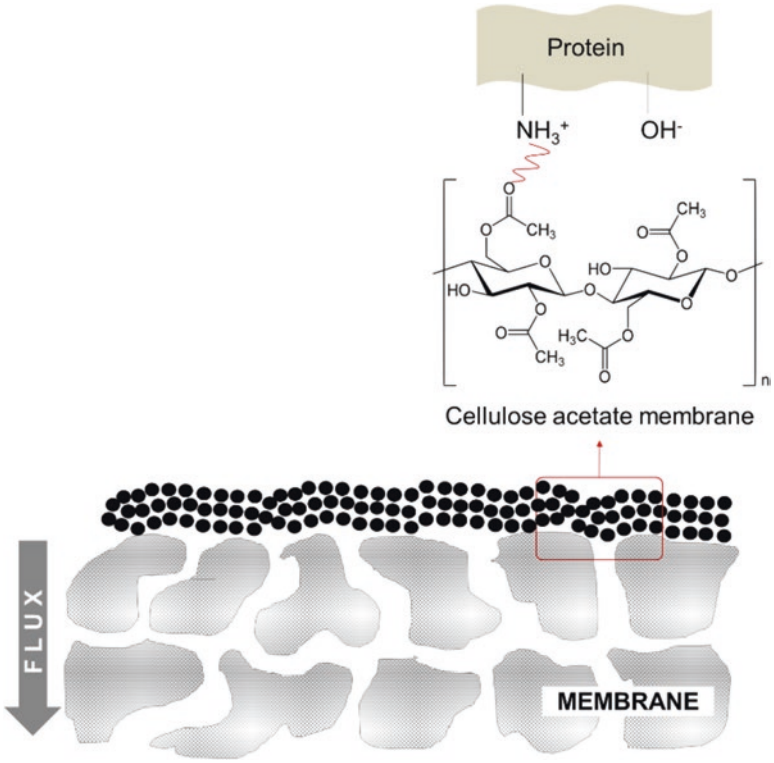

Fig. 9.2 Mechanism for membrane biofouling in a cellulose acetate membrane by biofilm formation

group) and those of the proteins (protonated amino group) (Pichardo-Romero et al. 2020).

Fouling and biofouling phenomena are the main drawbacks in pressure-driven membrane processes; however, in most cases, the membrane materials, the filtration configuration mode and the correct cleaning protocol (with acids, bases, oxides, disinfectants or surfactants) can reduce or mitigate obstructions or blockages (Choi et al. 2005; Cui and Muralidhara 2010; Drioli and Giorno 2016).

2.2 Pressure-Driven Membrane Processes as Methods for the Recovery of Compounds

The most important advantages of pressure-driven membrane processes over conventional methods (see Table 9.1) are the low energy consumption, shorter extraction time and separation efficiency. However, the separation efficiency is dependent on the physicochemical composition of the extract, the type of membrane and the operational conditions of process (Baker et al. 1991; Cassano et al. 2015; Chen et al. 2015; Hoffman 2003).

Thank to their multiple benefits that membrane-based technologies, they can used in large-scale treatments, the main application is focused on extracting compounds, such as organic acids (e.g. citric, folic, malic, glutamic and ascorbic acids), vitamins (e.g. vitamin C), pigments(e.g. betacyanins and betaxanthins) and sugars (e.g. sucrose, fructose and glucose) from natural extracts, fruits and juices, and as well as the treatment of waste and by-products from food industries (Cassano et al. 2007, 2008, 2010, 2011, 2015, 2017, 2009; Castro-Muñoz, Barragán-Huerta et al. 2018; Castro-Muñoz et al. 2016, 2018a; Cisse et al. 2011; de Carvalho et al. 2008; De Oliveira et al. 2012; Fuenmayor et al. 2014; Li and Chase 2010; Vladisavljević et al. 2003).

Individually, MF has been used to remove insoluble organicmatter and recover simple sucrose, fructose, glucose, anthocyanins and galacturonic and malicacids; UF has been applied to obtain specific compounds, such as inulin, proteins, betacyanins, flavonoids and betalains; whereas, NF has allowed to extractorganiccompoundswithlow molecular weight as are thepolyphenols; which are of interest in cosmetic and food industries (Cassano et al. 2018, 2011; Castro-Muñoz et al. 2014, 2016; Chen et al. 2015; Cisse et al. 2011; De Oliveira et al. 2012; Díaz-Reinoso et al. 2011; Fuenmayor et al. 2014; Tylkowski et al. 2011).

Nevertheless, the separation of compounds from microorganisms in a fermentation systems via membrane-based technologies has been rarely applied, but some researchers have documented their feasibility by smartly choosing and designing the membrane systems (Li and Chase 2010). The next section (Sect. 3) shows enough literature reports that demonstrated the potential application of membrane technology to recover compounds from fermentation broths.

3 Bioactive Compounds Extracted from Fermentation Broths

The production of high-added value compounds through fermentation is a latent pathway of generating such molecules but it represents a complicated task, since these depend on the nutrients (micro- and macronutrients) that are supplied to the medium, the process conditions (e.g. temperature, time, agitation and aeration) and type of microorganisms; additionally, the composition of the resulting fermentation broths are very diverse because they contain the non-metabolized nutrients and substrates, the extra- and intracellular products and by-products, and live and dead cells, therefore, the specific extraction of compounds of interest is challenging (Li et al. 2018; Najafpour 2007). The separation of these compounds needs prior treatment methods for their recovery; for example, if the interest compounds are intracellular, it is important to apply methods (e.g. physical, chemical or enzymatic) to break the cells and release them into the medium and subsequently apply the convenient extraction-purification methods (Hanson 1971; Kertes 1971; Prapulla and Karanth 2014).

The recovery of compounds via conventional extraction (downstream process, see Sect. 3.1) depends mainly on the type of solvent used, since the solvent-component interaction specifically derives from the chemical properties (e.g. polarity and transition energy). However, regardless of the component, there are a series of inconveniences that directly affect the extraction; for example, the affinity that solvents have for peptides or sugars makes challenging their total elimination, thereby, the bioactive activity of the compounds is significantly affected; this together with the environmental impact generated by the use of large volumes of solvents (Hansen 2007; Hrnčič et al. 2018; Marcano and Hasegawa 2002; Reichardt 1965; Tejeda et al. 1995). In this sense, membrane-based technologies turn out to be an alternative to replace these traditional extraction processes of bioactive compounds.

3.1 Downstream Processes to Recover of Compounds from Fermentation Broths

According to Clarke (2013), downstream processes are defined as unit operations that cause a physical change in the concentration and purity of a specific compound. The particularity of downstream processes is that follow a logical order and designing for the elimination of different organic materials. In fermentations, the processes begin with a pre-treatment for the removal of large particles, insoluble compounds and cells by physical or chemical methods (e.g. sedimentation, filtration, centrifugation or coagulation). The solids are washed to recover the cells, dried

and preserved for later reuse; but if there are intracellular compounds, the cells are subjected to mechanical, osmotic, chemical or thermal methods that allow the destruction of the cell membrane and thus release of compounds, which are extracted by UF or centrifugation. While the fermentation broth is concentrated and treated to extract the compounds from the medium via precipitation, liquid extraction, chromatography, electrophoresis or membrane techniques. Finally, the concentrated extracts are subjected to specific techniques (e.g. drying or crystallization) to preserve the compounds (Najafpour 2007); as summarized in Fig. 9.3.

Drioli (1986) described a traditional downstream process on industrial scale including 11 stages for bioactive compounds recovery from fermentation broths, as illustrated in Fig. 9.4. After the fermentation process (step 1), centrifugation is performed to remove the cells and particles in suspension (step 2); cells recovered are heat treated to cause lysis and recover the intracellular compounds (step 3), and the biomass is removed by vacuum filtration (step 4). The extract is precipitated by chemical agents (for example, flocculants) to trap compounds (step 5); and subsequently centrifuged to recover them (step 6); and then washed and precipitated with organic solvents (steps 7 and 8). Undiluted particles are removed with filtration (step 9); while the supernatant is purified with activated carbon (step 10); and activated carbon is removed with filtration (step 11) (Clarke 2013; Drioli 1986; Najafpour 2007).

A traditional downstream process employs complicated methodologies with chemical substances that generate certain disadvantages, therefore, Drioli (1986) proposed the modification of stages 5–11 of the downstream process, as depicted in Fig. 9.4; in which membrane technologies and other techniques (stages 5*, 7* and 8*) were proposed as an alternative for the recovery and purification of bioactive compounds (Clarke 2013; Drioli 1986; Najafpour 2007). This modified downstream process was tested to recover S-adeosyl-L-methionine, with a 10 kDa membrane (stage 5*), along with an ion exchange column (stage 6*) and a reverse osmosis membrane (stage 7*), achieving the recovery of 80 g S-adeosil-L-methionine L^{-1} at the end of the process (Drioli 1986).

Other adaptations proposed in downstream processes are the direct coupling of membranes in fermenters (i.e. membrane reactors) for the production and consecutive recovery compounds of fermentation broth. For example, Wang et al. (2018a, b, c) and Jang et al. (2018) used membrane reactors (implementing 0.01 μm hollow fibers) with *Clostridium* to produce ~17 and ~30 g ethanol L^{-1}, respectively. The variation in the results is mainly related to the mode of operation, as Wang et al. held the reactor in a discontinuous mode for the first 20 days, while Jang et al. maintained the operation in continuous mode. These processes arise from the need to constantly eliminate toxic by-products, e.g. ethanol inhibits the alcohol dehydrogenase enzyme, that interfere with the enzymatic activity within the same fermentation process (Drioli 1986).

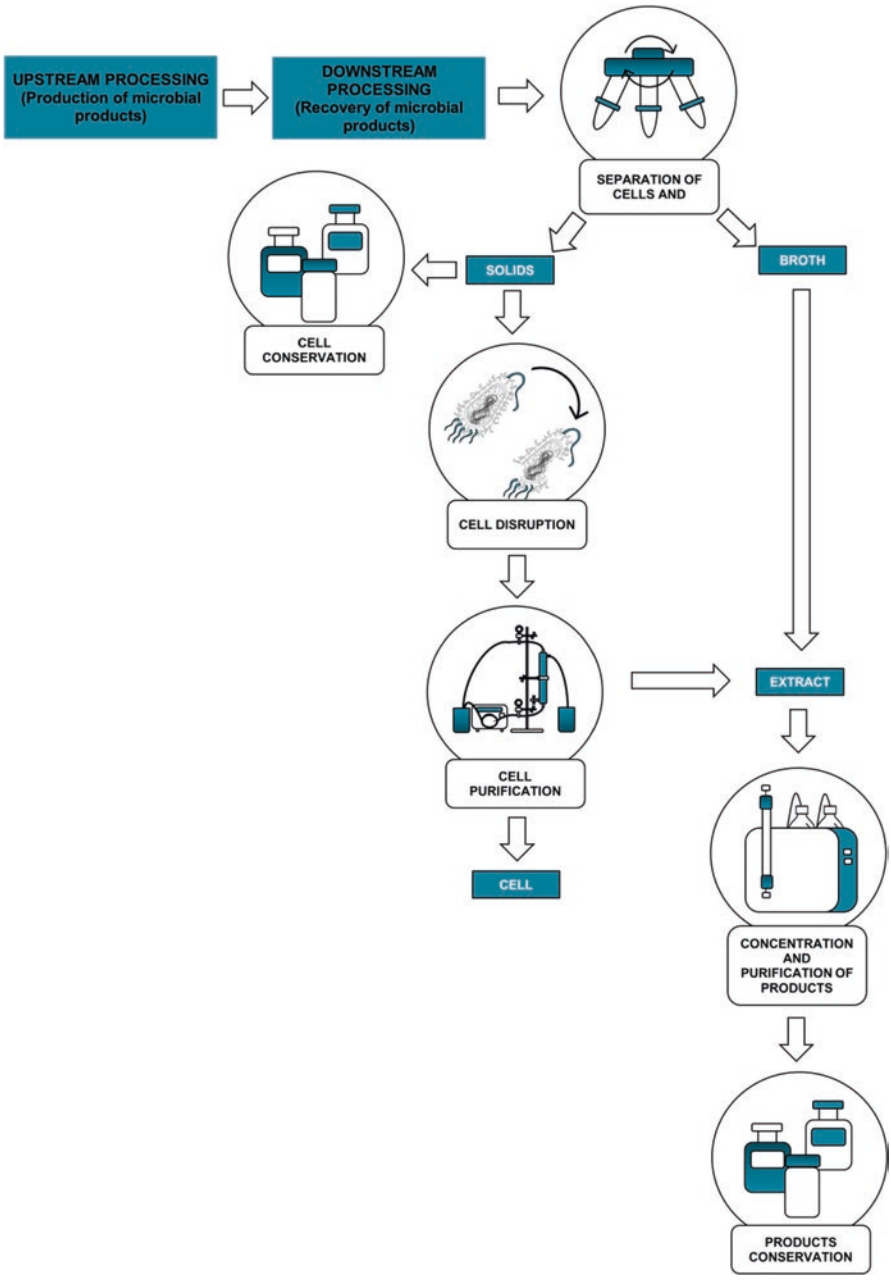

Fig. 9.3 Schematic depiction of main stages implied in the downstream processing of microbial products

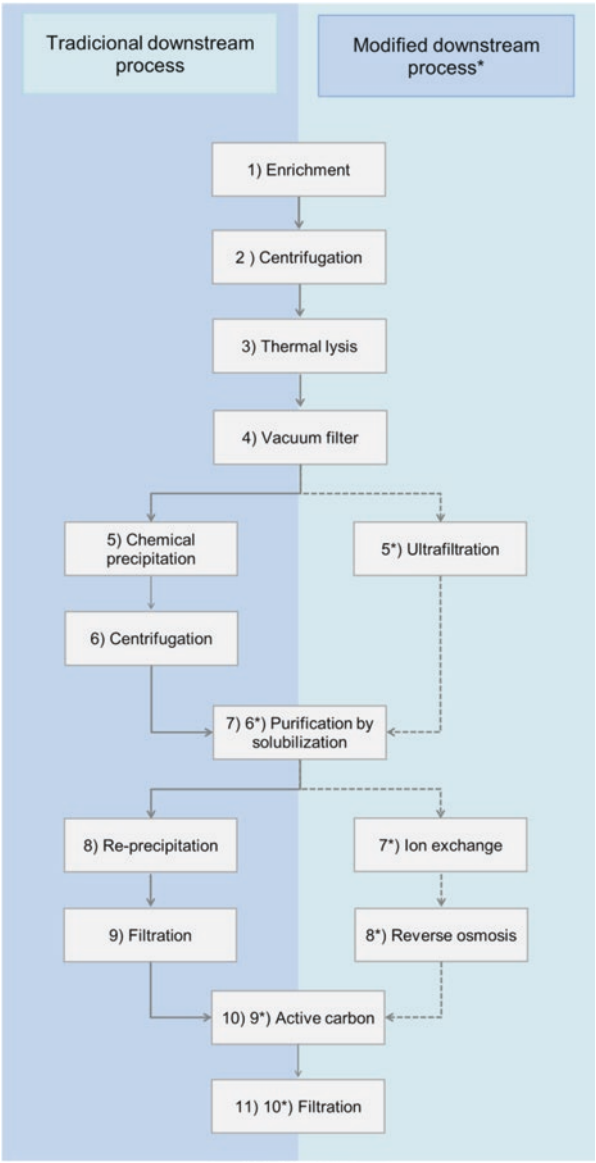

Fig. 9.4 Traditional and modified downstream processes used for the recovery of bioactive compounds from fermentation broths. (Modified from Drioli 1986)

3.2 The Role of Pressure-Driven Membrane Processes in Recovering Valuable Solutes from Fermentation Broths

Another advantage of pressure-driven membrane processes deals with their implementation and coupling to design the well-recognized integrated membrane processes. This concept has emerged in order to make a more efficient extraction, together with a simultaneous recovery of different compounds. Depending on membranes' MWCO, the processes can increase the purity of the compounds and reduce the fouling and biofouling phenomena in the subsequent membrane stages (Cassano et al. 2018; Knozowska et al. 2017; Thuy and Boontawan 2016).

In order to carry out the process of separating compounds from fermentation broths, it is typically correct to use the membranes from higher to lower MWCO, since a better filtration is achieved; the suggested membranes are made of hydrophilic polymers, since their nature maintains a low interaction with the compounds; while the tangential flow is more suitable because it allows a control of the flow, processing of larger volumes and also reduces the fouling phenomena (Choi et al. 2005; De and Mondal 2012; Saxena et al. 2009). Table 9.4 reports different single (MF, UF, or NF) pressure-driven membrane processes, integrated, as well as coupled with other technologies to recover compounds from fermentation broths.

It is important to mention that other highly selective membrane techniques, such as pervaporation (PV), have been involved in the extraction of organic solutes (such as ethanol, acetone, butanol, among others) produced in the fermentation (Castro-Muñoz et al. 2019a, b). Interestingly, PV technique can simultaneously assist the production of biofuels and proceed with their extraction through organophilic PV membranes (Castro-Muñoz et al. 2018b; Li et al. 2014). Today, PV is potentially considered to replace the conventional distillation techniques for the separation of azeotropic solvent mixtures. In addition to this, PV has initiated to be explored in the selective removal of ethanol from alcoholic drinks to manufacture alcohol-free beverages for the food market (Castro-Muñoz 2019).

4 Current Status of Processing Fermentation Broths by Means of Membrane Technologies

Many studies have shown in the previous section (Sect. 3) the ability of membrane processes in recovery compounds at laboratory-scale experiments. Additionally, this literature review gives an overview for the implementation of this technology as an industrial scale alternative for fractionation and high added value compounds from fermentation broths. Figure 9.5 shows some bioactive compounds that have been found in fermentation broths and thus successfully recovered by different pressure-governed membrane processes at lab scale, as summarized in Table 9.4. To

Table 9.4 Pressure-driven membrane processes used for the recovery of various compounds from fermentation broths

Membrane technologies	Membrane characteristics (MWCO/ Material/Configuration)	Recovered compound	Reference
Single membrane stage			
MF	0.1 μm/cellulose ester/hollow fiber	Glucose	Wu et al. (2017)*
NF	150–300 Da/n.r./thin-film	Glucose	Wang et al. (2017)*
	300 Da/polyester/spiral	Glucose	
UF	20 kDa/Polyethersulfone/n.r.	Oligodextran	Su et al. (2018)
	150 kDa/ceramic/n.r.	α,ω-dodecanedioic acid	Cao et al. (2018a)
	3 kDa/Polyethersulfone/ spiral-wound	α,ω-dodecanedioic acid	Cao et al. (2018b)
	0.05–2 μm/zirconium oxide stainless steel/tubular	Lactic acid	Wojtyniak et al. (2016)
	300 kDa/Polyethersulfone/cassette	Hyaluronic acid	Rajendran et al. (2016)
	10 kDa/Polyethersulfone/hollow fiber	Xylitol	Kresnowati et al. (2017)
NF	500 Da/Polyethersulfone/hollow fiber	Xylitol	
	600 Da/Polyethersulfone/hollow fiber	Xylitol	
	1 kDa/Polyethersulfone/hollow fiber	Xylitol	
	37 kDa/Polyethersulfone/n.r.	Xylitol	Faneer et al. (2017)*
	12.6 kDa/ Polyethersulfone-Pluronic/n.r.	Xylitol	
	150–300 Da/n.r./thin-film	Xylose	Wang et al. (2017)*
	300 Da/polyester/spiral	Xylose	
	37 kDa/Polyethersulfone/n.r.	Xylose	Faneer et al. (2017)*
	12.6 kDa/ Polyethersulfone-Pluronic/n.r.	Xylose	
	37 kDa/Polyethersulfone/n.r.	Arabinose	
	12.6 kDa/ Polyethersulfone-Pluronic/n.r.	Arabinose	
	150–300 Da/n.r./flat sheet	Succinate	Khunnonkwao et al. (2018)
	0.23–0.26 nm/polyimide/fibers	Succinate	Zaman et al. (2017)
	0.23–0.26 nm/polyimide/fibers	Formate	
	0.23–0.26 nm/polyimide/fibers	Acetate	
Integrated membrane system			
MDF-MF	(MF) 0.1 μm/Polysulfone/ hollow-fiber	Dextran	Díaz-Montes (2019)

(continued)

Table 9.4 (continued)

Membrane technologies	Membrane characteristics (MWCO/ Material/Configuration)	Recovered compound	Reference
MF-NF	(MF) 0.2 μm/ceramic/n.r.	Lactic acid	Alexandri et al. (2018)
	(NF) 150–300 Da/n.r./n.r.		
	(MF) 0.1 μm/n.r./spiral wound	D-lactic acid	Mai et al. (2018)
	(NF) 300 Da/n.r./spiral wound		
	(MF) n.r./ Polyvinylidenedifluoride/n.r.	Gluconic acid	Pal et al. (2018)
	(NF) 150–300 Da/polyamide/n.r.		
	(MF) n.r./ Polyvinylidenedifluoride/n.r.	Glucose	
	(NF) 150–300 Da/polyamide/n.r.		
UF-NF	(UF) 20 kDa/n.r./spiral wound	Ethanol	Wangpor et al. (2017)
	(NF) 200–400 Da/n.r./spiral wound		
	(UF) 1–5 kDa/Polysulfone/ hollow-fiber	Xylitol	Kresnowati et al. (2017)
	(NF) 150–300 Da/polyamide/spiral wound		
	(UF) 1–5 kDa/Polysulfone/ hollow-fiber	Xylose	
	(NF) 150–300 Da/polyamide/spiral wound		
	(UF) 1–5 kDa/Polysulfone/hollow fiber	Acetic acid	
	(NF) 150–300 Da/polyamide/spiral wound		
MF-NF	(MF) 0.1 μm/n.r./spiral wound	Succinic acid	Thuy and Boontawan (2016)
	(NF) 300 Da/n.r./spiral wound		
	(MF) 0.1 μm/n.r./spiral wound	Protein	Mai et al. (2018)
	(NF) 300 Da/n.r./spiral wound		
MF-UF-NF	(MF) 0.1 μm/n.r./n.r.	2,3-butanediol	Davey et al. (2016)
	(UF) 20 kDa/n.r./n.r.		
	(NF) 200–400 Da/polyamide/n.r.		
	(MF) 0.1 μm/n.r./n.r.	Acetate	
	(UF) 20 kDa/n.r./n.r.		
	(NF) 200–400 Da/polyamide/n.r.		
	(MF) 0.1 μm/n.r./n.r.	Ethanol	
	(UF) 20 kDa/n.r./n.r.		
	(NF) 200–400 Da/polyamide/n.r.		
Membranes coupled with other technologies			
MF-VE	(MF) 0.2 μm/n.r./hollow fiber	Sodium pyruvate	Ingle et al. (2015)
	(VE) [100 mBar, 50 °C]**		

(continued)

Table 9.4 (continued)

Membrane technologies	Membrane characteristics (MWCO/ Material/Configuration)	Recovered compound	Reference
MF-PV	(MF) 300 kDa/ceramic/tubular	Butanol	Knozowska et al. (2017)*
	(PV) [vacuum, 105 °C]**		
	(MF) 300 kDa/ceramic/tubular	Acetone	
	(PV) [vacuum, 105 °C]**		
	(MF) 300 kDa/ceramic/tubular	Ethanol	
	(PV) [vacuum, 105 °C]**		
UF-EDBM	(UF) 15 kDa/ceramic/tubular	Succinic acid	Prochaska et al. (2018)
	(EDBM) [10BM-10AEM-1CEM, 90–120 A m^{-2}, 180 min, 25 °C]**		
ED-NF	(ED) [3CEM-2AEM, 1.2–3.2 mA cm^{-2}, 0.75–2 A, 23 °C]**	Succinate	Sosa et al. (2016)*
	(NF) 150–400 Da/polyamide/thin film		
MF, UF, NF, IEX, TE, VE	(MF) 0.45 μm/chlorinated poly (vinyl chloride)/n.r.	Lactic acid	Lee et al. (2017)
	(UF) 20 kDa/Polyethersulfone/n.r.		
	(NF) n.r./polyamide/n.r.		
	(IEX) [anionic/cationic resins, 1 μS cm^{-1}]**		
	(VE) [vacuum, 80 °C]**		
	(TE) [120 °C]**		
MF-UF-RO	(MF) 2 μm/filter paper	Calcium - lactic acid	Phanthumchinda et al. (2018)
	(UF) 1–30 kDa/Polyethersulfone/flat sheet		
	(RO) 0.001 μm/polyamide/thin-film		
	(MF) 2 μm/filter paper	Sodium - lactic acid	Phanthumchinda et al. (2018)
	(UF) 1–30 kDa/Polyethersulfone/flat sheet		
	(RO) 0.001 μm/polyamide/thin-film		
	(MF) 2 μm/filter paper	Ammonium - lactic acid	
	(UF) 1–30 kDa/Polyethersulfone/flat sheet		
	(RO) 0.001 μm/polyamide/thin-film		

Modified from Díaz-Montes and Castro-Muñoz (2019)

*Experiments with simulated fermentation broths, ** Operating conditions, *ED* electrodialysis, *EDBM* bipolar membrane electrodialysis, *IEX* ion exchange, *PV* pervaporation, *RO* reverse osmosis, *TE* thermal evaporation, *VE* vacuum evaporation, *n.r.* no reported

date, MF processes have been used mainly for the elimination of microorganisms and insoluble material, hence, they are considered as pretreatment protocols; however, the MWCO intervals of the MF membranes have also allowed the retention of proteins and long-chain carbohydrates. The UF has in turn retained short-chain carbohydrates and volatile organic (e.g. ethanol, benzene and acetone) and phenolic

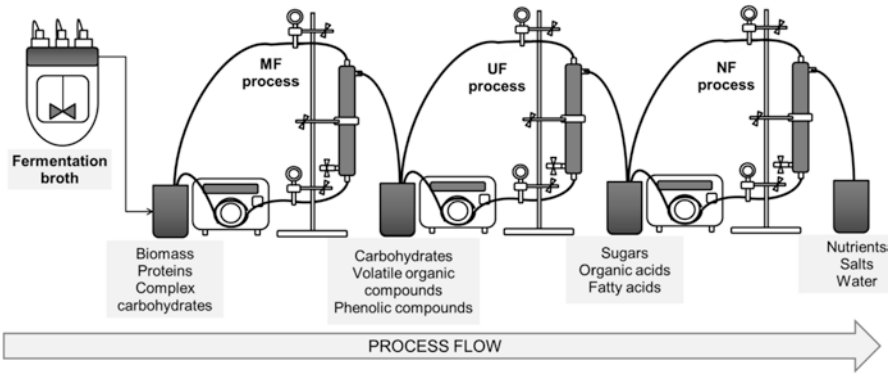

Fig. 9.5 A graphical depiction of compounds recovered from fermentation broths by integrated membrane processes (MF-UF-NF)

Table 9.5 Potential applications of bioactive compounds extracted from fermentation broths by membrane technologies

Bioactive compounds	Specific industrial area	Possible application	References
Proteins	Dairy products	Nutritional enrichment of processed products	Mulder et al. (2016)
Dextrans	Bakery	Texture enhancers (i.e. softness and firmness)	Wang et al. (2018b, c) and Zhang et al. (2018b)
Oligosaccharides (e.g. inulin and oligofructose)	Additives	Dietary fiber enrichrs	Murphy (2001)
Sugars (e.g. xylose, glucose, arabinose and xylitol)	Additives	Flavors and sweeteners	Wang et al. (2018b, c)
Phenolic compounds	Additives	Antioxidant agents	Moon et al. (2018) and Patra et al. (2018)

compounds. While NF processes allow the retention of sugars (e.g. glucose, arabinose and xylose) and derivatives (e.g. xylitol), and the permeation of nutrients, salts and water.

Depending on the source of origin, the high added value compounds from fermentation broths have a direct application into the food area. Fortunately, the food industry has been recently interested in developing new food products (i.e. functional foods) that provide benefits to the consumer through their nutritional content and biological contribution through bioactive compounds; this is due to the fact that the current way of life relates several diseases, such as obesity and chronic diseases, thanks to the inadequate food diet, that is, it lacks food with nutrients or includes products harmful to humans (Hawkes 2006; Kris-Etherton et al. 2002; Murphy 2001; Washi and Ageib 2010). Table 9.5, for instance, summarizes the possible

applications in food approaches of the most relevant compounds produced via fermentation.

5 Concluding Remarks

Considering the issues that arise in conventional extractions with the use of solvents, high temperatures and pressures, electrical pulses, and long process times, membrane-based technologies have proved to be a viable alternative in the recovery of specific organic acids (e.g. formic, acetic, butyric and lactic acids), sugars (e.g. glucose, xylose and arabinose), phenolic compounds, nutrients and pigments, with recovery rates exceeding 45%. Although membrane-based technologies have been sparingly used in fermentation broths, there is strong evidence of their ability to recover compounds from such complex systems. It is likely that fouling and biofouling are among the main drawbacks in such applications; in this way, the smart selection and designing of membrane steps in an integrated membrane process are the key factors not only in mitigating the fouling phenomenon but also in selectively separate various compounds. Importantly, the new researchers in the field should also investigate the possible interactions between the molecules contained in a fermentation broth and membrane since they greatly influence the efficiency of membrane-based unit operations.

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Chapter 10
Recovery of High Added Value Compounds from Microalgae Cultivation Using Membrane Technology

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Abstract Microalgae are one of the most promising raw sources for the production of biofuels (e.g., biodiesel, bioethanol, biohydrogen, and biogas) and high added value compounds (e.g., pigments, antioxidants, proteins, essential fatty acids, polysaccharides, vitamins, and minerals). Microalgae biomass and their cultivation are also explored for various applications such as food, feed animals, bioremediation (wastewater treatment and heavy metals biosorption), biofertilizers, biostimulants, and bioplastics. Nowadays, microalgae study is carried towards biorefinery and circular bioeconomy to have a greater benefit and cost reduction. Still, there are many challenges to developing an efficient process in microalgae cultivation, harvesting and drying of biomass, and recovery of high added value compounds. Membrane technology is one of the most efficient techniques in biomass harvesting, such as the

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pressure-driven membrane processes (e.g., microfiltration, ultrafiltration) and osmotically driven processes; nonetheless, the membrane fouling caused by the microalgae/debris cake layer and the fast permeate flux decrement is still the greatest issues. This chapter is aimed at summarized the current reports of membrane technology used for biomass harvesting and recovery of high added value compounds; advantages and disadvantages are discussed together with the strategies developed to find the best way of separation, purification, and concentration.

Keywords Microalgae · Membrane · Recovery · Biomass · Compounds

1 Introduction

Microalgae are photosynthetic microorganisms, they are able to transform inorganic compounds into organic compounds, which are fundamentally used for their cell structure and metabolism. They are inhabitants in fresh, brackish, and marine water. Their growth is mainly in autotrophic medium, where they use CO_2 as carbon source, light like an energy source, and inorganic salts. Also, under specific conditions, they can grow in a heterotrophic medium using organic carbon source such as glucose or glycerol), and in a mixotrophic medium. The microalgae size cell is between 2 and 200 μm, exist almost 800,000 species of microalga, nonetheless, only 50,000 species have been defined (Sharif et al. 2017); they can be unicellular, multicellular, or colonial. In the open sea, microalgae can fix carbon and nitrogen inorganic to produce organic matter and oxygen, the latter is an essential gas for the life of other organisms. Microalgae are also part of the aquatic food, and they can grow in almost every environment and habitat on the earth. Some of them are planktonic because they float in the water body, and others grow attached to plant surfaces, macroalgae, rocks, grains of sand, or any other rigid surface (Borowitzka 2018).

The term microalgae involve the eukaryotic and prokaryotic domains. The eukaryotic cell comes from the group of green algae, and the prokaryotic cell is identified as cyanobacteria (Varfolomeev and Wasserman 2011). The cyanobacteria are gram-negative, and they are classified into five subgroups (Stanier et al. 1979). The use of photosynthetic pigments that microalgae use to obtain light energy and thus the assimilation of carbon dioxide is essential, resulting in the release of oxygen and the formation of complex molecules of high value for the physiological processes of the microalgae cell. According with the type of microalgae pigment, they are grouped into specific groups and classified in green algae, red algae, brown algae and golden algae (Borowitzka 2018).

The main advantages of the cultivation of microalgae are attributed to the fact that its growth is faster than macroalgae; it can be harvested at any season of the year. The cultivation of microalgae does not compete with food agriculture, it does not need pesticide application, and nowadays the water resources can be recycled (Yu et al. 2019), and take advantage of the nutrients in wastewater (Gouveia et al. 2016). Also, they can be stressed by abiotic parameters (e.g., temperature, salinity,

nutrient starvation, pH, light, and UV radiation) to induce the maximum production of a specific valuable metabolite, it can be by accumulation (intracellular) or release (extracellular) of those compounds (Paliwal et al. 2017).

The microalgae biomass is a potential raw source for the production of biofuels (such as biodiesel, bioalcohol, biohydrogen, and biogas), bioproducts (such as pigments, essential fatty acids, proteins, carbohydrates, vitamins, minerals) and among others bioactive metabolites. They have been studied for various applications in foods, animal feed, bioremediation, biofertilizers, biostimulants, and bioplastics (Khan et al. 2018). Nowadays, microalgae are considered as a way of production of high added-value compounds, as illustrated in Fig. 10.1.

This chapter shows a complete overview on using microalgae as a high added value compounds factory, and their potential applications in biofuels, food, and feeds animals, bioremediation, bioplastics, biofertilizers and biostimulants. Secondly, it exposes the role of membrane technology in microalgae bioprocesses including microalgae cultivation, biomass harvesting, and its use for the recovery of high added-value compounds. Finally, the importance of protocols for membrane cleaning by microalgae fouling is also addressed.

Fig. 10.1 Microalgae as the emerging way of producing high added value compounds

2 Microalgae: The Latent Tool for Producing High Added-Value Compounds and Their Applications

2.1 Lipids and Carbohydrates for Biofuels

In a biorefinery, lipids and carbohydrates are among the main produced by microalgae, which can be extracted efficiently to biofuels production, however, other high added-value compounds can be extracted, such as polyunsaturated fatty acids, bioactive peptides, polysaccharides, pigments, vitamins, and minerals. Microalgae-based fuels are in fact recognized as the third generation of biofuels, with better environmental advantages compared with biofuels from crops. At this point, the oilseed microalgae are the most promising feedstock in biodiesel production. A microalgae strain is typically named oilseed when its oil content is between 20–70% of the dry weight of biomass. Some other promising strains for biodiesel production are *Ankistrodesmus*, *Isochrysis*, *Nannochloris*, and *Nitzschia* (Afzal et al. 2017), *Chlorella vulgaris, Chaetoceros mulleri,* among others. Still, oil production from microalgae is not highly competitive and it does not looks economically attractive in comparison with traditional oil crops, due to their high energy requirements for cultivation and processing of the biomass (Jez et al. 2017).

The main challenges are focused to explore new strains with higher capacity of oil production (Sadvakasova et al. 2019). For instance, the cultivation of known strains under stress conditions to achieve the maximum oil production can be handled through the starvation or limitation of nutrients (e.g., nitrogen, phosphorus, and sulfur), abiotic factors (light intensity/different wavelengths, carbon dioxide levels, salinity stress, temperature, stress to heavy metals, and the use of nanoparticles) (Luangpipat and Chisti 2017; Alishah Aratboni et al. 2019). Moreover, the optimization and design of bioreactors are priority (Lee et al. 2014), together with the improvement of biomass harvesting (Suparmaniam et al. 2019; Leam et al. 2020), extraction methods, to achieve the principles of biorefinery and circular bioeconomy (Naresh Kumar et al. 2019; Kumar et al. 2020). Here, the genetic and metabolic engineering coupled with nanotechnology offers a good strategy for enhancing microalgae oil production; in which microalgae models, such as *Chlamydomonas rehinhardtii* and species of *Nannochloropsis,* are the most explored (Alishah Aratboni et al. 2019).

On the other hand, microalgae cell walls are mainly based on cellulose but also have starch in the plastids. To some extent, these biopolymers can be converted into fermentable sugars. Interestingly, microalgae do not have lignin and a low content of hemicellulose, which are difficult to ferment or degrade by biological methods. In this way, microalgae represent a promising source of fermentable carbohydrates for biofuel production (Chen et al. 2013). In a recent study, 46 microalgae strains were evaluated about their carbohydrate content, the study showed that the carbohydrate content was ranged from 16.5% (*Mychonastes* sp. A313) to 71.6% (*Porphyridium purpureum* SAG 13801-1d). The main monosaccharide was glucose; in the second place were mannose, galactose, and rhamnose. Xylose and ribose

were also found in several species. Fucose and arabinose were rarely found. The proportion and quantity of monosaccharides were dependent on the microalgae specie, and culture conditions (Schulze et al. 2017). Since fermentable carbohydrate-rich biomass is an important feedstock to biofuels production; such as bioethanol, butanol, acetone, hydrogen, and methane. Theoretically, a bioethanol production of around 0.26 $g_{ethanol}/g_{biomass}$ is estimated from a carbohydrate-rich microalgae biomass, this biomass must contain approximately 50% of fermentable carbohydrates (de Farias Silva et al. 2019). To increase the microalgae carbohydrate content, the stress is generally done via nutrient starvation (mainly nitrogen), light energy supply, temperature variation, pH shift, and CO_2 supplement. The goal is primarily to increase the carbohydrate content without compromising the cell growth rate (Chen et al. 2013). Towards the increase of biomass production, the scale up is the recommended way to make more economically profitable process (de Farias Silva et al. 2019).

2.2 Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) are commonly obtained from selected seed plants, marine fish and certain mammals, nonetheless, their fast increasing demand has led to exploring alternative sources. Microalgae PUFAs production is increasing with special interest, even more for marine microalgae. Moreover, the nutritional value attributed to microalgae is for being a rich source of polyunsaturated fatty acids (PUFAs) or long-chain fatty acids. The nutritional value attributed to microalgae deals with a rich source of PUFAs, or long-chain fatty acids. Here, the nutritionally value from microalgae is Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA), among others (Ramesh Kumar et al. 2019). PUFAs are known by their role as an energy source and biological benefits in human health; they have been seen as influencing the inflammatory cascade, reducing oxidative stress, presenting neuroprotection, and cardiovascular protection. DHA in the human cell membrane (~50%) seems to contribute to the fast transport of rhodopsin on the two sides of the membrane, facilitating the initiation of the visual cascade, concurrently, the DHA rich membrane assures the differentials in Na^+ and K^+ necessary for signal transmission (Nagy 2017). Microalgae cultured under specific stress conditions can produce PUFAs reaching 40% of the total fatty acids produced, and its percentage varies from strain to strain (Ramesh Kumar et al. 2019). For example, the optimal EPA content of 34.6% (w/w) in *Porphyridium purpureum* biomass was found using for its growth a culture media with concentrations of 29.98 g/L of sodium chloride, 9.34 g/L of magnesium sulfate, and 1.86 g/L of sodium nitrate (Kavitha et al. 2016). Three main strategies have been suggested to improve DHA and EPA productivity: i) regulating the cultivation conditions to maximize the physiological potential for switching the cell metabolism to lipid and DHA + EPA synthesis, ii) escalate the biomass and lipid productivity through the breeding of strains, iii) genetic engineering approach for EPA and DHA production (Ramesh Kumar et al. 2019).

2.3 Bioactive Extracellular Polysaccharides

The production of extracellular polysaccharides has recently received interest. Microalgae species considered as potential source are *Calothrix* sp., *Nostoc* sp., *Nostoc calcicola*, *Nostoc muscorum*, *Nostoc punctiformae*, *Nostoc carneum*, *Anabaena* sp., *Cylindropermum* sp., *Gleocapsa* (Singh and Das 2011), *Chlamydomonas reinhardtii* (Bafana 2013), *Porphyridium sp.*(Geresh et al. 2002), *Porphyridium cruentum* (Patel et al. 2013), *Rhodella maculata, Schizochlamydella capsulata, Chlorella stigmatophora* (Gasljevic et al. 2008), *Synechocystis aquatilis* (Flamm and Blaschek 2014), just mention a few. These polysaccharides have immunomodulatory, antitumor, antiviral, antioxidant, anti-inflammatory, anticancer, antithrombotic, anticoagulant activity, biolubrication property (De Jesus Raposo et al. 2013) and emulsifying capacity (Morales-Jiménez et al. 2020). To date, it is known that *Porphyridium cruentum* polysaccharides are sulfated, and due to the complexity of its structure, its structural elucidation is still explored. An average molar mass of 2.39×10^5 g/mol is reported for *Porphyridium cruentum* exopolysaccharide (Patel et al. 2013), and 2.3×10^6 g/mol for *Porphyridium* sp.'s exopolysaccharide (Geresh et al. 2002).

2.4 Pigments

As mentioned previously, microalgae biomass is also a promising source for natural pigments, such as carotenoids (e.g., β-carotene, lutein, and astaxanthin), chlorophyll, and phycobiliprotein (e.g., phycoerythrins, phycocyanins, phycoerythrocyanins, and allophycocyanins). These pigments can act as a color agent for foods (as a natural healthy ingredient), and at the same time due to their biological activity, they can be used in the nutraceutical and pharmaceutical applications (Dufossé 2018). *Haematococcus pluvialis* is one of the most commercial microalgae strains due to its astaxanthin production (Bustos-Garza et al. 2013). These microalgae can accumulate astaxanthin between 3.8 and 5% of dry cell weight depending on the cultivation conditions and photobioreactor design (Khoo et al. 2019). Production of lutein is led by *Chlorella* species, and the halotolerant microalgae as *Dunaliella salina, Scenedesmus almeriensis, Galdieria sulphuraria* (Přibyl et al. 2015; Sun et al. 2015). Specific strategies have been done to increase yields including cultivation for long periods and under abiotic stress (e.g., nutrient stress, high light intensity, and high salinity) to led progress the carotenogenesis until getting cell of orange-red color at the end (Sun et al. 2015; Khoo et al. 2019). Also, *Spirulina platensis* can produce phycocyanin (Soni et al. 2017). β-phycoerythrin and R-phycocyanin can be obtained from *Porphyridium cruentum, Nostoc* sp., and other Rhodophyta species (Román et al. 2002; Johnson et al. 2014).

2.5 Proteins-Bioactive Peptides

Spirulina is the most successful source of protein for downstream applications, it has between 60 to 70% of its weight (Soni et al. 2017). *Chlorella vulgaris* cells contain approximately 42%, *Nannochloropsis oculata* 42%, *Phaeodactylum tricornutum* 39%, *Porphyridium cruentum* 35%, and *Haematococcus pluvialis* 25%. Owing to the high content of protein in microalgae has been attributed to them nutritive value, which supports its application in human food (Matos 2019). Within this characteristic, the content, proportion, and availability of amino acids, specifically essential amino acids, are the main parameter. Regarding the bioactive peptides are a short specific sequence of amino acids that display biological activity on human health, such as mineral binding, immunomodulatory, antimicrobial, antioxidant, antithrombotic, hypocholesterolemic, and antihypertensive. These kinds of molecules are obtained from *Spirulina* to a large degree (Ovando et al. 2018), nonetheless, some other strains are being studied (Alzahrani et al. 2018). The bioactive peptides are typically used as ingredients in health-promoting foods, dietary supplements, pharmaceutical and cosmetic applications (Castro-Muñoz and Fíla 2018; Apone et al. 2019).

2.6 Vitamins

Microalgae as a vitamin source is an important parameter to consider for the use of microalgae biomass as a food supplement, even more with promising benefits on human health. *Nannochloropsis oceanica* was able to produce vitamin D3 up to 1.0 μg/g underexposure ultraviolet-B light (Ljubic et al. 2020). *Anabaena cylindrica* was identified as a rich source of vitamin K1, around 200 μg/g on a dry weight basis, after an optimization of growth conditions, an increase of vitamin K1 was found and its biomass also showed 11.6 μg/g of riboflavin (B2), 5.8 μg/g of thiamine (B1), 1.5 μg/g of cobalamin (B12), and 0.18 μg/g of biotin (Tarento et al. 2018). A recent study evaluated commercial powders of microalgae, the study showed a riboflavin content between 21 to 41 μg/g, while niacin content varied from 0.13 to 0.28 mg/g in *Chlorella* sp., *Spirulina* (*Arthrospira* sp.) and *Nannochloropsis gaditana* powders. *Chlorella* powders showed 19.7 μg/g of total folate and *Spirulina* powders showed 3.5 μg/g. *Chlorella* sp., and *N. gaditana* powders contained active vitamin B12 up to 2.1 μg/g. *Spirulina* powers contained high amounts of pseudovitamin B12, a no bioactive form of vitamin B12 (Edelmann et al. 2019). In the case of vitamin B12 from microalgae, there are two scenarios, many eukaryotic microalgae require exogenous B vitamins for growth, while marine cyanobacteria can synthesize pseudovitamins; new findings explain that certain microalgae species can turn the inactive vitamin B12 into its biologically active form through a process named vitamin remodeling. This has been identified as an important criterion to survive in the photic environment (Grossman 2016). For vitamin E, commercial

Spirulina has 1.3 mg of vitamin E (α-tocopherol)/100 g of dry mass (Gómez-Coronado et al. 2004).

2.7 Minerals

The essential minerals for human health and animal life are classified according to the level of requirement in two general categories, more importantly calcium, phosphorous, potassium, sodium, chlorine, magnesium, and sulfur; and secondly, trace minerals, such as iron, zinc, manganese, molybdenum, chromium, and copper. Most trace minerals usually act in the human body as cofactors for the correct functioning of enzymes (Costa-Pinto and Gantner 2020). Calcium and phosphorus are the main structural components in hard and soft tissues. These minerals are also implicated in osmoregulation process, nerve/muscle function, acid/base equilibrium, and cell membrane functionality, among others. Microalgae as a mineral source is also an important criterion to use in the biomass as a food supplement; its mineral content varies between marine or freshwater microalgae, and from one species to another (Fox and Zimba 2018). For example, *Spirulina* sp. biomass has 13,630 μg/g of potassium, 1950 μg/g of magnesium, 1200 μg/g of calcium, 10,480 μg/g of sodium, 285 μg/g of iron, and 20 μg/g of zinc. *Anabaena cylindrical* biomass has 9530 μg/g of potassium, 3840 μg/g μg/g of magnesium, 3140 μg/g of calcium, 2330 μg/g of sodium, 593 μg/g of iron, 16.3 μg/g of zinc (Tarento et al. 2018). Regarding marine microalgae, *Biddulphia* sp. is rich in calcium (18.23 g/Kg), *Amphora* sp. in phosphorus (12.39 g/Kg), *Achnanthes* sp. in potassium (20.88 g/Kg), *Thalassiosira* sp. in sodium (321.38 g/Kg) and zinc (39.55 mg/Kg), *Phaeodactylum limnetica* in magnesium (37.15 g/Kg), and *Navicula* sp. in iron (1912.98 mg/Kg), and copper (9.49 mg/Kg) (Silva et al. 2015).

2.8 Other Bioactive Compounds

Microalgae can also produce other interesting biomolecules, e.g., enzymes, such as cellulases, amylases, galactosidases, proteases, lipases, phytases, laccases, antioxidant enzymes, and enzymes involved in carbohydrate accumulation and carbon concentration (dos Brasil et al. 2017). Phytohormones including auxin, abscisic acid, cytokinin, ethylene and gibberellins (Lu and Xu 2015). Phytochemicals can be produced as well, such as flavonoids, alkaloids, saponins (El Semary and Abd El Naby 2010). While cyanotoxins, such as microcystin, nodularin, saxitoxin, anatoxins, cylindrospermopsin, lipopolysaccharides, have been reported and utilized for potential application as allelochemicals, herbicides, and insecticides. Cyanobacterial siderophores are recognized as iron chelators, and as photoprotective UV-screening compounds for mycosporine-like amino acids and scytonemin (Rastogi and Sinha 2009).

2.9 Microalgae for Food and Feed Animals

Microalgae biomass has nutritional value in terms of high content of protein, carbohydrates, fatty acids, and biologically active compounds. To date, there are a few microalgae that are commercialized as dietary supplements, such as the biomass of *Chlorella*, *Spirulina*, and *Nostoc*. *Chlorella* but displaying low digestibility. It is documented that *Spirulina* has been eaten by the Aztecs from Mexico, this strain is considered a superfood by its high protein content, fatty acids, vitamins, minerals, antioxidants, and others bioactive compounds (Soni et al. 2017). It is estimated that more than 12,000 tons of *Spirulina* biomass are produced every year (Matos 2019). Some studies have shown the application of its biomass and other high added-value compounds in food matrices. *Chlorella vulgaris* (green), *Chlorella vulgaris* (orange) and *Haematococcus pluvialis* (red) biomass have been used as coloring and antioxidant agent in emulsions (Gouveia et al. 2006). *Chlorella vulgaris* (green) biomass has been used as a color ingredient in butter cookies (Gouveia et al. 2007). Specific polyunsaturated fatty acids from *Isochrysis galbana* biomass were proposed to enrich the nutritional value and enhance the texture properties of biscuits (Gouveia et al. 2008), while *Haematococcus pluvialis* and *Spirulina maxima* biomass were employed for vegetarian food gels (Paula et al. 2012). Spaghetti enriched with *Chlorella vulgaris* and *Spirulina maxima* biomass were used to enhance the quality parameters of the product (Fradique et al. 2010).

To animal feed, the biomass of *Porphyridium* sp. was incorporated into chicken to reduce cholesterol in the egg (Ginzberg et al. 2000). Carotenoids from *Chlorella vulgaris* (orange) and *Haematococcus pluvialis* were blended in fish (rainbow trout and gilthead seabream) as a pigmentation supplement (Gouveia and Empis 2003). The oil extracted from microalgae was incorporated in the feed of pigs to partially replace corn and soybean meal (Foltz et al. 2016). Lambs were feeding in a dietary supplementation with docosahexaenoic acid-rich microalgae to produce an increase in polyunsaturated fatty acids in intramuscular fat (Díaz et al. 2017).

2.10 Bioremediation

When dealing with environmental matters, microalgae can assimilate carbon dioxide (CO_2), which is a greenhouse gas (Castro-Muñoz et al. 2019a). Their cultivation can reduce the CO_2 emissions produced by combustion; and also release oxygen. Microalgae can fix 1.83 Kg CO_2 while generating 1.0 Kg of biomass (Gupta et al. 2019). To date, CO_2 concentrations in the environment exceed 400 parts per million (Panchenko et al. 2020); therefore, there is today an interest in developing suitable and environmentally friendly capturing technologies of CO_2 from the environment or flue gas (Martin-Gil et al. 2019; Ahmad et al. 2021), in which microalgae cultivation represents an alternative, the main goal here is to get pure CO_2 without toxic gases, such as NOx and SOx (Rahaman et al. 2011).

Microalgae have been proven for wastewater treatment as bioremediation using this wastewater as a culture medium: basically, the aim is to recover nutrients from municipal, agricultural and industrial wastewaters for microalgae growth. In this way, the reduction of costs of microalgae cultivation, harvesting, and downstream of their bioproducts, simultaneous lipid, protein, and carbohydrates production are done. The most common nutrients to remove from wastewater are nitrate and phosphate, which represent a source of nitrogen and phosphorus, respectively. For the screening of microalgae strains suitable for the wastewater treatment, some criteria are established such as fast growth rate, high nutrient removal rate, strong adaptability to different types of wastewater, strong adaptability to local climate, and high biomass productivity (Li et al. 2019). At this purpose, *Chlorella* and *Scenedesmus* species are the most successful strains, nonetheless, many other strains have been proposed. For example, pig biogas slurry was mixed with municipal wastewater for *Chlorella zofingiensis* cultivation, an 8% of pig biogas slurry was found as the best to get 2.5 g/L biomass, and the removal 93% total nitrogen and 90% total phosphorus (Zhou et al. 2018). Nejayote, which is identified as the main by-product of Nixtamalization processes (Castro-Muñoz et al. 2019c), and swine wastewater have been evaluated for *Arthrospira maxima* and *Chlorella vulgaris* growth (López-Pacheco et al. 2019). *Scenedesmus quadricauda* and *Tetraselmis suecica* were cultivated using dairy wastewater (Daneshvar et al. 2019). Also, symbiotic growth may be possible, e.g., microalgae and bacteria were co-cultivated (Makut et al. 2019).

The biomass could also be a removal pollutant matrix. Immobilized *Phormidium* sp. was used to remove reactive dyes (such as remazol blue, Reactive Black B) from a model dye-rich wastewater (Ertu and Bak 2007). The toxic and heavy metals that result from industrial processes are priority pollutants to be removed due to their great damage to the environment (Castro-Muñoz et al. 2021). *Chlorella vulgaris* and *Scenedesmus spinosus* were tested due to their biosorbent capacity towards metal ions, *C. vulgaris* had a higher tolerance than *S. spinosus*, and it showed a capacity to remove Cu and Mo from metal mine tailings water (Urrutia et al. 2019). In particular, *Synechocystis* PCC6803 has shown its potential in the bioremediation of heavy metals via biosorption, such as Cr (VI), Cd (II), Cu (II), Pb (II), Ni (II), Mn (II), Mn (IV), As (III), As (V), Cs and Hg (Pembroke et al. 2015). The microalgae extracellular polymeric substances could be potentially useful too. The exopolysaccharide of *Synechocystis* sp. has shown antimony trapping capacity in concentrations of 5–100 mg/L, where 32.4–48.5% of the chemical was absorbed (Zhang et al. 2012).

Although the capacities of microalgae to reduce the impact of pollutants have been demonstrated, their application in bioremediation processes is scarce. Therefore, it is worth exploring this research topic further given the advantages of microalgae.

2.11 Biofertilizers and Biostimulants from Microalgae

The serious effects on the environment, animal, and human health caused by the use of chemical fertilizers in agriculture crops have been driven the research toward alternative sources, environmentally friendly and cost-effective strategies. In this sense, microalgae dry biomass has been explored as biofertilizer; *Spirulina platensis* and *Chlorella vulgaris* biomass were used separately and blended with cow dung as fertilizer in onion cultivation. The growth parameters, yield attributes, and biochemical composition were high in *Spirulina platensis* and cow dung mixes (Dineshkumar et al. 2020). De-oiled biomass waste (residual biomass) of *Scenedesmus* sp., was used to reduce chemical fertilizers in rice crops. The combined application of microalgae with chemical fertilizers resulted in an increased yield and quality of rice (Nayak et al. 2019).

Cyanobacteria are known for their potential to fix atmospheric nitrogen and make it available for plants; specifically, Diazotrophes, which are useful for ecofriendly biofertilizers. The most efficient nitrogen-fixing cyanobacteria are *Nostoc linkia*, *Anabaena variabilis*, *Aulosira fertilisima*, *Calothrix* sp., *Tolipothrix* sp., and *Scytonema* sp. *Anabaena* and *Nostoc,* which can fix up to 20–25 Kg/ha atmospheric nitrogen. In addition to biofertilizer, there are numerous advantages of using living cells of cyanobacteria, such as make porous soil and produce adhesive substances, excretion of phytohormones (growth-stimulating hormones), vitamins and amino acid, improve the water holding capacity of soil through their characteristic jelly structure, increase in biomass of soil after their death and decomposition decrease in soil salinity, controls weeds growth, availability of soil phosphate by excretion of organic acids, and efficient absorption of heavy metals on the microbial surface (bioremediation) (Chittora et al. 2020). Microalgae extracts are also a potential biostimulating of plants due to their content of bioactive compounds including polysaccharides, lipids, proteins, phenolic compounds, phytohormones, and polyamines (Chiaiese et al. 2018). The application of crude polysaccharides extracts from *Arthrospira* platensis, *Dunaliella salina* and *Porphyridium* sp. on tomato plants improved nodes number, shoot dry weight, shoot length, pigments content, proteins content, and change in fatty acids, sterol and alkanes profiles (Rachidi et al. 2020); however, it is still necessary to know the specific effect of microalgae biostimulating on plant metabolism.

2.12 Microalgae-Based Bioplastics

The biodegradable bio-based polymers are generally based on proteins (e.g., casein, collagen, albumin, and keratin), and polysaccharides (e.g., starch, cellulose, alginate, carrageenan, polylactic acid, and polyhydroxyalkanoates). Today, there a clear trend in producing bio-based polymers to replace the chemically synthesized ones that represent an important environmental issue (Castro-Muñoz and

González-Valdez 2019; Díaz-Montes and Castro-muñoz 2021). It is known that the lipids are not polymers strictly, nonetheless, they are included in this group. Biopolymers can be produced from plants, animals, microorganisms and their derived metabolites. The bioplastics can be manufactured in different ways but always presenting biodegradable nature (Niaounakis 2015). Microalga biomass and their extracellular polymeric substances could be a potential raw source for bioplastics and bioactive film production due to their content of lipids, proteins, polysaccharides, and some other high added-value compounds. Antimicrobial edible films for food packaging were done using *Arthrospira platensis* protein and lysozyme (Benelhadj et al. 2016). Similarly, transparent and flexible bioactive films were obtained from extracellular biopolymers from *Nostoc* sp., and *Porphyridium purpureum* (Morales-Jiménez et al. 2020). Furthermore, biodegradable films were prepared with a blend of *Heterochlorella luteoviridis* and *Dunaliella tertiolecta* biomass/biomass extract and cassava starch (Carissimi et al. 2018). Another strategy was to get bioplastics made of wheat gluten and *Spirulina platensis* biomass like a filler (Ciapponi et al. 2019). Thermoplastic corn starch biocomposites were prepared with the addition of biomass from *Nannochloropsis*, *Spirulina*, and *Scenedesmus* (Fabra et al. 2018)., *Nostoc muscorum* can accumulate intracellularly poly-β-hydroxybutyrate under carbon stress (Haase et al. 2012), this polymer was proposed as a potential substitute for plastics.

3 The Role of Membrane Technology in Microalgae Bioprocessing

Membrane technologies for microalgae processing is currently gaining great interest due to their efficiencies in the separation of particles, macromolecules and micromolecules (Castro-Muñoz et al. 2016). Their main advantages concern to the non-chemical, biological or thermal change of the component (Cui et al. 2010). Some other advantages, such as ease of operation, high separation efficiency and scalability, increase the usefulness of the membrane-based technologies for microalgae bioprocessing (Kumar et al. 2020). Membrane processes have a wide range of applications, specifically pressure-driven processes can be divided by the pore size of the membrane used and the required transmembrane pressure (Castro-Muñoz et al. 2019b). In general, such processes can be classified as microfiltration (MF), ultrafiltration (UF), nanofiltration (NF) and reverse osmosis (RO) (Cui et al. 2010). Figure 10.2 gives an overview of the pore size of the membranes and their application to separate specific molecules. Due to the complex nature of microalgae cultivation media, MF has been mainly studied for microalgae harvesting, it means, the dewatering of the biomass until the concentration stage, and this is possible due to cell sizes of microalgae (2–200 μm). The needing of the microalgae bioprocessing has led the application of membrane process in the microalgae cultivation, pretreatment of wastewater, recovery, and purification of CO_2 to culture, and

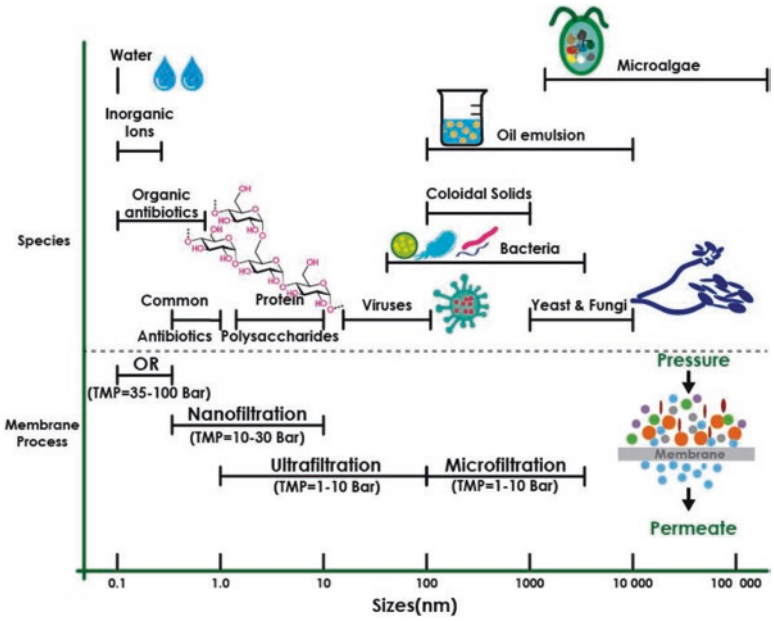

Fig. 10.2 Membrane processes and their applicability range based on pore size. (Adapted from Cui et al. 2010; Padaki et al. 2015)

implementation of membrane photobioreactors. Moreover, the membrane processes are being useful in the recovery of high added-value compounds from microalgae within isolation and purification strategies. The following section provide a clear overview of the uses of membrane processes in these applications.

3.1 Membrane Technology for Microalgae Cultivation

3.1.1 Pretreatment of Wastewater as a Culture Medium for Microalgae Cultivation

Wastewater is a promising source of culture medium and represents an excellent alternative to reduce the costs of nutrients for the microalgae culture. Due to the complexity of wastewater, there are still many challenges to solve in these aspects, such as organic and inorganic nutrients concentration, pH, color, total dissolved solids, and microbial contaminants (Li et al. 2019). These parameters are generally extreme when compared with the optimum values for microalgae growth, making it inappropriate for direct application on the cultivation. In this case, the pretreatment of the wastewater is strictly necessary. To reduce the microbial contaminants, the wastewater is exposed to UV light or autoclaved, nonetheless, for a large-scale system the operation cost increases. MF and UF could be excellent alternatives.

Sandefur et al. (2016) evaluated the potential use of UF technology to remove inorganic solids and bacteria as biological contaminant from swine wastewater, which was latest used for the cultivation of *Porphyridium cruentum*. A hollow fiber membrane cartridge of 50,000 MWCO was used to eliminate coliforms, and 75% of total solids; membrane system was optimized at 27 °C and a transmembrane pressure of 17.5 psi (Sandefur et al. 2016). After the microalgae biomass harvest, the spent culture medium still contents nutrients, these can be used to cultivate microalgae again under a water and nutrients recycling approach. To reuse spent microalgae culture medium from large-scale outdoor ponds, the presence of bacteria and some other organisms are identified as the main drawback due to the microbes consume nutrients and oxygen during their growth, moreover, their metabolites influence the physicochemical properties of the medium, including pH, along with the limitation of the available light for microalgae growth. Yu et al. (2019) showed that MF membranes were useful to remove microbial contaminants of the spent culture medium from *Arthrospira platensis* biomass harvesting process, in a large-scale outdoor raceway pond. At this point, polystyrene membrane of 0.1 μm of nominal pore size was used to reject bacteria and micro zooplankton from the residual medium (Yu et al. 2019).

3.1.2 Membrane Technologies Coupled to Photobioreactors

To simultaneously improve the cultivation, harvesting, and dewatering, a novel strategy has been recently implemented combining membrane processes and photobioreactors. When the membrane module is adapted inside of the photobioreactor, the membrane is useful for carbonation or biomass retention; also, biomass retention by membrane module can be installed outside the photobioreactor, as illustrated in Fig. 10.3. A carbonation membrane photobioreactor can act as a contactor system to enhance the fixation and delivery of CO_2 into the culture media. On the other hand, a biomass retention in photobioreactor via membranes allows obtaining spent culture medium through permeate stream. This strategy has been especially useful for wastewater treatment and biomass production simultaneously. The factors affecting microalgae growth and nutrients removal rates in biomass retention are lightning conditions, CO_2 carbonation (between 0.15–8.0 L/min), nutrients concentrations, hydraulic retention time, and biomass retention time (Zhang et al. 2019). Membrane photobioreactor processes have still many issues to be overcome and optimized, e.g., membrane fouling (Liao et al. 2018). It is important to highlight that the fouling phenomenon is identified as the main drawback of membrane technologies. In these applications, the membrane tend to be prone to "biofouling" (Pichardo-Romero et al. 2020), which is implies the adhesion of micro- or macro organisms as membrane foulant, and it is the "vulnerable" part of the microalgae harvesting by these technologies.

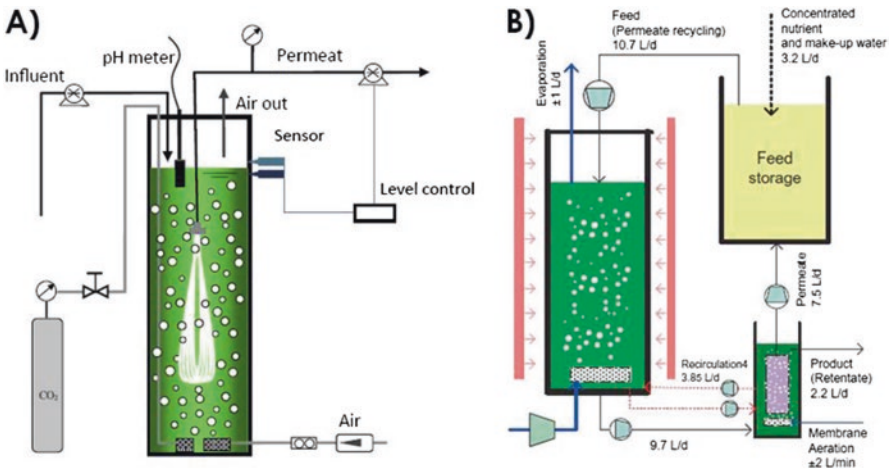

Fig. 10.3 Membrane photobioreactor for biomass production: (**a**) membrane inside the photobioreactor (**b**) membrane outside the photobioreactor (Bilad et al. 2014; Gao et al. 2019)

3.2 Membrane Technology for Microalgae Biomass Harvesting

Microalgae biomass harvesting is a process where the biomass is separated from the spent culture medium. This microalgae process is particularly complex due to the small size of the microalgae cell, suspended in a big volume of the medium. Their high cost, which is up to 20–30% of the total biomass production cost, is also a relevant factor (Fuad et al. 2018; Yin et al. 2020). Harvesting methods are classified as chemical (flocculation), physical (centrifugation, filtration, gravity sedimentation, flotation, electrophoretic separation), biological (bioflocculation and autoflocculation), and magnetic (Yin et al. 2020). In specific cases, the synergy of different methods offers better harvesting efficiency, for example, flocculation followed by membrane filtration (Zhao et al. 2020). Flocculation is the most useful harvesting method due to its ease of operation, recovery efficiency (70–99%), and cost, however, the use of chemical flocculants causes contamination to the biomass and the culture medium, it driven to limited chances to recycle the culture medium. Choosing the best microalgae harvesting method according to the objective is still a challenge. The harvesting method can be selected according to the microalgae species, type of products in the downstream process, the versatility of the method, and the possibility of re-use the spent culture medium (Yin et al. 2020).

Membrane technology for microalgae harvesting has been widely studied over 20 years. For microalgae harvesting, MF and UF have shown similar results in terms of permeate flux, under the same operating conditions at low transmembrane pressure (Sun et al. 2013). The membrane filtration allows biomass recovery

efficiencies up to 100%, biomass free of chemical additives, and culture medium with the possibility to reuse. Also, they offer important characteristics for improving the quality in the downstream process, diminish the water footprint, reusing nutrients, reducing costs, and being environmentally friendly. Hwang and Rittman (2017) evaluated the effect of permeate recycling on the growth of *Synechocystis* sp. PCC 6803. Permeate was obtained by the MF process. The results showed that the highest biomass concentration was 0.63 g/L at the end of the experiment using a permeate ratio of 50% and complemented with 50% of the BG11 medium. The reuse of permeate two times (two runs) had no negative impact on *Synechocystis* sp. PCC 6803 growth. Growth inhibition was observed during run 3 probably caused by nutrient deficiency, presence of cell debris, and extracellular substances. A degradation process was necessary to reuse permeate after run 2 (Hwang and Rittmann 2017). For such a scenario, Monte et al. (2019) demonstrated the viability of recycling cultivation medium from *Dunaliella salina* after the membrane harvesting (ultrafiltration) of the biomass, the permeate stream was recovered and treated by advanced oxidation to degrade the organic compounds. Cultivation medium treated and no treated was used to *Dunaliella salina* growth and carotenoid production. The maximum volumetric productivity of carotenoids was 6.93 ± 0.48 mg/L·d for the untreated permeate and 5.98 ± 0.41 mg/L·d for the treatment with oxidation (Monte et al. 2019).

One of the determining criteria for microalgae harvesting using membrane technology is the energy consumption and cost analysis. Monte et al. (2018) compared the energy consumption using centrifuge and membrane unit to recover efficiently the biomass and consequently the cost involved, for the harvesting of *Dunaliella salina* at pilot scale. Harvesting with UF pre-concentration led to a 45% reduction in energy and a 52% reduction in the total cost of ownership when compared with only centrifugation (Monte et al. 2018). Nowadays, deeper cost analysis is mandatory according to microalgae strain, membrane equipment used, operation conditions, and energy consumption as done by Gerardo et al. (2015), who evaluated the influence of operating conditions and scale-up effect to diminish the cost through energy consumption. They have shown that by manipulating parameters such as transmembrane pressure, initial biomass concentration, energy intake, temperature, and membrane area, it is possible to reduce the total energy consumption around 56% in the pilot-scale cross-flow MF of *Chlorella minutissima* (Gerardo et al. 2015).

Other criteria for membrane microalgae harvesting are the optimized operating conditions and the membrane material selection. At this purpose, several membrane materials have been explored including polyvinylidene fluoride, polyacrylonitrile, polyethersulfone, cellulose acetate, and inorganic materials (see Table 10.1). The selection is based in biomass concentration, species characteristics, surface charge, hydrophobicity, and feed flow parameters (Leam et al. 2020). Rossi et al. (2004) evaluated 11 commercial membranes to harvest *Arthrospira platensis*. Polyacrylonitrile membrane of 40 kDa, having a neutral and hydrophilic nature,

Table 10.1 Recent reports of microalgae biomass harvesting using membrane technologies

Microalgae	Membrane process				References
	Process	Membrane characteristics	Operating conditions	Findings	
Dunaliella salina	Ultrafiltration (pilot scale)	Polysulfone, MCWO: 100 kDa, EFA: 6.1 m^2.	Cross-flow velocity: 0.30 m/s, TMP:0.30 ± 0.16 bar, 21 ± 3 °C	At concentration factor of 10, average permeate flux of 21 ± 3 L/(m^2h) was obtained. Initial concentration of 2.8x10^5 cells/mL to a final concentration of 2.9x10^6 cells/mL.	Monte et al. (2020))
Tetraselmis sp., *Picochlorum* sp.	Ultrafiltration (pilot scale)	Hollow fiber, polyacrylonitrile, MWCO: 10 kDa. EFA: 25 cm^2	Temperature: 23–27 °C.	Effect of the salinity culture: As the salinity of the culture increased, the permeate flux declined. 100% efficiency of the membrane in separating the cells from the cultures. An increase in culture salinity would reduce the membrane capacity both in terms of filtrating culture volume and final biomass concentration.	Das et al. (2019)
Chlorella vulgaris	Microfiltration	Hollow fiber, polyvinylidene floride, PS: 0.2 μm, EFA: 0.25 m^2	Turbulent jet, TMP: 100 kPa.	Through the turbulent jet, permeate flux at the steady-state increased by 126%, and the specific energy for filtrating out a unit volume of permeate was reduced by 38% relative to the conventional type.	Kim et al. (2019)
Dunaliella salina	Ultrafiltration (pilot scale)	Polyethersulfone. MWCO: 150 kDa. EFA: 2.4 m^2	Cross-flow velocity: 0.6 m/s. TMP: 0.25 bar.	Consecutive steps allowed reaching a final concentration factor of 16.4 with an average permeate flux of 22 L/ (m^2h). Minimal loss of cell integrity of 13%.	Monte et al. (2018)

(continued)

Table 10.1 (continued)

Microalgae	Membrane process				References
	Process	Membrane characteristics	Operating conditions	Findings	
Chlorella sp.	Microfiltration	Circular disk, cellulose acetate, PS: 1.2 μm, EFA: $7.07x10^{-4}$ m^2	Cross-flow velocity: 0.13–4.0 m/s. TMP: 0.5–1.5 bar.	Effect of the transmembrane pressure: 1.5 bar was the optimal. Effect of the cross-flow velocity: The highest permeate flux was obtained at 4.0 m/s. An increase in the CFV and a decrease in the TMP result in a reduction in the cake layer formation.	Ahmad et al. (2012)
Chlorella sorokiniana	Microfiltration	Anopore inorganic disk, PS: 0.2 μm, EFA: $7.29x10^{-4}$ m^2.	Cross-flow	Effect of cross-flow velocity: Less deposition of polysaccharides and protein was observed at 0.1 m/s. Threshold flux was inversely proportional to concentration.	Wicaksana et al. (2012)

MWCO molecular weight cut off, *PS* pore size, *EFA* effective filtration area, *TMP* transmembrane pressure, *CFV* cross-flow velocity

was the best in terms of permeation flux, and clean ability (Rossi et al. 2004). More lately, Marbelia et al. (2016) used polyacrylonitrile membranes to filter microalgae and they evaluated the influence of porosity, surface charge, and microalgae species on membrane fouling. They found that large pores were easily blocked by foulants, negatively charged membranes reduced membrane fouling, and also microalgae with non-spherical shape (*Scenedesmus* and *Phaeodactylum*), large size and rigid cell wall were easier to filter than microalgae without a cell wall (*Isochrysis*) and microalgae with a flexible cell wall (*Pseudanabaena*). Importanly, the filtration performance was determined by a cake layer formation (Marbelia et al. 2016).

To date, the main bottleneck concerns to solve the severe membrane fouling since conducts to a short useful life of the membrane, and consequently increases the cost of operation. The membrane fouling is promoted by operating conditions, membrane characteristics, algae species, and foulant compounds. The fouling can take places in several ways, such as internal fouling (including pore plugging and adsorption) and external fouling, which implies cake deposition. The fouling could be reversible or irreversible depending on the nature of the foulant (Rickman et al. 2012; Díaz-Montes et al. 2020). The foulants from microalgae are generally complete cells, cell debris and algogenic organic matter. The algogenic organic matter is released by algal metabolism into the extracellular medium, and its production strongly depends on the growing conditions, including temperature, pH, and nutrients content. It has been observed that changes in the nitrogen-phosphorus ratio may affect the composition of algogenic organic matter, which can be composed of protein, neutral and charged polysaccharides, nucleic acids, lipids, and small molecules (Huang et al. 2012). Zhang et al. (2016), for instance, studied the impact of the released algogenic organic matter from *Microcystis aeruginosa* and *Chlorella* sp. culture on the membrane fouling according to the growth phase; herein, a MF unit was proposed using a ceramic membrane. The results showed that the MF filtration stage of the algogenic organic matter from both algal species at the stationary phase (35 days) caused a more severe flux decline compared with the corresponding to the log phase (12 days). This fact was attributed to the stationary phase containing significantly greater amounts of high fouling potential components (e.g., protein and humic-like substances) (Zhang et al. 2016).

Various strategies have been developed to diminish the membrane fouling during the filtration process. Zhang and Fu (2018) pointed out strategies, such as pretreating the feed water (e.g., adding Ca^{+2} and changing the pH, adding coagulants, oxidants, or adsorbents), changing the membrane properties (e.g., pore size, hydrophilicity/hydrophobicity surface, and charge), and enhancing the hydrodynamic conditions (e.g., cross-flow rate, using aeration, and dynamic filtration systems near the membrane surface) (Zhang and Fu 2018), to obtain more efficient recovery efficiencies. The application of any of these strategies must be carefully selected according to the subsequent processes to avoid counterproductive effects that lead to more serious fouling of the membrane.

Table 10.2 The role of membrane technology in recovering high added value compounds from microalgae

Microalgae extract	Pretreatment	Membrane process						References
		Process	PS/ MWCO	Membrane material/EFA	Flow rate, temperature	TMP/VRF	Remarks/Findings	
Parachlorella kessleri (extraction in phosphate buffer, pH 7.4)	Centrifugation	Ultrafiltration (pilot scale)	500 kDa	Polyacrylonitrile, 130 cm^2	Concentration stage. Cross-flow 1 m/s, 30 °C	0.4 bar, VRF: 2	Permeation flux: 34–41 L/h m^2 0.29–0.3 g/L of lipids, 0.27–0.60 g/L of proteins, and 0.50–0.95 g/L of sugar at the retentate. The lipids were wholly retained.	(Clavijo Rivera et al. (2020)

Nannochloropsis (biomass sonicated)	–	Ultrafiltration	100 kDa	Regenerated cellusaawlose, 1.73	Concentration mode: Cross flow 0.6 m/s,	VRF: 5	Separation of cell fragments from small compounds. Flux: 20 L/h m^2 94% of chlorophyll a, 56% of protein, 36% of glucose, 28% of triacylglycerol at the retentate.	Giorno et al. (2013)
			30 kDa		Concentration mode: Cross flow 0.48 m/s	0.15 bar, VRF: 5	Lipids separation Permeation flux: 22 L/h m^2 85% of chlorophyll a, 88% of protein, 44% of glucose, 24% of triacylglycerol at the retentate.	

(continued)

Table 10.2 (continued)

Microalgae extract	Pretreatment	Membrane process						References
		Process	PS/ MWCO	Membrane material/EFA	Flow rate, temperature	TMP/VRF	Remarks/Findings	
Porphyridium cruentum (extraction in water)	Centrifugation, then filtration using glass discs (10–40 μm)	Ultrafiltration (pilot scale)	300 kDa	Polyethersulfone, 0.1 m^2	Concentration stage: Tangential flow, 20 °C	1.0 bar, VRF:2.5	20% of polysaccharides, 37% of proteins, and 41% of β-phycoerythrin of the initial feedstock were quantified in the retentate at the end of the diafiltration step.	(Marcati et al. (2014)
					Diafiltration stage	1.0 bar, VRF: 2 diavolumes		
			10 kDa		Concentration stage	1.0 bar, VRF: 3.5	48% of the β-phycoerythrin content in the initial feedstock was recovered in the retentate. β-phycoerythrin purity index increased from 1.0 to 1.7 at the end of concentration, and it reached 2.3 at the end of diafiltration stage.	
					Diafiltration stage	1.0 bar, VRF: 2 diavolumes		

Spirulina sp. (extraction in phosphate buffer, pH 7.0)	Centrifugation	Microfiltration	5 µm	Non-woven polypropylene, 0.15 m^2	150 mL/min	–	−88.6% of phycocyanin recovery.	Chaiklahan et al. (2011)
			0.8/0.2 µm	Polyethersulfone, 0.02 m^2	100 mL/min	–	82.9% of phycocyanin recovery.	
		Ultrafiltration	50 kDa	Polyethersulfone, 0.005 m^2	75 mL/min	69 kPa	Concentration of phycocyanin at the end of filtration: 6.17 mg/mL. Purity ratio: 1.07	
Spirulina platensis, Chlorella pyrenoidosa, Chaetoceros muelleri, Haematococcus pluvialis, Nostoc commune, Nostoc sphaeroides.(extracellular medium)	–	Microfiltration	0.3 µm	Polypropylene, 0.42 m^2	1.5–2.0 L/min of flow rate	–	–	Li et al. (2011)
		Ultrafiltration (pilot scale)	5000 Da	Polyethersulfone, 0.5 m^2	Tangential flow mode	0.5–0.6 bar	Effect of the temperature: 30–40 °C would be appropriated due to the permeate flux increased. Effect of pH: Alkaline pH may be beneficial to EPS ultrafiltration. Average permeate flux obtained: 39 L/m^2 h EPS yield varied between 3.5–231.3 mg/L	

(continued)

Table 10.2 (continued)

Microalgae extract	Pretreatment	Membrane process						References
		Process	PS/ MWCO	Membrane material/EFA	Flow rate, temperature	TMP/VRF	Remarks/Findings	
Porphyridium cruentum (extracellular medium)	–	Microfiltration (pilot scale)	0.14 μm	Ceramic, 0.032 m^2	Concentration stage: Cross flow (2.5, 3.3, 4.2 $m \cdot s^{-1}$), 20 °C	4.0 bar, VRF: 7–10	Polysaccharides were concentrated 6.3–10.4 times. Final concentration reached 1.74–2.26 g/L.	Balti et al. (2018)
					Diafiltration stage: 3.3 $m \cdot s^{-1}$, 20 °C	4.0 bar	Diafiltration as EPS pre-purification step.	

MWCO molecular weight cut off, *PS* pore size, *EFA* effective filtration area, *TMP* transmembrane pressure, *VRF* volume reduction factor, *EPS* extracellular polysaccharides

3.3 Membrane Technology for the Recovery of High Added Value Compounds from Microalgae

The recovery of high value compounds requires processes that guarantee maximum efficiency due to the costs that are involved. For microalgae processes, membrane technology is indeed a promising technique in the recovery of lipids, triacylglycerol, polysaccharides, glucose, proteins, and pigments (such as chlorophyll a, β-phycoerythrin, and phycocyanin) (see Table 10.2). Here, the membrane technology is implemented as a purification step, where the degree of purity is one of the most important parameters. Patel et al. (2013) showed in their study a comparison of three methods for the separation of extracellular polysaccharides from the *Porphyridium cruentum* culture media. Membrane separation in a diafiltration mode using a membrane of 300 kDa molecular weight cut off was the most efficient for a large scale process, and the extracellular polysaccharides were obtained with a high degree of purity (Patel et al. 2013). The diafiltration step allows the cleaning of the compound of interest through washing with deionized water (or a buffer) until it reaches its maximum purity, it is necessary to monitor the decrease in the contaminant. The diafiltration step is generally performing after the concentration step, especially in the recovery of compounds from marine microalgae having high content of salt. Continuous steps of filtration in a gradual reduction of molecular cut is an adequate strategy in the separation of high added-value compounds. As seen in Table 10.2, microalgae extract is performed before the membrane process to release the intracellular compounds; and therefore the extracellular compounds from the spent extracellular medium can be directly processed. The membrane pressure-driven processes used mainly in the pre-purification stage of high-added value compounds are microfiltration and ultrafiltration. For this purpose, a pretreatment must be developed to eliminate cells and cell debris of the extract obtained. Centrifugation is the most used together with conventional filtration using glass discs or gauze.

3.4 The Importance of Protocols for Membrane Cleaning by Microalgae Fouling

Despite the great advantages that membrane technology offers in microalgae processes, the main drawback is the membrane fouling, which causes a severe decline in the fluxes, growing transmembrane pressure, increase the cleaning frequency, and energy consumption, and consequently a short lifespan of the membrane. For the microalgae process, fouling is generally provoked by foulants such as microalgae cell debris, inorganic colloidal particles, natural organic matters, extracellular

organic matters, and soluble microbial products (Liao et al. 2018). For microalgae biomass harvesting, several factors affecting membrane fouling include membrane pore size, pressure, and temperature (Leam et al. 2020). Also, some other factors are involved in the membrane fouling, e.g., Liao et al. 2018 have very recently explored and analyzed multiple factors involved in membrane photobioreactor process, however, some of these factors apply to the microalgae membrane process overall. They identified that the membrane fouling is caused by factors such as the hydrodynamic conditions (e.g., sparging intensity and cross flow-velocity), process operation conditions (e.g., hydraulic retention time and solids retention time), environmental conditions of the culture media (e.g., pH, temperature, and nutrients), microalgae concentration, and microalgae characteristics (e.g., specie, cell size, particle size distribution, surface properties such as extracellular polysaccharides and soluble microbial products content and composition, hydrophobicity and zeta potential) (Liao et al. 2018). Some strategies to diminish membrane fouling involving feed pretreatments, optimization of operational conditions, membrane surface modification, and intensive physical and chemical cleaning of the membrane (e.g., aeration, membrane relaxation, backflushing, and ultrasonication) (Leam et al. 2020). Membrane maintenance is mainly determined by the cleaning process, while each microalgae strain shows a particular behavior onto the membrane fouling, which drives complex strategies for cleaning up the membrane. At this point, it is likely that more efficient cleaning protocols need to be developed, where the selection of the physical method and variables, such as cleaning agent, concentration, and temperature, will require to be optimized. Particularly, Ahmad et al. (2014) investigated different chemical cleaning agents as an important criterion for the cleanup of membranes. A cellulose acetate membrane (1.2 um of the pore size) was used for harvesting *Chlorella* sp. The water flux recovery and the foulant removal were tested, showing that 0.75% of NaOCl exhibited the best cleaning performance, and a 98% of flux recovery was obtained while removing mostly major foulants (Ahmad et al. 2014).

4 Concluding Remarks

Over the course of this chapter, microalgae have proved to be a promising source of compounds with high-added value. The study and application of each strain depends on the scope of research and the production of compounds of interest. When dealing with the recovery of their metabolites, membrane technology is a potential tool for upstream and downstream microalgae processing thanks to their well-defined molecular sieving, however, severe membrane fouling issue, mainly in biomass harvesting, limit its long-term application and profitable use. To date,

various strategies have been developed to lessen its ravages but it is still a bottleneck to solve.

Towards the recovery of high-added value compounds, the membrane technology has proven its ability as a purification step of the various compounds. Importantly, pretreatment steps seem to be required for a more efficient recovery to concurrently mitigate the membrane fouling. Today, there is a current trend in developing integrated membrane systems to fractionate a complex feed bulk solutions, along with decreasing the biofouling (Castro-Muñoz and Yáñez-Fernández 2015; Díaz-Montes and Castro-Muñoz 2019). Interestingly, these integrated membrane systems may also provide the possibility to implement continuous processes for possible large-scale applications.

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Part IV
Novel Membrane Processes for the Separation of Bioactive Compounds

Chapter 11
Coupling of Membrane Technology with Emerging Technologies for the Recovery of Bioactives

D. Shanthana Lakshmi, K. S. Radha, and S. Ananda Kumar

Abstract In this chapter an overview of the bioactive extraction techniques by the combination of membrane processes and coupling it with new emerging technologies is provided. The main classes of bio actives, their classification with their potential health benefits is discussed. The importance of food bio actives, increasing consumer awareness and their economical extraction processes without significant loss in their original characteristics are highlighted. Specific applications of different membrane unit operations and their multi stage integration in certain selected areas of bioactive extraction of natural sources (artichoke waters, olive oil mill waters, blood orange Juice, Pomegranate juice, whey waters) are also reviewed and discussed, The potential of membrane techniques with respect to the separation, concentration and retention of high-added-value compounds such as Phenolics flavonoids, polyphenols, lactoferrin and their vital role in food quality improvement and reduction of environmental foot print are analyzed in detail.

Keywords Bioactives · Integrated membrane process · Ultrafiltration · Microfiltration · Nanofiltration · Osmotic distillation · Vacuum membrane distillation · Reverse osmosis · Microwave extraction · Pressurized liquid extraction · Encapsulation · Polyphenols · Flavonoids · Lactoferrin

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1 Introduction

Over recent years, consumers have become more concerned about the quality of ingredients being used in foods and beverages (Galiano et al. 2019; Castro-Muñoz 2019). The growing prevalence of risk factors, such as stress, obesity, diabetes, and high blood pressure, has increased the awareness about the need for the adoption of a healthy diet to stay healthy and fit. Apparently, plant-based bio-actives play a vital role, which are vegan extracts having high potential usage in food and beverages, dietary supplements, animal nutrition, and personal care products as well (Castro-Muñoz et al. 2020a, b; Castro-Muñoz 2020a). The rising trends in naturally sourced products along with a preference for plant-based derivatives over animal-sourced will positively influence the industry's expansion.

In addition, a systematic nutritional approach, including the administration of food bio-actives and micro-nutrients, also have the potential to augment immune function and defend against the prevailing COVID-19 pandemic. The supplementation of well-established antioxidant, antiviral, antimicrobial, anti-inflammatory and cytotoxic properties of food bio-actives such as polyphenols, flavonoids, carotenoids have shown to be exceptionally beneficial in enhancing immunity against several viral infections (Cassano et al. 2018; Valencia-Arredondo et al. 2020; Díaz-Montes et al. 2020a).

Owing to the above said increasing consumer awareness and conscience to use vegetarian products have resulted in an increase in plant-based bio-actives market growth. These factors are encouraging vendors to introduce innovative products that have high nutritional value, thereby fuelling the market growth. According to the latest market research report published by Global Market Estimates (GME), a high Compound Annual Growth Rate (CAGR) of 8.27% for the plant-based bio-actives over the forecast period from 2021 to 2026.

1.1 Bioactive Extraction

Food waste is the potential bioresource for the extraction of nutraceuticals and bioactive compounds. Various investigations have demonstrated that the food wastes obtained from sources like fruits, vegetables, cereal and other food processing industries can be used as potential sources of bioactive which has significant application in treating various ailments (Castro-Muñoz et al. 2018; Tarazona et al. 2018; Cassano et al. 2016). Food waste is generated in all stages of the food life cycle (Castro-Muñoz et al. 2017a). Up to 42% of food waste is produced by household activities, 39% losses occurring in the food manufacturing industry and 14% in foodservice sectors such as restaurants, catering services, tiffin centers, etc. while 5% is lost during distribution. Food waste is expected to rise to about 126 Mt. by 2020 if any prevention policy or activities are not undertaken (Mirabella et al. 2014). Significant action is being taken to achieve the prevention of multiplying wastes

through the extraction of high-value components from them which can be re-used as nutraceuticals and functional ingredients. Bioactive components present in such agricultural waste can be recovered using various techniques.

1.2 Advantages of Membrane Technology

Membrane technologies are the most promising tool that appears as a valid approach to bioactive extraction from natural resources having been identified for their varied benefits compared to the existing conventional techniques (Castro-Muñoz 2020b; Díaz-Montes et al. 2020b). The major key points which include less time and energy consumption, zero use of chemical or biological additives, modular and simple design, optimum pressure, temperature conditions, without loss of biological properties in the extracts and very minimal risk of product contamination (Díaz-Montes et al. 2020a; Castro-Muñoz et al. 2019a; Haq et al. 2021). They are also characterized by very high selectivity and specificity with respect to separation involving very easy steps of processing (Castro-Muñoz et al. 2018). Especially, the pressure-driven techniques such as microfiltration (MF), ultrafiltration (UF), nanofiltration (NF) and reverse osmosis (RO) are the emerging technologies for clarification, fractionation, concentration and separation of bio-actives from food products and their derivatives due to their intrinsic properties and sustainable attributes. Further to this approach, other state of art technologies, such as pervaporation (PV) (Galiano et al. 2019; Castro-Muñoz 2020b; Castro-Muñoz et al. 2020c), osmotic distillation (OD) (Conidi et al. 2020), membrane distillation (MD) (Gontarek et al. 2019, 2021), are also employed in recent years for the recovery strategies (Conidi et al. 2020).

1.3 Recovery of Bioactives Based on Membrane Technologies

Membrane technology has proven to be an ideal alternative to the traditional juice clarification and UF and MF treatments are successfully used for processing fruit and vegetable juices (Castro-Muñoz et al. 2016; Galanakis et al. 2016). Ideally, UF clarifies and concentrates the bioactives based on the molecular weight cut off of the membranes and it also clears and segregates the components i.e., microorganisms, colloids, proteins, tannins, yeast, moulds etc. that pollutes and thereby preserves biologically properties of the final stable extract. While MF facilitates mainly juice clarification (Cassano et al. 2019). Results reveal that there is more membrane fouling in UF conditions than in MF operations (Pichardo-Romero et al. 2020). Hence, MF has been used as a pre-treatment step in the extraction process in order to reduce the fouling encountered in UF membranes. Both the processes operate at different efficiency levels in the recovery process. Nanofiltration (NF) membranes are utilized for fruit juice concentration to regulate sugar concentration and also to separate phenolic compounds from sugars (Castro-Muñoz et al. 2019a; Cassano et al.

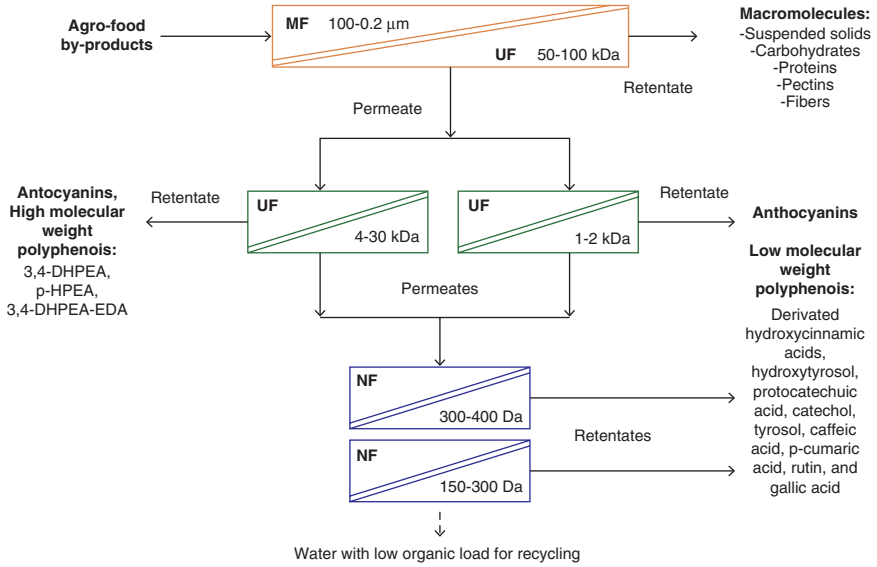


Fig. 11.1 Recovery of high-added value components by integrated membrane processes (Castro-Muñoz et al. 2019a)

2015). As a general overview, Fig. 11.1 illustrates the various bioactive compounds recovered and the Table 11.1 enlists the recovery rate of such pressure-driven membrane technologies towards various bioactive compounds.

Bioactives generated have confirmed the essence of fruits' complete health benefits due to the presence of phenolic attributes containing remarkably a higher dosage of hydrolyzable tannins, as well as anthocyanins exhibiting high antioxidant activity (Castro-Muñoz 2019). Hence, membrane processes are considered the leading technology and very efficient unit operations in the recovery of food bioactives, such a phenolic compound, antocyanins, peptides, amino acids, among others (Castro-Muñoz et al. 2021a). In the recent past, a novel and innovative approach arise from the combination of

(i) Different membrane unit operations (UF, MF, NF, RO, OD, MD) (Gontarek-Castro et al. 2021; Castro-Muñoz et al. 2019b, 2021b) or
(ii) Membrane operations and conventional separation technologies (Soxhlet, maceration, hydro distillation) or
(iii) Membrane-based technologies with emerging technologies, such as ultrasound, microwave with a rationale of intensification of the extraction process (Drioli and Romano 2001).

As shown in Figs. 11.2 and 11.3 the main class of bioactive compounds including polyphenols, carotenoids, flavonoids, vitamins, omega-3 fatty acids, tannins and organic acids, have attracted great attention due to their role in the prevention of several chronic diseases. Also, Fig. 11.4 reports the main biological activity of such

Table 11.1 Recovery rate of MF, UF and NF membranes towards several biomolecules (Castro-Muñoz et al. 2019a)

No.	Membrane technology	Recovery rate	Bioactives generated
1.	MF	47–100% in permeate	Anthocyanins, glutamine, isoproline, proline, betanin, isobetanin, sugars, galacturonic acid and some phenolic compounds.
2.	UF	44–99% in permeate	Anthocyanins, glutamine, isoproline, proline, betanin, isobetanin, sugars, galacturonic acid and some phenolic compounds.
3.	NF	50–99% in retentate	Anthocyanins, glutamine, isoproline, proline, betanin, isobetanin, sugars, galacturonic acid and some phenolic compounds.

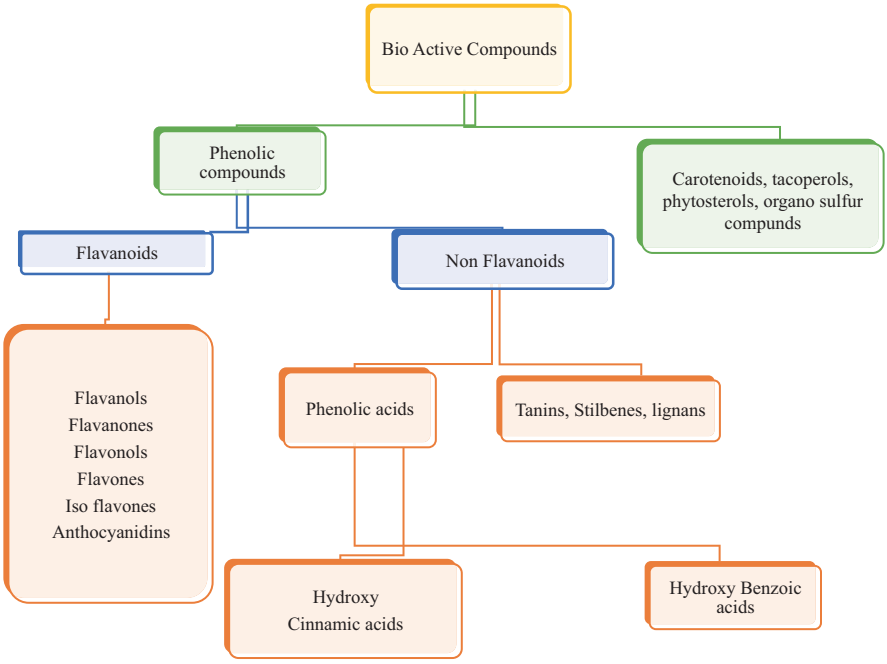


Fig. 11.2 The main classes of bioactive compounds

high-added value compound and their main sources in natural products. They are extra-nutritional constituents that are found in small quantities in foods providing health benefits besides the basic nutritional value of the product. The extraction of bioactive compounds starts with the selection of suitable methods, protocols, sample preparation, and extensive literature survey. During the extraction, the major concern lies in minimizing the interference of unwanted materials that may co-extract with the focused compounds. A number of extraction techniques have been introduced along with the existing traditional classical extraction methodology

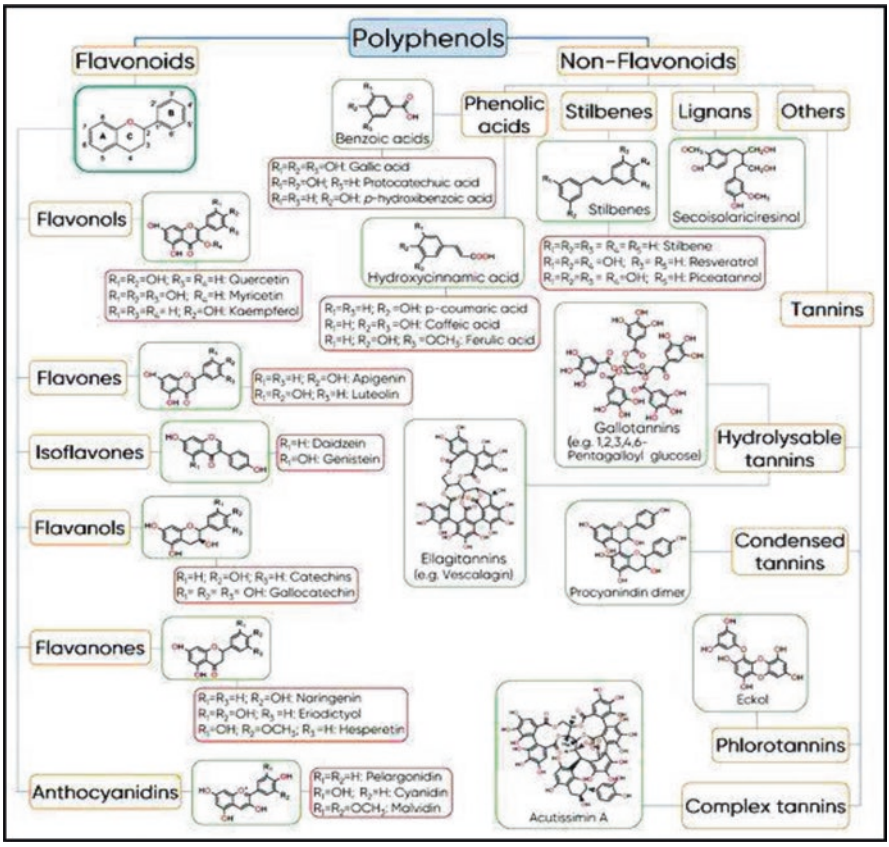


Fig. 11.3 Classification and structure of polyphenols (Câmara 2021)

(Valencia-Arredondo et al. 2020; Díaz-Montes et al. 2020b). But researchers are in the process of developing an eco-friendly single standard energy-saving method for extracting bioactive compounds from food wastes. There are various parameters like the nature of the plant matrix, the chemistry of bioactives, and scientific expertise that influence the efficiencies of conventional and emerging technological extraction.

2 Combined Membrane Unit Operations and Bioactive Food Products

Integrating the membrane technologies for the recovery of bioactives is recommended as the best method in place of traditional technologies. The following are the examples that indicate the importance of integrated membrane operational processes towards bioactive recovery.

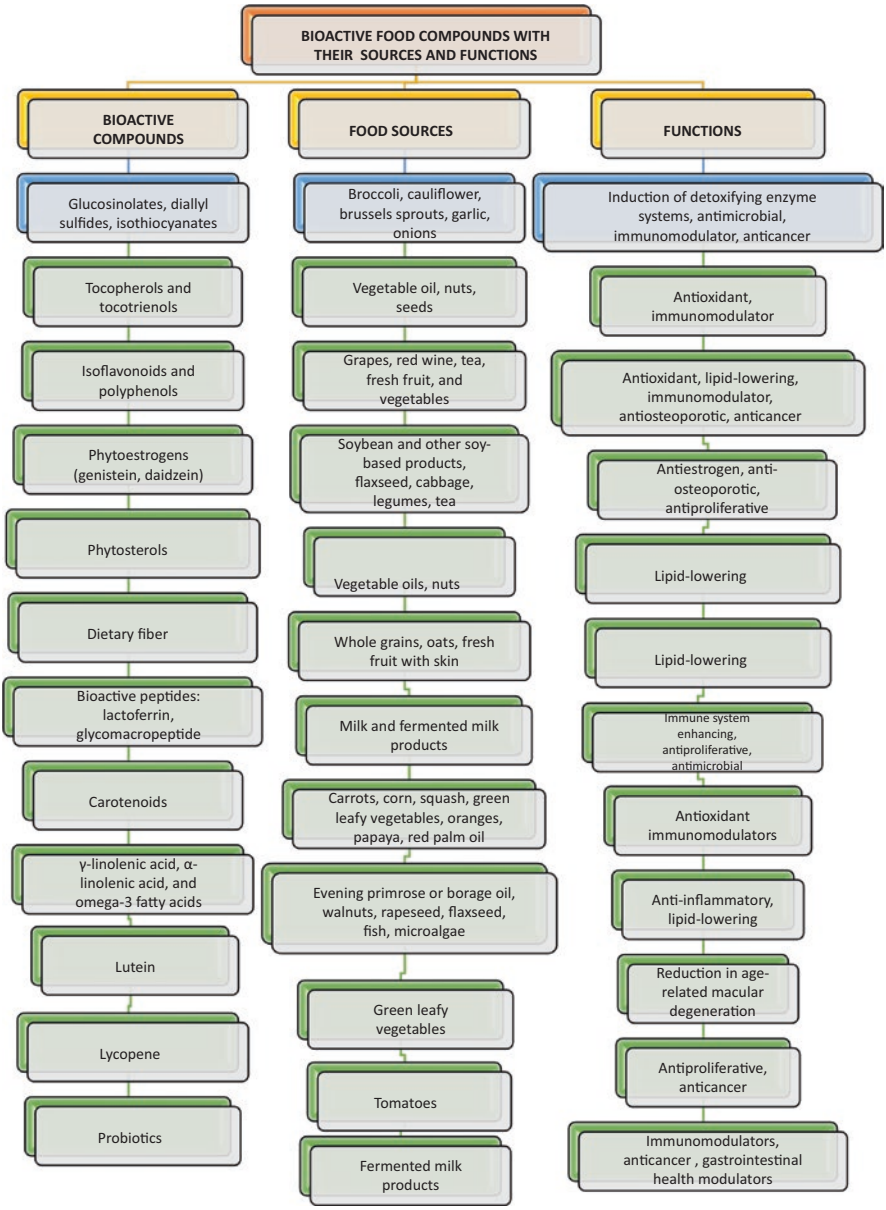


Fig. 11.4 Bioactive food compounds with their sources and functions

2.1 Two Stage Integrated Process

MF and UF processes are coupled to study the recovery of various bioactive compounds in different combinations. Laorko et al. (Laorko et al. 2010) established that the 0.2 μm polysulfone MF membrane was best suited for the treatment of pineapple juice due to the highest permeate flux and the highest recovery of polyphenols and other antioxidant compounds in comparison to UF membranes (MWCO in the range of 30-100 kDa) in a hollow fiber configuration. One more analysis was performed by Cassano et al. (2010) with PVDF MF (0.2 μm) and UF membranes with MWCO of 200 kDa in the flat-sheet configuration on the physicochemical composition of cactus pear juice, indicated better performance of the MF process in terms of permeation flux and recovery of phenolic compounds in the permeate stream. However, both membrane processes permitted a clarified juice with enriched physicochemical and nutritional properties comparable to those of the fresh cactus juice. Similarly, there are several other investigations with UF membranes variation in the membrane material (PS, PVDF) or configuration (flat sheet, spiral wound, hollow fiber) or of MWCO (0.15 kDa to 150 kDa) for the extraction of bioactive. In all

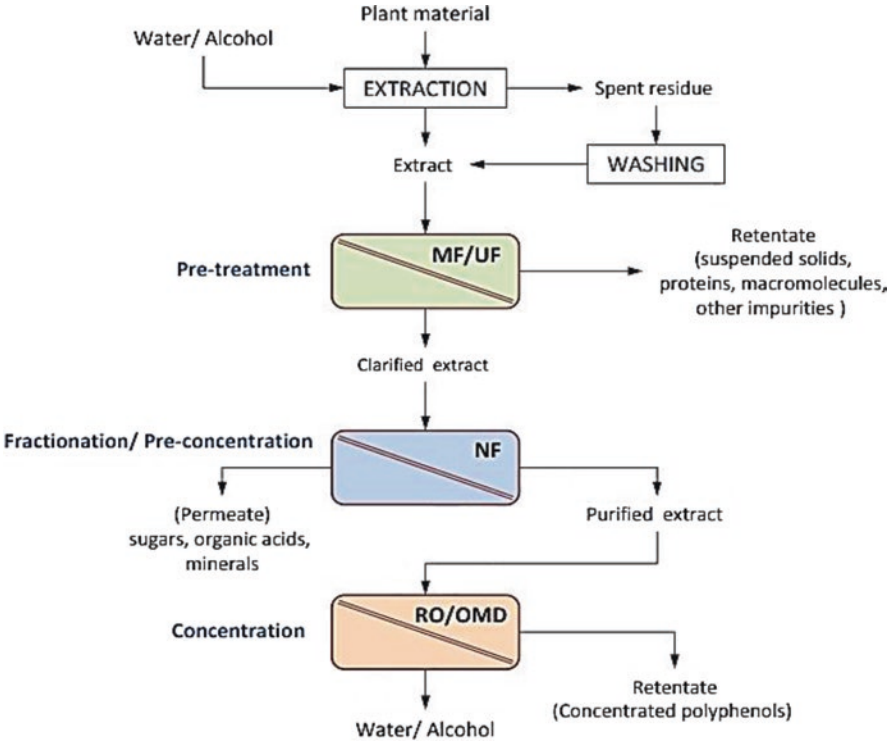


Fig. 11.5 General flow sheet for the recovery of phenolic compounds from vegetable sources by membrane processing (Conidi 2018)

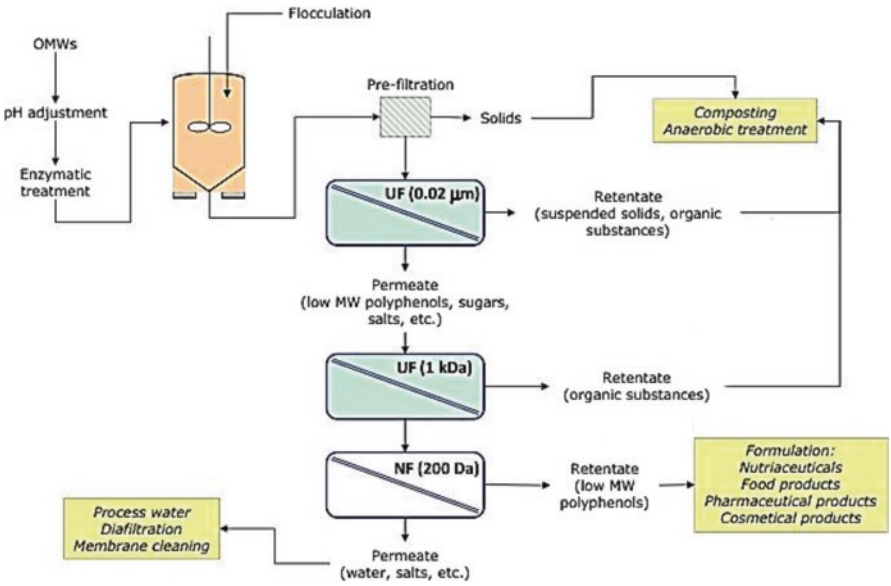


Fig. 11.6 Conceptual proposed design for the recovery of polyphenols from olive mill wastewaters (Conidi 2018)

these investigations, observed retentions of total anthocyanins, total polyphenols and TAA were in the range of 80–97%, Thus the pressure-driven membrane processes are becoming a real alternative to traditional separation systems for recovering the bioactive compounds (Conidi et al. 2018) (Figs. 11.5 and 11.6).

Cassano et al. (2011) presented a novel integration of the UF and OD process for the production of concentrated pomegranate juice enriched with bioactive compounds. Fresh fruit juice clarified through hollow fiber UF membranes then concentrated by OD. The highlights of Cassano's works are summarized in Table 11.2**.**

Cisse et al. (2005) subjected the Orange juice cross-flow microfiltration (CFM) through a 0.2 µm ceramic membrane. The clarified orange juice (permeate) was then concentrated at low temperatures by osmotic evaporation (OE) in two stages. The integrated process, of CFM together with OE, represents an attractive technical and ideal alternative to thermal technologies because it preserves the juice's original quality better and progressively increases the vitamin C content of the concentrate towards the levels found in the initial juice without comprising the original color of the product. In another work, Alves and Coelhoso (2006) made a comparison between the two processes namely OE and Membrane distillation (MD) and concluded from the results that OE is the best alternative for orange juice extraction in terms of aroma retention, mass transfer resistance and water flux.

Balyan and Sarkar (2016) evaluated the potential of an integrated membrane process, by employing a suitable combination of membrane systems to extract phenolic compounds from Jamun seed extract using water as a solvent. In particular, aqueous Jamun seed extract undergoes a preliminary treatment process using UF

Table 11.2 Process integration of different membrane-based technologies for the recovery of bioactives from pomegranate juice (Cassano et al. 2011)

Technique employed	Process carried out	Bioactives recovered	Results and concluding remarks
UF coupled with OD Natural source: Pomegranate juice Two stage process	First step is the clarification of non-depectinized juice by hollow-fiber UF membranes; The second step is the concentration of the clarified juice by using an OD apparatus. Operating conditions: Ambient temperature (25 ± 2 C) Total soluble solids (TSS) content of 162 g kg1 and 520 g kg1, respectively	Organic acids (malic, ascorbic and citric acids), total polyphenols and anthocyanins (cyanidin 3,5-diglucoside, delphinidin 3- glucoside, etc.)	Clarification results in unchanged physico-chemical and nutritional properties as those of the fresh juice by UF The total antioxidant activity of the OD retentate at 52 °brix was only 4% lower than the TAA of the clarified juice. The antioxidant activity of pomegranate juice, attributed largely to total phenols and anthocyanins content preserved more efficiently during the concentration step independently over the level of total soluble solids obtained.

membranes, followed by a concentration using an NF process. Table 11.3 reports the main insights and concluding remarks provided by Balyan and Sarkar (2016).

2.2 Three Stage Integrated Process

Torun et al. (2014) recently examined an integrated membrane process including MF, RO, OD for producing concentrated sage (*Salvia fruticosa* Miller) extract for the recovery of polyphenols, as detailed in Table 11.4. Dried sage leaves (*Salvia fruticosa* Miller) are processed using hot water. An integrated membrane process was employed to extract the concentrate (32.4 w/w%). Retention and loss studies were carried out for the determination of a number of total polyphenols, flavonoids and also the antioxidant activity of the recovered bioactives. Finally, the composition of phenols in the final extract was identified with the HPLC technique.

In a similar way, Conidi et al. (2014) analyzed another three-stage membrane integrated process on artichoke wastewaters by using one UF and two different NF membranes in a sequential combination (see Table 11.5). The authors proposed the recovery of bioactives from artichoke derivatives since this natural source contains different biomolecules with potential health benefits, as represented in Fig. 11.3. As illustrated in Fig. 11.4**,** the strategy implied a smart sequence of various types of

Table 11.3 Process integration of different membrane-based technologies for the recovery of bioactives from pomegranate juice (Balyan and Sarkar 2016)

Technique employed	Process carried out	Bioactives recovered	Results and concluding remarks
UF coupled with NF Natural source: Jamun (Syzygium cumini L.) seed extracts Two stage process	First step in the process is cross flow ultrafiltration for initial clarification, followed by concentration using nanofiltration under batch concentration mode. Operating conditions: Optimal condition (temperature: 49.2 °C, time: 89.4 min, and liquid to solid ratio: 51.6:1 mL/g)	Phenolic compounds – Poly phenols and flavonoids	Experimental results revealed that purity of the UF clarified phenolic extract was increased from 39.2 to 53%. Further, the UF clarified extract, with an initial total polyphenol content of 942 mg GAE/L, was concentrated by nanofiltration up to a factor of 3.2 This membrane showed a retention towards total polyphenols and total flavonoids of 78 and 100%, respectively. NF retentate showed higher antioxidant activity (94.6%) of inhibition than the UF permeate showing 75.5 ± 1.8% of inhibition by DPPH method and FRAP method results 530 ± 10 μM Fe(II)/L and 430 ± 10 μM Fe(II)/L of higher polyphenols content.

membranes, along with adsorption processes for the successful recovery of the compounds (Figs. 11.7 and 11.8).

By comparing several works developed by Cassano's group, Fig. 11.9 shows a comparison of the rejection rates towards various phenolics using different integrated processes. In general, chlorogenic acid, cynarin and apigenin-7-O- were completely rejected by most of the proposed recovery techniques (Fig. 11.10).

Integrated membrane processes targeting to remove sugar compounds from phenolic compounds have also been proposed for by-products of the citrus processing industry, such as orange press liquor and bergamot juice. Similar to Artichoke, citrus fruits, such as blood orange, also contains plenty of biomolecules with a related biological activity, as can be seen in Fig. 11.11. In the experiments, an integrated process (Cassano et al. 2014) involving based on the use of UF, NF and OD processes for the recovery and concentration of flavonoids from orange press liquor was investigated and reported accordingly. This UF process allowed removing all suspended solids from the raw press liquor while flavonoids and anthocyanins were recovered in the clarified fraction (rejections towards flavanones and anthocyanins were lower than 1%). The NF process produced concentrated extracts enriched in

Table 11.4 Process integration of different membrane-based technologies for the recovery of bioactives from *Salvia fruticosa* Miller extract (Torun et al. 2014)

Technique employed	Process carried out	Bioactives recovered	Results and concluding remarks
MF coupled with RO and OD Natural source: Sage (Salvia fruticosa Miller) extracts. Three stage process	In first stage, they used a multi-tubular ceramic MF membrane for concentration of preliminary bioactive extract. Operating temperature (30 °C) and fixed recirculation flow rate (500 Lh^{-1}). The permeate from the MF stream was pre-concentrated by using RO flat-sheet membrane. Operating temperature (30 °C) and fixed recirculation flow rate (600 L h^{-1}). And the last procedure is done with osmatic distillation using poly propylene hollow fibre membrane module.	4 phenolic compounds (caffeic-acid, p-coumaric 8 acid, ferulic acid and rosmarinic acid) and 4 flavonoids (rutin, luteolin, hesperetin and 9 apigenin and Flavanoids	It is well observed that all the biochemical properties i.e., total phenolic content, total flavonoid content and anti-oxidant activity possessed around 60% of retention during RO process (63%, 56%, 56%, respectively) and during OD process it was observed to reach higher than that 90% of retention (95, 96, 99%, respectively).

bioactive compounds due to the high rejection measured flavanones (97.4%) and anthocyanins (98.9%) (Figs. 11.12 and 11.13, Table 11.6).

Conidi et al. (2011) investigated the extraction and concentration of phenolic compounds from bergamot juice (a by-product of essential oil production) using UF and NF membranes, as described as follows (Table 11.7):

The fractionation of phenolic compounds from sugars in clarified bergamot juice was also investigated by using three NF membranes (NF PES10, N30F and NF270) in spiral-wound configuration with varying MWCO (150, 400 and 1000 Da) and polymeric material (Polypiperazine amide and PES) (Conidi and Cassano 2015). For NF PES 10 membrane, with an MWCO of 1000 Da, measured rejection of flavonoids (naringin, nehesperidin and hesperidin) was found to be between 88.4 and 90.1%, while the rejection of sugars was 35%.

In an attempt with tight UF and NF membranes to recover specific derivative phenolic compounds, such as hydroxytyrosol, catechol, tyrosol, caffeic and p-cumaric acids, displayed over 80% recovery rate with high antioxidant activity (2175 mg L-1 Trolox). A conceptual process design for the recovery of phenolic compounds from OMWs was proposed by Cassano et al. (2013) (Figs. 11.14, 11.15, 11.16, and 11.17, Table 11.8).

In this context of integrated membrane techniques, a combination of NF and RO membranes has also been successfully used for the recovery of valuable compounds from OMWs. Previously, Paraskeva et al. (2007) compared the performance of NF

Table 11.5 Integrated membrane system for the recovery of phenolic from artichoke wastewaters (Conidi et al. 2014)

Technique employed	Process carried out	Recovered bioactives	Results and concluding remarks
UF coupled with two different NF Natural source: Artichoke wastewaters Three stage process	During the first stage, waste waters were ultrafiltered. In the second stage process, the raw were clarified using poly ether sulfone NF membrane NP030(400 Da) and followed by a cross linked aromatic polyamide NF membrane Desal DL (150-300 Da).	Phenolic compounds analysed (chlorogenic acid, cynarin and apigenin-7-O-glucoside)	The UF treatment preserved the phenolic bio actives such as chlorogenic acid, apigenin-7-0-glucoside and cynarin, TAA and sugars such as glucose, fructose etc. in the clarified stream due to the low rejection measured in the range of 1.2-8.6% while suspended solids were 100% completely retained in the retentate. The performance of both the NF membranes was compared. They showed high retentivity towards phenolic compounds in the range of 82-96%.: The permeate from the first NF membrane was deprived of sugars due to the high rejection values obtained and they were recovered in the permeate stream of the second NF membrane in which the rejection was in the range 3.4-5.5%.

and RO membranes in the concentration of pre-treated OMWs. Raw wastewaters were pre-filtered with a Polypropylene membrane (pore size of 80 μm) and treated via multichannel ceramic membranes having the pore size of 100 nm. This step produced a rejection of high MW constituents including fats, lipids and suspended particles. The permeate was then processed by using two different NF and RO polymeric spiral-wound membranes with MWCO of 200 and 100 Da, respectively. The concentrate contains more than 95% of phenolic compounds; however, better efficiency was achieved by applying RO.

In addition to the varied attempts in the recovery of bioactive through an integrated process, evaluation of its potential based on the use of membrane technology and adsorbent resins for the recovery, concentration and purification of phenolic compounds from artichoke wastewaters as a novel approach (Conidi et al. 2015) (Fig. 11.18, Table 11.9).

NF experiments were conducted extensively by Giacobbo et al. (2013), who used five different membranes for the fractionation of a winery effluent and recovery of the polysaccharides of low molecular weight and polyphenols. Three laboratory-made cellulose acetate membranes and two commercial membranes used: Evaluation was based on the analysis of rejection coefficients to polysaccharides, polyphenols, conductivity and total organic carbon. The rejection coefficients of polyphenols were overall lower than the ones of polysaccharides, showing that the polyphenols

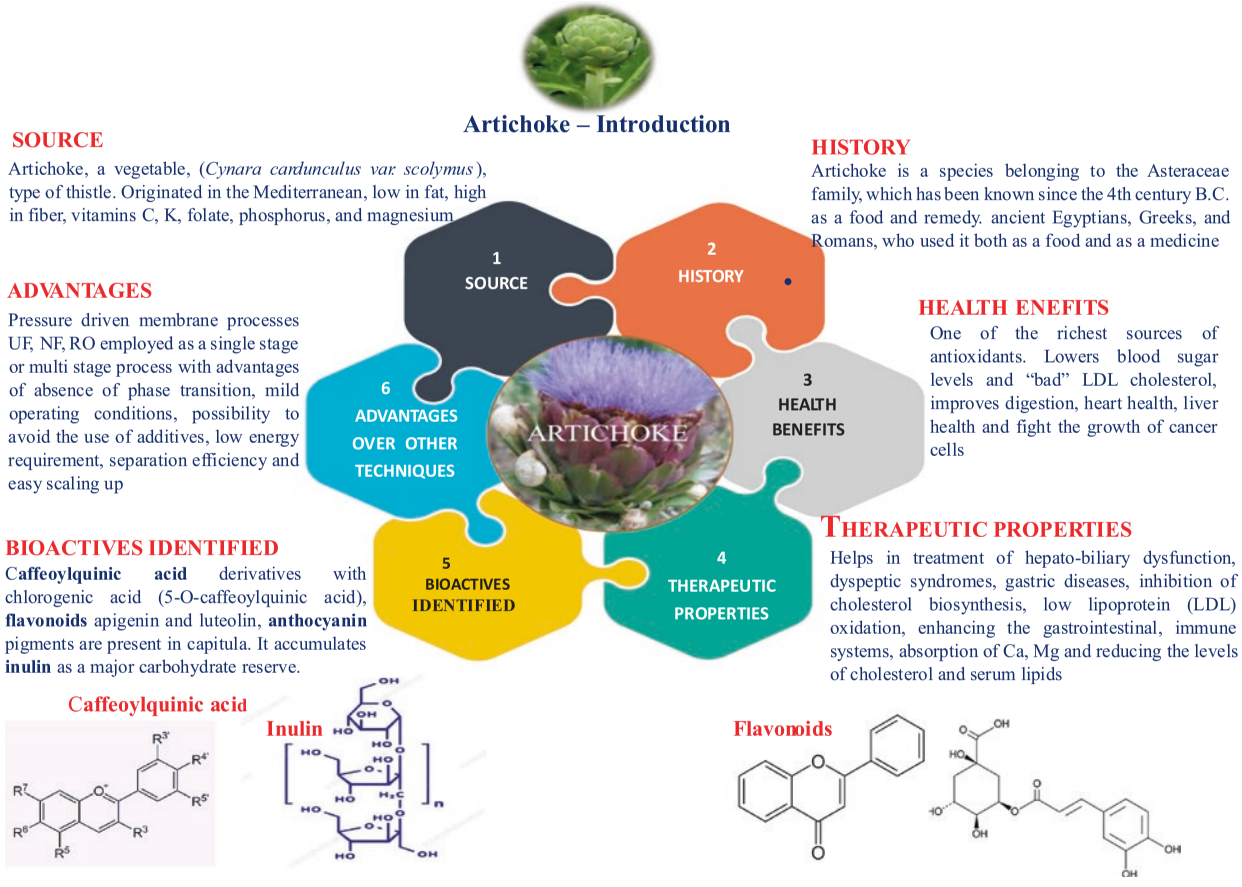


Fig. 11.7 Background on advantages, bioactive compounds and related health benefits in Artichoke

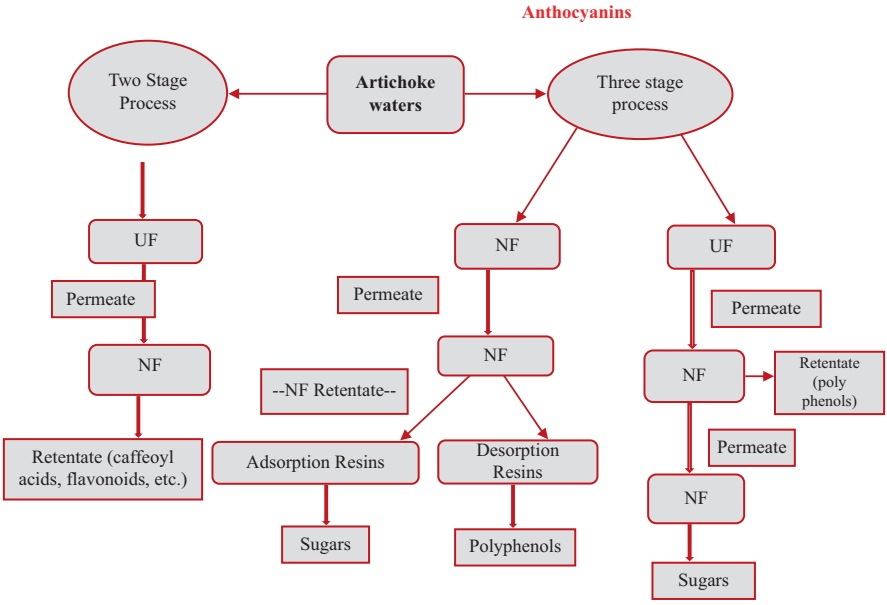


Fig. 11.8 Strategy description for the recovery of phenolic from artichoke wastewaters (Conidi et al. 2014)

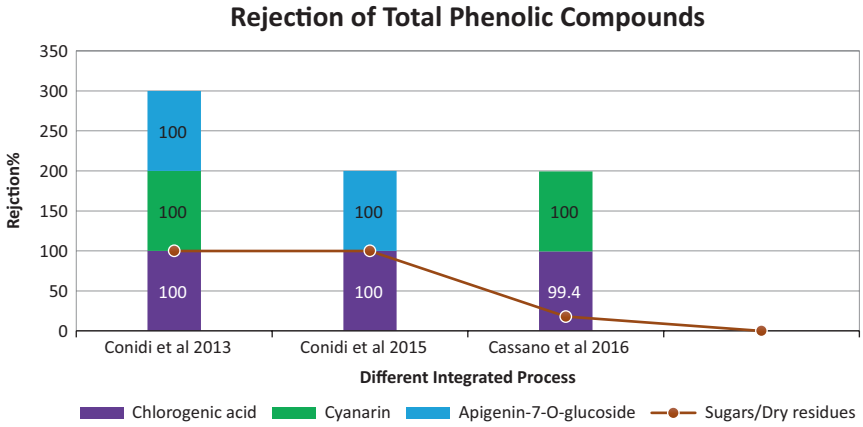


Fig. 11.9 Analytical studies and comparison among different studies reported by Cassano's group

permeate preferentially through all the membranes. The highest rejection coefficients were observed by the usage of NF270 membrane in the order of 93.8% and 99% for polyphenols and polysaccharides, respectively and the ETNA01PP membrane displayed the lowest rejection coefficients of 27% to polyphenols and 72% to polysaccharides.

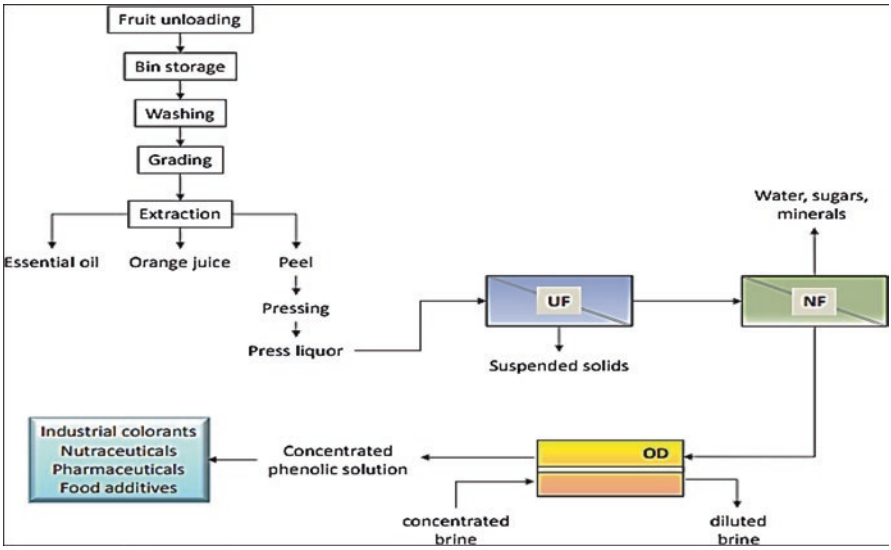


Fig. 11.10 Schematic of the integrated membrane process proposed for the recovery of flavonoids from orange press liquor (Cassano et al. 2014)

Another versatile integrated membrane process for the treatment of Nixtamalization wastewaters commonly known as Nejayote (Castro-Muñoz et al. 2015, 2017b; Ramírez-Jiménez and Castro-Muñoz 2020). It was carried out as a sequence of one MF pre-treatment step followed by two UF processes was investigated on a laboratory scale operating in selected process conditions (Castro-Muñoz and Yáñez-Fernández 2015) (Table 11.10).

Onsekizoglu (2013) demonstrated the capacity of membrane integrated process by OD and coupled MD process than performance compared with the thermal evaporation process (Figs. 11.19, 11.20, and 11.21, Table 11.11).

Conidi et al. (2017) investigated the use of flat-sheet UF and NF membranes with MWCO ranging from 1 to 4 k Da for the recovery of phenolic compounds from clarified pomegranate juice (Figs. 11.22 and 11.23, Table 11.12).

2.3 Four Stage Integrated Process

One another interesting example of an integrated membrane process for the recovery, purification and concentration of polyphenols from OMWs was demonstrated by Garcia-Castello et al. (2010) (Figs. 11.24, 11.25, and 11.26, Table 11.13).

MF/UF and NF/RO membranes in a sequential design allowed the recovery of water and bioactive compounds from Olive Mill Wastewaters (OMWs) was demonstrated by Russo (2007) (Table 11.14).

Piacentini et al. (2016) designed an innovative process for water recovery and polyphenols encapsulation from olive mill wastewaters (OMWWs) (Table 11.15).

2.4 Five Stage Integrated Process

Alberto et al. (2019) established that the wine lees extracted from wastewaters during the winemaking process possess a high concentration of bioactive molecules that can be used to obtain extracts or semi-finished products for food, nutraceutical and pharmaceutical applications. This was facilitated by means of integrating the new emerging technologies such micro wave assisted extraction with the pressure-driven membrane-based operations, for the recovery of phenolic compounds (Table 11.16).

Tamires Vitor Pereira et al. (2020) integrated the pressurized liquid extraction technique with NF and sequential MF-NF processes in the cross-flow filtration system cross and investigated the bioactive extraction and reported that it is an efficient method for the recovery and concentration of bioactive compounds from grape marc and a promising technique for obtaining functional products with high added value (Table 11.17).

Investigations performed on single membrane techniques so far establish that MF, UF, NF have been able to perform a primary purification of plant resources and microorganism sources due to their intrinsic properties (high efficiency, simple equipment, convenient operation and low energy consumption). These techniques can however be used in conjunction with other separation processes, to achieve various higher levels of fractionation. Further research is still going on to improve the inherent high throughout characteristics to convert the membrane-based techniques as the best productivity tools for the purification of bioactives.

Bagci et al. (2019) in their recent work, investigated a very novel way by coupling the RO and OD process using a commercial thin-film composite (TFC) polyamide reverse osmosis (RO) membrane which is activated by surface modification using a low-pressure nitrogen plasma.

A remarkable increase in water flux of the LPNP modified RO membrane with increased hydrophilicity was observed throughout the RO process. Substantial increase of higher soluble solids content (SSC) values in the concentrated juice at the same period of time rather than an untreated RO membrane. It also enabled 30% time-saving during the further osmotic distillation process.

2.5 Lactoferrin (Lf) isolation – Integrated Membrane Systems

Lu et al. (2007) isolated LF from bovine colostrum using UF followed by purification with a fast flow strong cation exchange chromatography system on a production scale (Figs. 11.27 and 11.28, Table 11.18).

SOURCE

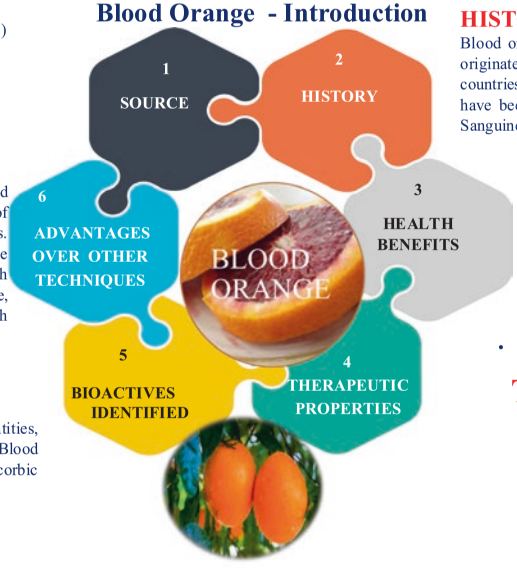
The **blood orange** is a variety of orange (*Citrus* × *sinensis*) with crimson, almost blood-colored flesh. Chrysanthemin (cyanidin 3-*O*-glucoside) is the main compound found in red oranges. The distinctive dark flesh color is due to the presence of anthocyanins.

ADVANTAGES

MD and OD are emerging technologies which have attracted a growing interest in recent years for the concentration of food products, including dairy products and fruit juices. Both the processes are driven by a vapor pressure difference between porous hydrophobic membrane surfaces, through which only water vapor molecules can pass. Therefore, concentration polarization is not a limiting factor and high solid contents can be achieved

BIOACTIVES IDENTIFIED

Flavones, flavonols, anthocyanins and, in greater quantities, flavanones are four types of flavonoids present in Blood Oranges. Hydroxycinnamic acids, Caroeoids and Ascorbic acids are the other bioactives found in them.



HISTORY

Blood oranges are Citrus sinensis (Rutaceae family) varieties originates from Malta or Sicily and have been cultivated in many countries, especially in the Mediterranean region where they have been grown since the 18th century. Moro, Tarocco and Sanguinello are the most common cultivars.

HEALTH BENEFITS

The blood oranges are rich in anthocyanins that helps fight off free radicals and inflammation and they are rich in vitamin c which helps treat or prevent scurvy disease. They also contain vitamin A to maintain the health of the skin and some tissues in the body along with folic acid to fight off some cancers and heart disease

THERAPEUTICPROPERTIES

The organic orange extracts showed a higher total antioxidant activity with higher content of total phenolics, total anthocyanins, and ascorbic acid. It also has extraordinary antiobesity effect on fat accumulation and the anti-inflammatory effects. It plays a substantial role in preventing chronic pathological conditions such as cardiovascular diseases and in many forms of cancers

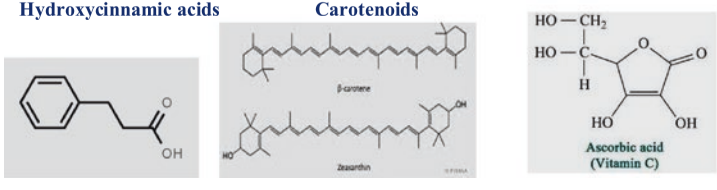


Fig. 11.11 Background on advantages, bioactive compounds and related health benefits in blood orange

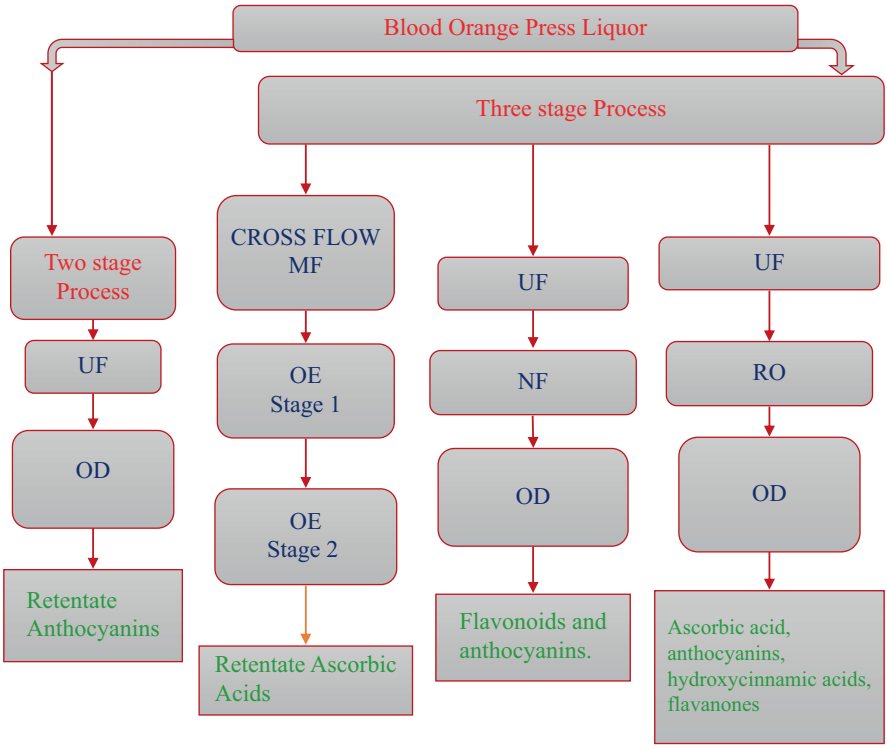


Fig. 11.12 Extraction of Bioactive - Integrated Membrane process in blood orange press liquor (Cassano et al. 2014)

The separation of high-value minor protein lactoferrin from crude dairy streams is a great challenge for the dairy industry. Wang et al. (Wang et al. 2020) investigated an electrodialysis with a UF filtration membrane (EDFM) approach to separate lactoferrin (LF) and immunoglobulins (Ig) from other dairy proteins (Table 11.19).

Brisson et al. (2007) superimposed an electrical field to a conventional membrane filtration unit and established that electrically-enhanced membrane filtration (EMF) increased the selectivity of LF separation in a mixed solution using a whey protein isolate (WPI) as a model (Table 11.20).

3 Conclusion and Future Prospects

Integration of various membrane technologies with better efficiency for bioactive component recovery will not only nurture the value for food waste but also reduce the cost of formulated products and thus minimize the use of synthetic chemicals in such formulations. An increasing amount of food and agriculture wastes are

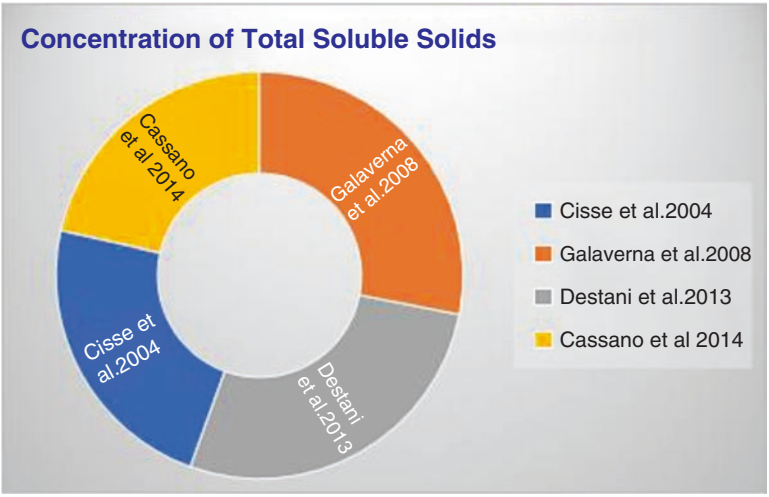


Fig. 11.13 Analytical studies and comparison among different studies reported Galaverna et al. (2008) based on the new integrated membrane technique produced a high-quality concentrated blood orange juice as an alternative to thermal evaporation

Table 11.6 Integrated membrane system for the recovery of anthocyanins from orange press liquors (Galaverna et al. 2008)

Technique employed	Process carried out	Bioactives recovered	Results and concluding remarks
UF coupled with RO followed by OD Natural source: Orange press liquor Three stage process	The process was based on the initial clarification of freshly squeezed juice by UF; the clarified juice was successively concentrated by two consecutive processes: First RO, used as a pre-concentration technique (up to 25–30^0 Bx), then OD, up to a final concentration of about 60^{0}Bx	Ascorbic acid, anthocyanins, hydroxycinnamic acids, flavanones.	Integrated membrane process may be proposed as a very good alternative to obtain high quality concentrated juice, as end product also showed a very high antioxidant activity. Recovery of huge amount of natural bioactive components, showing a brilliant red colour and a pleasant aroma, characteristics that were predominantly lost when thermal evaporation was carried out.

Table 11.7 Integrated membrane system for the recovery of polyphenols from Bergamot juice

Technique employed	Process carried out	Bioactives recovered	Results and concluding remarks
UF assisted two NF process Natural source: Bergamot juice Three stage process	The clarified juice was treated with a fluoropolymer UF membrane with a MWCO of 1 kDa (Etna 01PP, alfa Laval) The second step is the concentration of permeate in two different ceramic NF membranes (Inopor) with MWCO of 750 and 450 Da in order to evaluate the effect of the MWCO on the rejection of the membranes.	Polyphenols, flavonoids	The results indicated that the best separation of polyphenols from sugars occurred with the 450 Da membrane (higher rejection towards flavonoids and moderate rejection towards sugars). Permeate was a clear solution enriched in sugar and organic acids; The phenolic compounds were recovered on the retentate side, as also confirmed by high total antioxidant activity of the NF retentate

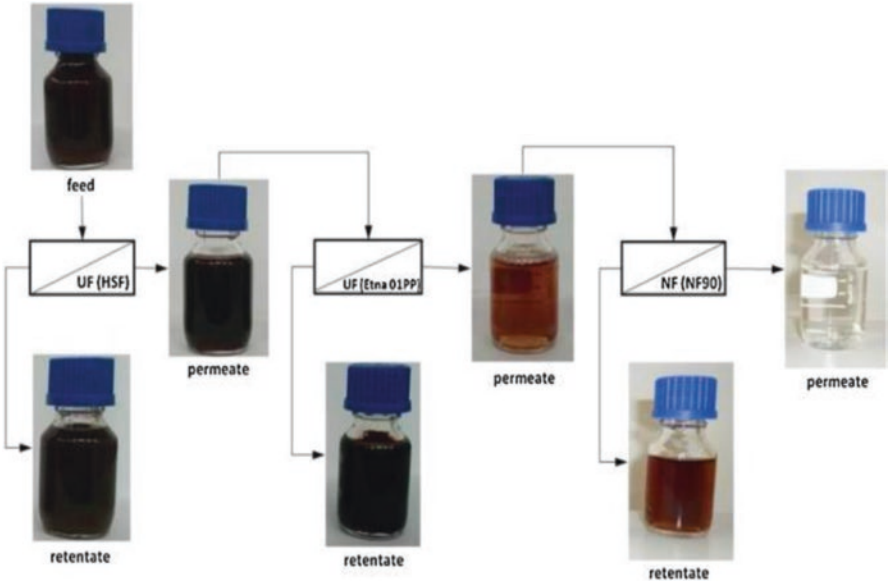


Fig. 11.14 Permeate and retentate samples obtained in the treatment of OMWs by integrated membrane operations (Cassano 2013)

SOURCE

Olive tree (Olea europaea L.) a traditional tree of Mediterranean Basin since the 8th millennium BC. Olive oil is a liquid fat obtained from olives, produced by pressing whole olives and extracting the oil. Olive mill wastewater (OMW) is generated from olive oil extraction systems.

ADVANTAGES

The advantages of membrane processing include a low energy requirement, no additives, mild operating conditions, separation efficiency and easy scaling up. MF, UF, NF, RO processes, mostly in a sequential form, successfully meet the requirement for the recovery, purification and concentration of polyphenols from OMWs with regard to their specific molecular weight cut-off (MWCO) values, as well as other new treatment processes such as VMD and OD.

BIOACTIVES IDENTIFIED

Olive oil contains traces of phenolics (about 0.5%), such as esters of tyrosol, hydroxytyrosol, oleocanthal and oleuropein, and a source of phenolic compounds like elenolic acid, alpha-tocopherol, one of the eight members of the Vitamin E family. Oleuropein, together with 10-hydroxyoleuropein, ligstroside and 10-hydroxyligstroside, are tyrosol esters of elenolic acid. Other phenolic constituents include flavonoids, lignans and pinoresinol.

HISTORY

Fossil evidence indicates the olive tree had its origins 20–40 million years ago in the Oligocene, in what is now corresponding to Italy and the eastern Mediterranean Basin. The edible olive seems to have coexisted with humans for about 5,000 to 6,000 years, going back to the early Bronze Age (3150 to 1200 BC).

HEALTH BENEFITS

OMWs exhibit antimicrobial activity and protective properties against plant pathogens and excellent biological properties in terms of antioxidant, free radical scavenging, antimicrobial and anticarcinogenic activities possibly due to the presence of biophenols and polysaccharides

THERAPEUTICPROPERTIES

Hydroxytyrosol, tyrosol, and a hydroxytyrosol derivatives a exhibited the most potent antioxidant activity and anti-inflammatory activity. Metal chelators had a potent free radical scavenging activity. Biophenols and 4-Methylcatechol are effective bactericidal compound, phenols are effective in enzyme inhibition, antiviral activity and molluscicidal activity

Fig. 11.15 Background on advantages, bioactive compounds and related health benefits in Olive Mill water

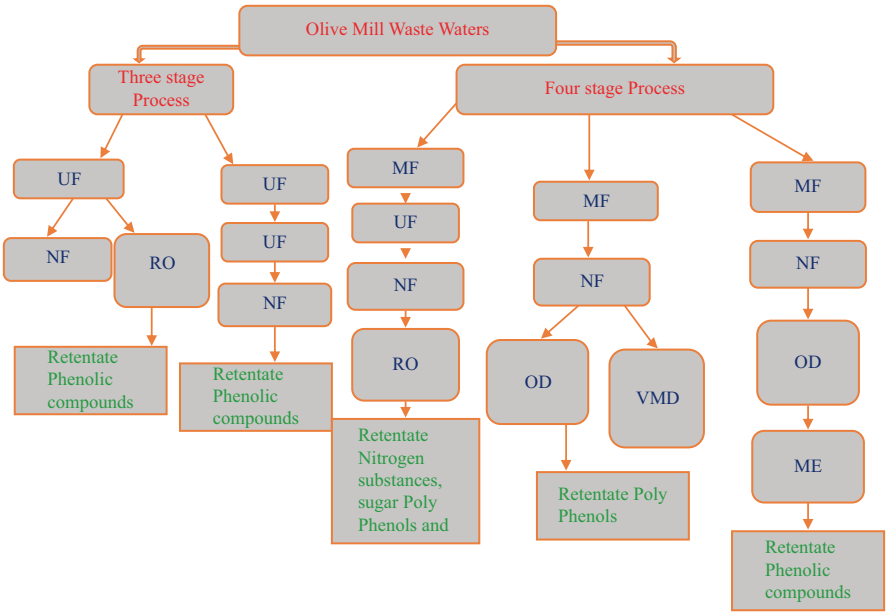


Fig. 11.16 Extraction of Bioactive - Integrated Membrane process in Olive Mill waste waters

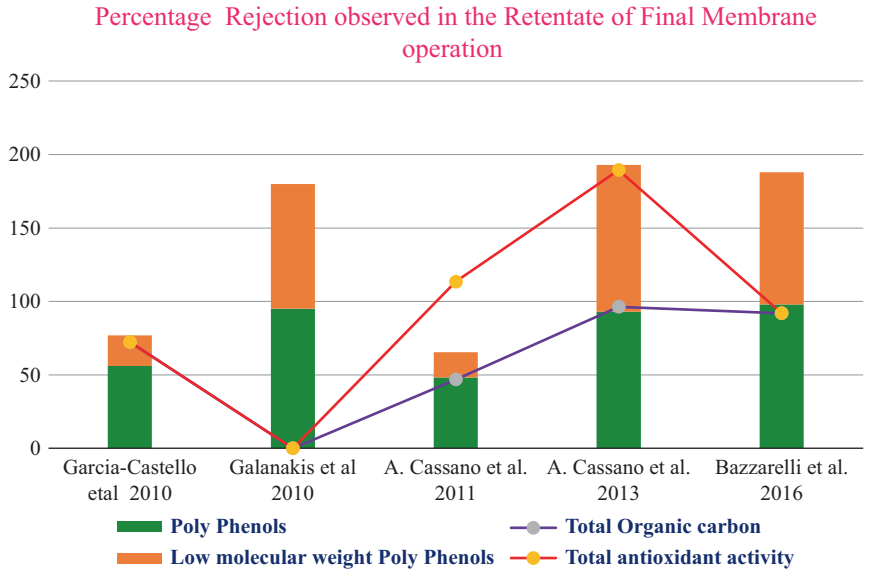


Fig. 11.17 Analytical studies and comparison among different studies reported

Table 11.8 Integrated membrane system for the recovery of polyphenols from Olive Mill waters

Technique employed	Process carried out	Bioactives recovered	Results and concluding remarks
Two different UF steps coupled with NF membrane. Natural source: Olive Mill waste waters Three stage process	First UF step performed with hollow fibre membranes with a nominal pore size of 0.02. The UF permeate was then processed with a flat-sheet UF membrane (Etna 01PP, alfa Laval) with a MWCO of 1000 Da. The UF permeate form the second UF step concentrated by NF using a spiral-wound membrane (NF90, Filmtec/Dow)	Purified fraction containing more than 85 mg/L of low molecular weight polyphenols (including hydroxytyrosol, protocatechuic acid, catechol, tyrosol, caffeic acid, and p-cumaric acid) was obtained	Ultrafiltration process ensured the complete removal of suspended solids and also showed low rejections towards low molecular weight polyphenols (2.1 and 17.6% respectively). The NF membrane retained all the analyzed phenolic compounds producing a permeate depleted in phenolic compounds. These recovered fractions were considered of interest for cosmetic, food and pharmaceutical industries as liquid, frozen, dried or lyophilized formulations.

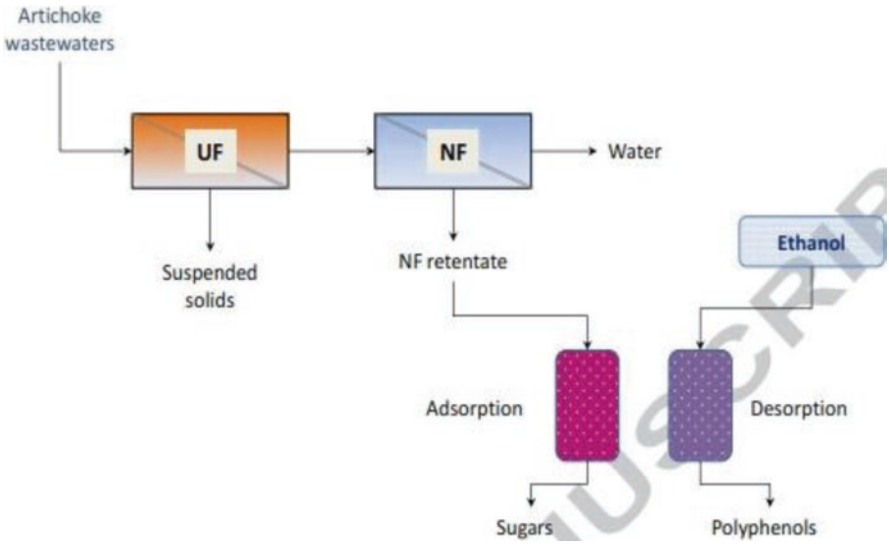


Fig. 11.18 General scheme of the investigated process (Conidi et al. 2015)

available from food processing industries and post-harvest losses of fruits and vegetables and their utilization as a source of nutritious bioactive compounds would certainly increase the financial status of farmers across the globe and decrease the burden of waste management (Kumar et al. 2017). Enhancement of

Table 11.9 Integrated membrane system for the recovery of phenolic compunds from Artichoke Waste waters

Technique employed	Process carried out	Bioactives recovered	Results and concluding remarks
UF, NF and adsorption-desorption tests Natural source: Artichoke waste waters Three stage process	Initial step is pre-treatment by UF. The UF permeate was submitted to a NF process. Three different macroporous resins were tested through adsorption/desorption methods	Phenolic compounds, such as chlorogenic acid (CA) and apigenin 7-O-glucoside (AOG)	Suspended solids and macromolecular compounds were completely removed from the artichoke wastewaters by UF producing a permeate stream enriched in phenolic compounds and sugars. Phenolic compounds concentrated by NF with a production of a retentate stream containing about 1.6 g/L of CA and 0.3 g/L of AOG. Among the three different tested resins, the S 7968 offered the best performance in terms of adsorption/desorption ratio for CA, with a Total adsorption desorption yield (TADY) of 63.39%; while for the AOG the S 7968 and the S 2328 resins showed a TADY in the range 68.31-78.45%

membrane technology through an innovative approach in extraction technology with lesser or no use of solvent will be of great significance to achieve a sustainable bioprocess. Added to that, serious environmental issues related to the disposal of agricultural and industrial wastes in the current scenario in our country and the rest of the world can very well be managed and subsequently by the rational use of the bioresources through the realization of suitable and appropriate membrane technologies coupled together. In this regard, a thorough analysis and assessment of the waste generated, complete utilization as nutraceuticals with many commercial ventures by setting up membrane operation units would help to establish the usage of bioactive residues to eliminate environmental implications in the future. The functional properties of the compounds are preserved since the product is not subjected to high temperatures and no physical changes in the solvent and the process itself is energy saving. Due to the ever-increasing demand and cost of energy, integrated membrane processes are inevitable which are gaining prominence in food processing and they will be widely used by the food and allied industries in the years to come.

Table 11.10 Integrated membrane system for the recovery of poly phenols from Nixtamalization wastewaters

Technique employed	Process carried out	Bioactives recovered	Results and concluding remarks
MF followed by two UF process Natural source: Nixtamalization wastewaters Three stage process	Nejayote was submitted to a preliminary MF process Permeate obtained from MF was submitted to a UF step. The UF unit was equipped with two different polysulfone hollow fiber membranes	Poly phenols	1. MF retentate contains concentrated solution rich in suspended solids, parts of the grain and macromolecules that could be used as feed on livestock or can be used as carbon source to a biotechnological process in order to produce biogas, bioethanol or other type of biotechnological products. 2. UF retentate (100 kDa) concentrated fractions can be used to food additives. 3. UF retentate (1 kDa) concentrated fractions containing components of soluble calcium can be reused in the Nixtamalization process of maize. 4. The clear permeate (1 kDa UF) enriched in polyphenols could be used in cosmetic, food, and pharmaceutical industries as well as liquid formulations after fractionation by NF membranes or concentration by reverse osmosis. 5. In addition, the process of treatment of Nejayote by membrane process avoids water pollution and provides an environmental solution to decrease the biochemical oxygen demand.

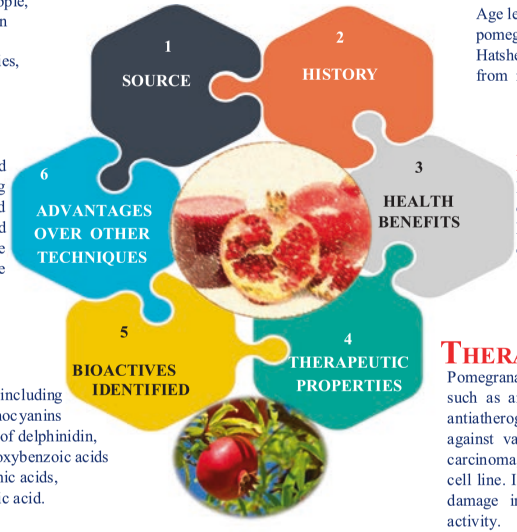
Pomegranate Juice - Introduction

SOURCE

The pomegranate (Punica granatum) is a fruit-bearing deciduous shrub in the family Lythraceae, subfamily Punicoideae), also called "seeded apple" or "granular apple, that grows between 5 and 10 m tall. It grows in Northern Hemisphere from October to February, and in Southern Hemisphere from March to May. Mediterranean countries, India, Iran and California are the main producers.

HISTORY

Pomegranate may have been domesticated as early as the fifth millennium BC, as it was one of the first fruit trees in eastern Mediterranean region. Carbonized exocarp of the fruit has been identified in early Bronze Age levels in West Bank, and late Bronze Age levels. A large, dry pomegranate was found in the tomb of Djehuty, the butler of Queen Hatshepsut in Egypt; Mesopotamian cuneiform records mention them from mid-third millennium BC onwards.



ADVANTAGES

Membrane separation processes represent a valid alternative to without changing phase and preserving chemical, physical and nutritional properties of food components. More specifially, MF, UF, NF and RO and new membrane processes including MD, OD, PV have been investigated in the last years for fruit juice concentration and recovery of aroma compounds.

HEALTH BENEFITS

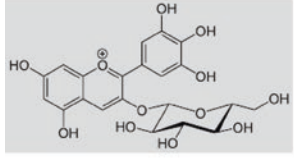
It is an anti-inflammatory fruit because of its high antioxidant content. Good source of of folate, potassium, and vitamin K. Fiber is crucial for digestive health and reduces the risk of heart disease, obesity, type 2 diabetes, and certain types of cancer.

BIOACTIVES IDENTIFIED

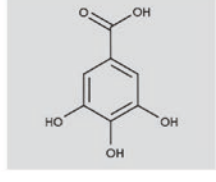
Pomegranate juice is an important source of flavonoids including flavonols (catechin, epicatechin, gallocatechin) and anthocyanins Anthocyanins include 3-glucosides and 3,5-glucosides of delphinidin, cyanidin, and pelargonidin. Phenolic acidsinclude hydroxybenzoic acids (mainly gallic acid and ellagic acid) and hydroxycinnamic acids, principally caffeic acid, chlorogenic acid and p-coumaric acid.

THERAPEUTICPROPERTIES

Pomegranate juice, has shown many health-related properties, such as antioxidant, anti-inflammatory, antihypertensive and antiatherogenic effects. It is also an antitumorigenic agent against various cancers including prostate cancer, renal cell carcinoma, papillary thyroid carcinoma cells and cervical cancer cell line. Its juice exhibits a protective effect against oxidative damage in Parkinson's disease as well as antileishmanial activity.



3,5-glucosides of delphinidin



Gallic Acid

Chlorogenic Acid

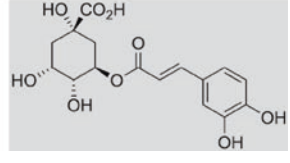


Fig. 11.19 Background on advantages, bioactive compounds and related health benefits in Pomegranate Juice

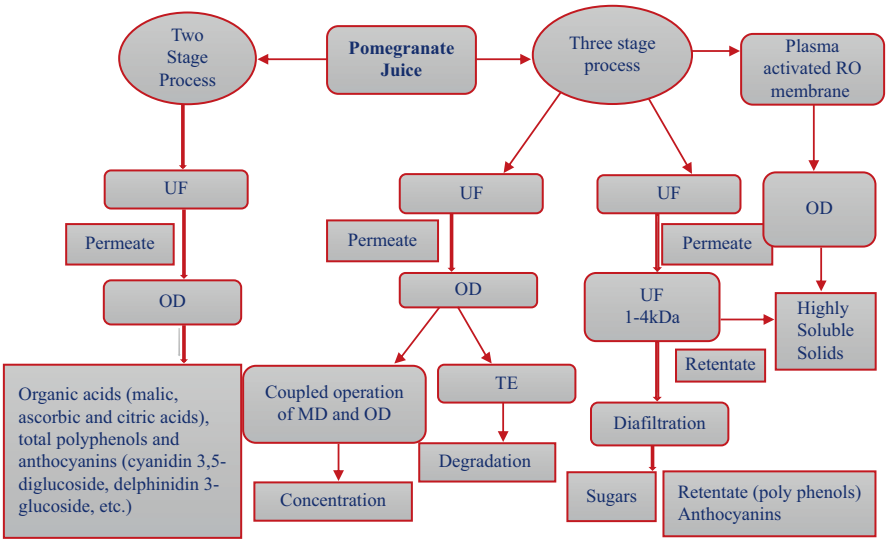


Fig. 11.20 Extraction of Bioactive - Integrated Membrane process in Pomegranate Juice

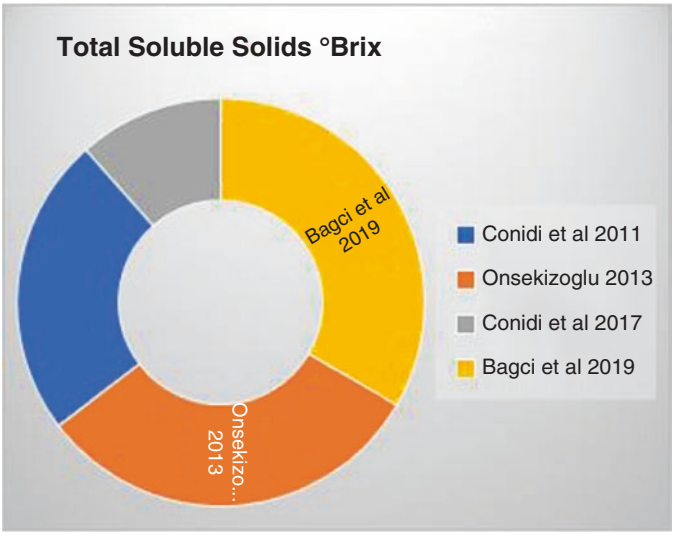


Fig. 11.21 Analytical studies and comparison among different studies reported

Table 11.11 Integrated membrane system for the recovery of Anthocyanins from Pomegranate juice

Technique employed	Process carried out	Bioactives recovered	Results and concluding remarks
UF, OD and coupled membrane distillation (CO) Natural source: Pomegranate juice Three stage process	Initial step is pre-treatment by UF. The clarified juice was subsequently submitted to a concentration procedure using both membrane-based processes (OD and coupled membrane distillation) and traditional thermal evaporation (TE).	Hydrolyzable tannins, anthocyanins and ellagic acid derivatives	The performance of ultrafiltration system was improved by the pre-clarification of pomegranate juice by lesser amounts of gelatin and bentonite, in comparison with conventional applications. The clarified pomegranate juice was concentrated up to 55.5 ° Bx in 390 min with OD, the CO yielded a concentration of the clarified pomegranate juice up to a value of 57.4^{0}Bx in 240 min (Fig. 11.4), confirming enhancement of process performance. The approach for coupled operation of MD and OD concept was more promising for concentration of pomegranate juice, allowing higher concentration to be reached in shorter periods of operation with a slight increase in juice temperature.

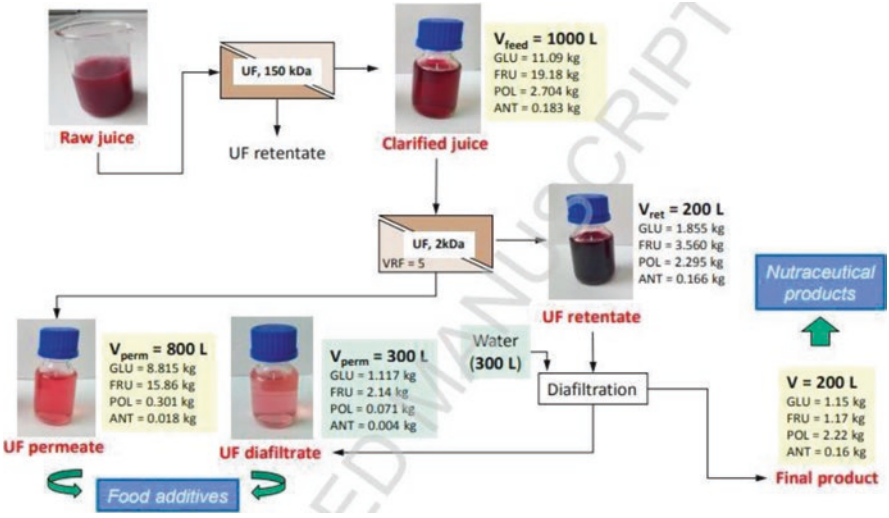


Fig. 11.22 Mass balance of the fractionation process of the pomegranate clarified juice with Desal GK membrane (Conidi 2017)

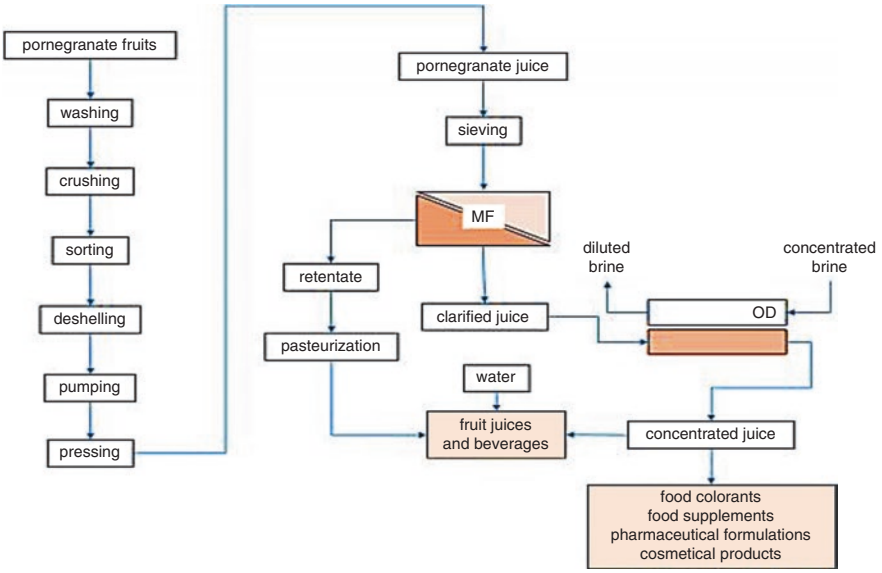


Fig. 11.23 Integrated membrane process for the production of high-quality concentrated pomegranate juice (Conidi 2020)

Fig. 11.24 -Flowchart representing the activities carried out for the recovery, purification and concentration of polyphenols from olive mill wastewaters. (Garcia-Castello et al. 2010)

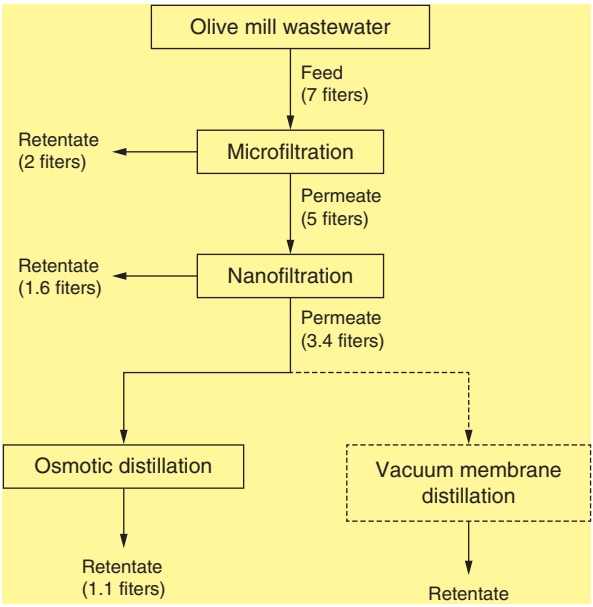


Table 11.12 Integrated membrane system for the recovery of Polyphenols from Pomegranate juice(Conidi et al. 2017)

Technique employed	Process carried out	Bioactives recovered	Results and concluding remarks
(UF)coupled with (NF) Natural source: Pomegranate juice Three stage process	Raw juice was clarified using UF membranes In the second step, the permeate was treated with four different flat-sheet UF membranes having a MWCO ranging from 1-4 kDa Retentate stream was concentrated via diafiltration step.	Polyphenols and anthocyanins	From the observed results, mass balance of the membrane fractionation process was carried out in order to quantify the amount of bioactives and sugars recovered in the varied permeate and retentate samples collected. In the 200 L of final concentrated solution obtained, yield of polyphenols and anthocyanins in the retentate stream are of the order of 84.8% and 90.7%, respectively. After diafiltration, efficiency of glucose and fructose recovery can be increased up to 90% and 93%, respectively. Final retentate with very high antioxidant activity can be reused for the formulation of nutraceutical products or as a natural colorant in alternative to the use of synthetic substances; Residual permeate and diafiltrate streams, containing high content of sugars, can be reused as food additives or as bases for soft drinks.

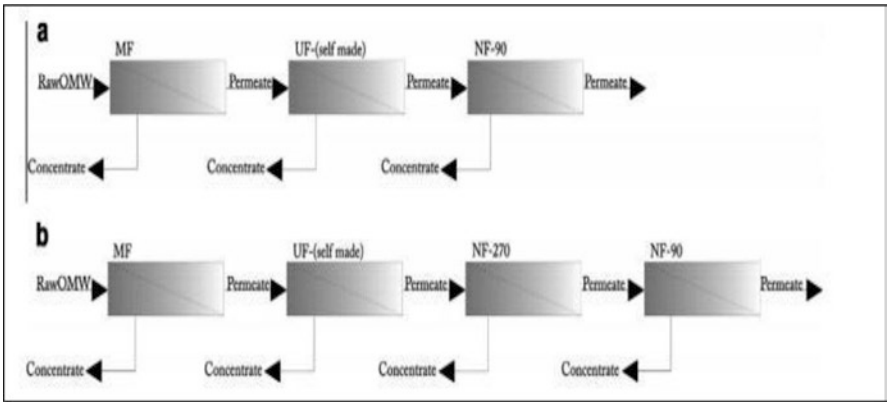


Fig. 11.25 Schematic of two different IMS arrangement used (Zirehpour et al. 2012)

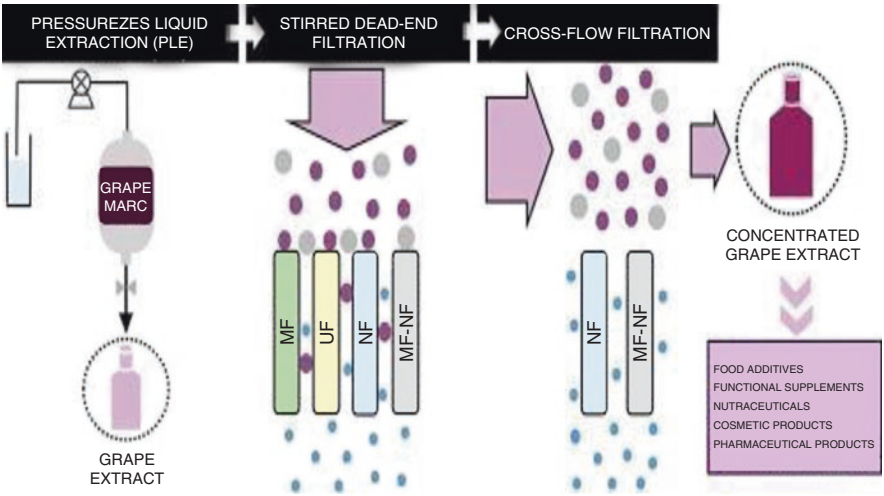


Fig. 11.26 Schematic of the integrated membrane process proposed for the recovery of bioactive from grape marc (Tamires Vitor et al. 2020)

Table 11.13 Integrated membrane system for the recovery of Polyphenols from Olive Mill wastewaters(Garcia-Castello et al. 2010)

Technique employed	Process carried out	Bioactives recovered	Results and Concluding remarks
UF coupled with NF followed by osmotic and vacuum distillation Natural source: Olive mill waters Three stage process	The olive mill waters were first clarified using by using a tubular Al_2O_3 MF membrane with a pore size of 200 nm. Sample was treated with a NF spiral-wound membrane. In the third step, the permeate was separated by OD using PP hollow-fibre membrane module and vacuum membrane distillation (VMD)	Poly phenols	Permeate from MF membrane contained 78% of phenolic derivatives, total amount of suspended solids 91% and TOC reduced to 26%. The NF treatment step lead to further reduction of TOC from 15 g/L to 5.6 g/L with concentration of low molecular weight polyphenols in NF permeate with record of low rejection observed from 1% to 21%. The concentrated solution of OD contained about 0.5 g/L of free low molecular weight polyphenols.

Table 11.14 Integrated membrane system for the recovery of Polyphenols from olive Mill waters

Technique employed	Process carried out	Bioactives recovered	Results and concluding remarks
MF coupled with UF with NF/RO Natural source: Olive mill wastewaters Four stage process	Initial MF step, was performed by ceramic membranes of 0.8 and 0.45 μm and a polymeric spiral-wound membrane 500 kDa. In the second step, the permeate was treated with a flat-sheet UF membrane having a MWCO in the range of 1-80 kDa Permeate stream was concentrated with a NF membrane. Finally, RO concentrates all the components of UF permeate.	Low molecular weight free polyphenols (hydroxyl-tyrosol, and oleuropein.	The content of free low molecular weight polyphenols in the untreated OMWs was lower (55.38 mg/L than that measured in the MF permeate (349.18 mg/L). For free polyphenols, the UF 6 kDa membrane showed a rejection of about 45%. Rejections for oleuropein and hydroxytyrosol were 75% and 45%, respectively. Effect of a nanofiltration step (NF) on UF permeate, in terms of selectivity, purification and yield of hydroxytyrosol, is not reported. RO shows a rejection of 99.9% respect to nitrogen substances, sugars and polyphenols and between 83% and 99% respect the ionic species.

Table 11.15 Integrated membrane system for the recovery of Polyphenols from olive Mill water (Piacentini et al. 2016)

Technique employed	Process carried out	Bioactives recovered	Results and concluding remarks
MF and NF coupled with OD and membrane emulsification (ME) Natural source: Olive mill waters Four stage process	First step, olive mill waters was treated by MF process to remove suspended solids. Then OMWWs were processed by NF in order to obtain water from the permeate side and a concentrated polyphenolic solution from retentate side. NF retentate was passed through OD to remove water and concentrated polyphenolic stream was encapsulated in a water-in-oil emulsion by ME.	Poly phenols	Concentration of polyphenolic solution from retentate of OD produced very high fraction of low molecular weight polyphenols according to a concentration factor of 7. This fraction which is formulated by the ME process resulted in the encapsulation efficiency of 90%. According to this process mass balance, 1000 L of treated OMWWs, fractionated 1463 g of phenolic compounds (85% of the initial phenolic content) and recovered 800 L (80% of the initial volume) of purified water.

Table 11.16 Integrated membrane system for the recovery of Phenolics from wine lees (Alberto et al. 2019)

Technique employed	Process carried out	Bioactives recovered	Results and concluding remarks
Microwave assisted extraction coupled with MF and processed by UF and two different nanofiltration process Natural source: Wine lees Five stage process	First step, wine lees was subjected to different microwave power (range: 90–350 W) and exposure time (range: 0.5 − 3 min). Total of 12 replicated trials were carried out. The red wine lees extract was previously microfiltered by using a polyvinylidene fluoride (PVDF) membrane with a membrane pore size of 0.15 m. Then the clarified solution from MF was treated by using three different flat-sheet membranes (one UF and two NF membranes) with a molecular weight cut off in the range 150–1000 Da.	Phenolics, proantho-cyanidins	The retention of the MF membrane towards proanthocyanidins resulted of about 42%; Combination of MF and NF, an attractive alternative process for producing, at low temperatures, preconcentrated extracts from wine lees without thermal damage before final concentration (vacuum evaporation, osmotic evaporation) or spray drying. Hydro-alcoholic extracts were clarified by microfiltration. Among the selected membrane, the ETNA 01PP exhibited the highest productivity in selected operating conditions but lower retention of phenolic compounds and sugars in comparison with the other membranes. On the other hand, the NFT-50 membrane presented retention coefficients higher than 70% for all detected free low molecular weight phenolics.

Table 11.17 Integrated membrane system for the recovery of Phenolics from grape Marc (Tamires Vitor et al. 2020)

Technique employed	Process carried out	Recovered bioactives	Results and concluding remarks
Pressurised liquid extraction coupled with dead end and cross flow NF and sequential MF-NF processes Natural source: Grape Marc Multi stage process	First step, four NF membranes were tested in terms of permeate mass flux and retention index of total monomeric anthocyanins and total phenolics. Second step, the use of MF and UF processes were evaluated as alternatives to improve the concentration performance and reduce membrane fouling in the NF step. After the preliminary tests in stirred dead-end module, selection of membranes, a cross-flow filtration system was used. NF and sequential MF-NF processes were investigated in the cross-flow filtration system Usage of non-toxic solvent (water–- ethanol pH 2.0 (50% w/w)) at moderate temperature (40 °C) under high pressure (10 MPa)	Phenolics, anthocyanidins	Highest retention of antioxidant capacity (52%) was observed with MF-NF sequential process. The maximum retentions of monomeric anthocyanins were obtained with NP030 (98%), followed by NF270, NP010, and MV020-NP010 membranes, with 84.0, 78.6, and 78.2%, respectively. Added to that, NP030 membrane also provided a very high retention value for total phenolics (91%), whereas NP010, NF270, and MV020-NP010 achieved values of 79%, 74%, and 71%, respectively. Moreover, NP030 membrane obtained the highest retention of total solids (43%), and the MV020-NP010 process achieved the lowest value (5%). Due to the previous treatment with the MV020 membrane, the concentrated extract obtained from the sequential process MV020-NP010 is more purified, mainly in terms of the total solids content.

SOURCE

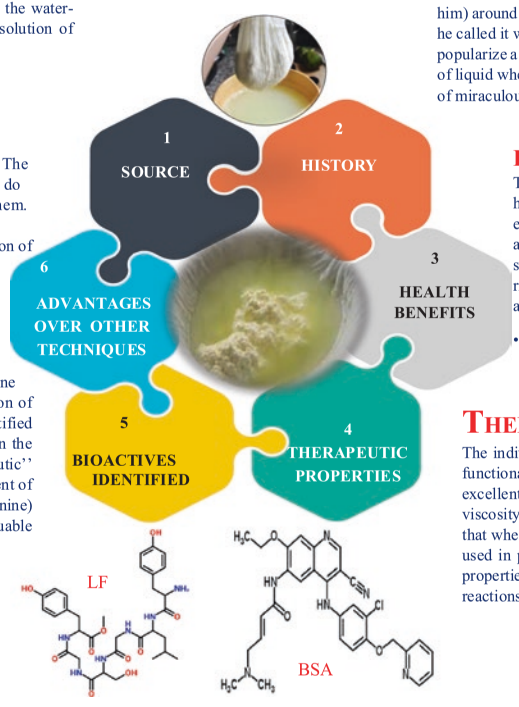
Whey is a liquid, formed as a byproduct during the process of cheese production. It is composed of 93% of water and 50% of total solids from milk. Lactose is the major component of the whey. Whey, watery fraction that forms along with curd when milk coagulates. It contains the water-soluble constituents of milk and is essentially a 5 percent solution of lactose in water, with some minerals and lactalbumin.

ADVANTAGES

Whey protein fractionation is done using membrane filtration processes such as MF, UF, associated with DF, ED and RO. The operations of the membranes are very simple, competitive and do not required any specialized knowledge to handle or operate them. To get the desired results, it is ideal to use a combination of membranes technology rather than single system and integration of various already developed membrane operations.

BIOACTIVES IDENTIFIED

A-lactalbumin, Bovine Serum albumin (BSA), Bovine immunoglobulins (Ig), Lactoferrin (LF), termostable fraction of proteose peptones and lactoperoxidase are bioactives identified which have strong antibacterial activity and can be used in the development of improved infant formula, ''therapeutic'' cosmetics, and mouthwash solutions. Due to the high content of essential aminoacids (notably lysine, cysteine and methionine) and cystin, whey proteins are one of nutritionally most valuable proteins.



HISTORY

Around 5,500 BC in Kujawy, Poland farmers noticed a liquid that separated itself from curds when preserving goats' milk. Hippocrates, the Father of Modern Medicine (the Hippocratic Oath is named after him) around 460 BC starts prescribing whey to his patients. "Serum" as he called it was given to patients as an immune-system booster. Italians popularize a method for separating liquid whey from dairy. Availability of liquid whey leads to the rediscovery of its classic benefits and stories of miraculous cures spread.

HEALTH ENEFITS

This liquid is loaded with natural proteins and has several health benefits:• Builds muscle strength.• Provides cellular energy.• Improves immunity.• Prevents diseases like cancer and HIV.• Lowers blood pressure to healthy levels without side effects, unlike blood pressure medications.• Reduces the risk of thrombosis, thereby helping to prevent heart attacks and strokes.

• Improves prostate health and prevents prostate cancer.

THERAPEUTICPROPERTIES

The individual whey proteins have their own unique nutritional, functional, and biological characteristics. Whey proteins have excellent functional properties like good solubility, good viscosity, good emulsifying and gelation abilities. Due to the fact that whey proteins have much higher digestibility, they are often used in production of infant formulas. They have antimicrobial properties and have the ability to reduce or even inhibit allergic reactions.

Fig. 11.27 Background on advantages, bioactive compounds and related health benefits in Whey water Proteins

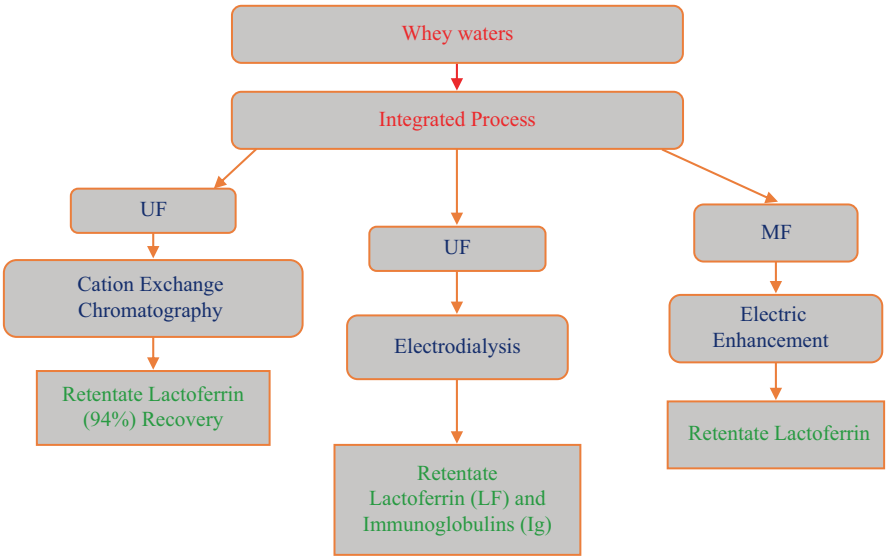


Fig. 11.28 Extraction of Bioactive – integrated Membrane process in Whey waters

Table 11.18 Integrated membrane system for the recovery of lactoferrin from Bovine Skim Colostrum Whey (Lu et al. 2007)

Technique employed	Process carried out	Bio actives recovered	Results and concluding remarks
Separation and concentration of LF by UF followed by purification of the crude LF using fast flow cation exchange chromatography Natural source: Bovine skim colostrum whey Two stage process	Two-step UF process was performed with membranes of nominal molecular weight cut-offs of 100 kDa for UF-1 and 10 kDa in UF-2. UF-1 performed at fixed transmembrane pressure (TMP), Tangential flow velocity and temperature equivalent to 200 kPa, 5 m/s, 25 °C and UF-2 at 4 m/s, 150 kPa, 50 °C. A stepwise procedure for purification of the crude LF was conducted using strong cation exchange chromatography	Lactoferrin (LF)	LF concentrated in the UF-2 retentate reached a purity of 30.88% (w/w) and a recovery of 94.04%. By using a strong cation exchanger, the purity and recovery of the final LF product was increased to 94.20% and 82.46% suitable for pharmaceutical applications. Low-temperature with no side reactions or additives makes it further acceptable as product of consumer quality

Table 11.19 Integrated membrane system for the recovery of lactoferrin from crude dairy streams (Wang et al. 2020)

Technique employed	Process carried out	Recovered bioactives	Results and concluding remarks
Electrodialysis with filtration membrane (EDFM) Natural source: Crude dairy whey streams. Novel in house coupled process	The EDFM comprises of polyvinyl alcohol (PVA) prepared by phase inversion in a coagulation bath with 80% ethanol to serve as the filtration membrane. Also, the setup contains two restriction membranes (polyacrylamide (PAm) with MWCO of 5 kDa and a pair of electrodes. The feed solution passes on one side of the membrane, with a buffer solution passing on the permeate side. Restriction membranes are used to allow the passage of ions to conduct the electric current, while preventing the proteins from entering into the electrode compartments. Two electric field strengths (38.5 and 77 V/cm) were then investigated within the electrical cell.	Lactoferrin (LF) and immunoglobulins (Ig)	Filtration membrane prepared in-house offered strong rejection for LF and Ig while allowing a high flux of other proteins. EDUF processes are found to be highly effective in separating large molecules with biological activity and uses no solvents or other chemicals that can add to the environmental footprint of the operation.

Table 11.20 Integrated membrane system for the recovery of lactoferrin from whey protein isolate (Brisson et al. 2007)

Technique employed	Process carried out	Recovered bioactives	Results and concluding remarks
Electrically enhanced membrane filtration using the conventional MF membranes. Natural source: Whey protein isolate Integrated process	Electrically-enhanced membrane filtration (EMF) process were performed on a purpose-built flat-sheet module with low transmembrane pressure (0.7×105 pa) and feed velocity ($0.05\ m\ s - 1$). Electrical field acts as additional driving force to the transmembrane pressure (PT).	Lactoferrin (LF)	Differences in protein electrophoretic mobility are coupled to the membrane sieving effect to enhance the selectivity of membrane fractionation in EMF, also to improve protein permeation flux (JP) by preventing concentration polarization and membrane fouling. The iron-binding properties of LF have been used to modify its transmission coefficient behaviour in EMF in presence of whey proteins and improve the separation selectivity. The potential of EMF for separation of more complex protein mixture such as cheese whey LF is evident.

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Chapter 12
Ionic-Liquid Membranes (Microemulsions) for the Separation of Bioactive Compounds

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Abstract Bioactive compounds have shown to be beneficial when used in different studies on food, nutraceuticals and pharmaceutical industry. In the present chapter, preparation methods, characterization and designing techniques of ionic liquids (microemulsions, MEs) which are used for the solubilization, separation, extraction and purification of various bioactive compounds, will be discussed. ME systems are efficiently applicable for oil recovery enhancement, protein extraction, isolation of phenolic compounds and purification of carotenoids and other bioactive compounds. ME liquid membranes that can be considered as nano-carriers, are also able to simultaneously extract and stabilize a vast range of both hydrophilic and lipophilic bioactive compounds in the food, nutraceuticals and drug industry sector.

Keywords Ionic liquids · Microemulsions · Bioactive compounds · Separation · Stabilization

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1 Introduction

Bioactive compounds are the secondary metabolites of almost all plant materials with insignificant quantities which are not necessarily essential for plants growth but have health-promoting effects on human and animals, pharmacologically or toxicologically (Azmir et al. 2013). However, beside plant-based materials, there are compounds obtained from animals containing bioactive compounds, such as polyunsaturated fatty acids, extracellular vesicles, conjugated linolenic acid, postbiotics, and bioactive peptides. Bioactive compounds have various metabolic functions both in prevention of health-related disorders and enhancing body tissues functionalities such as gastrointestinal tract modulatory, brain perceptual and cardiovascular activity owing to their biologically various chemical structures as esterified, hydroxylated, glycosylated and thiolyated) (Aadil et al. 2019; Babazadeh et al. 2020), and other biological activities including anticancer, antioxidant, antithrombotic, antiestrogen, anti-osteoporotic, anti-proliferative, anti-inflammatory, antimicrobial, immune-modulatory, and cholesterol reduction properties (do Prado et al. 2018). Bioactive compounds are mainly categorized as glucosinolates, diallyl sulfides, isothiocyanates, tocopherols and tocotrienols, isoflavonoids and polyphenols, phytoestrogens (genistein, daidzein), phytosterols, dietary fibers, essential fatty acids (γ-linolenic acid, α-linolenic acid, omega-3), carotenoids, bioactive peptides (e.g. lactoferrin, glycomacropeptide), and probiotics (da Silva et al. 2016).

Bioactive compounds are conventionally extracted by different techniques including Soxhlet, maceration, hydrodistillation and solid-liquid extraction in which the extracting power of various organic solvents under preparations by heating and mixing is the basic concept. The conventional methods have major challenges like solvent toxicity and high costs, longer extraction time, need for high purity solvents, a large amounts of solvents evaporation and environmental pollutions along with low extraction selectivity and decomposition of compounds that are sensitive to heat (Jalali-Jivan and Abbasi 2019). To overcome these drawbacks, novel promising extraction techniques are introduced. Ionic liquids (IL) exhibit favorable properties in extraction processes like lower vapor pressure, non-flammability, good stability against heat and repeatability (Kaur et al. 2018). Therefore, ILs can be used as efficient alternatives for organic solvents. However, comparing to conventional organic solvents, high viscosity of ILs may have the ability to lower the mass transfer rate. In addition, this approach is still poorly explored for food ingredients separation, especially because in downstream processes, a recyclable solvent may be required in order to extract natural compounds of a primary waste. Ability to be industrialized, minimization of the toxic residuals in the final product and chemical stability maintenance of the food stuffs are considered as advantages of this method. Therefore, several studies on the application of microemulsions (MEs) based on ILs extraction approach have recently been conducted as a potential method to selective recovery of the bioactive molecules from foods, pharmaceutics and chemical materials.

MEs are transparent (or translucent) monophasic thermodynamically stable colloidal systems that two initially immiscible liquids coexist in one phase owing to rearrangement of surfactant molecules in interface monolayer. These systems, take more attention owning to their low-energy formation, self-assembled structure, fine droplets, easier handling and scaling (Jalali-Jivan et al. 2014). In addition, MEs form spontaneously due to negative ultra-low values of interfacial tension of their small droplets (diameter < 200 nm), whilst high energy requiring processes such as operations involving heating, shearing, homogenization and microfluidization is not needed (Sonia and Anupama 2011). Amphiphilic, non-polar and polar phase are the least three sections included in these isotropic emulsions (Jalali-Jivan et al. 2019). However, most of the time, an only used surfactant is not able to adequately lower the interfacial tension, therefore, in order to have various desirable curvatures to form MEs, addition of co-surfactants is necessary. It is worth mentioning that, although these co-surfactants combine with the interfacial membrane, they are not defined as surfactants and consequently do not have the ability to form micelles themselves.

From the structural viewpoint, MEs can be formed as oil in water (O/W) and water in oil (W/O) which respectively are also known as direct and reverse MEs (Fig. 12.1), and bicontinuous types. The classification of MEs is firstly described by Winsor (1948), nowadays MEs generally are categorized into four types as follow. Winsor I, in which O/W ME is prepared by the solubilization of surfactant molecules in aqueous phase and the water phase with surfactants in it accompanies with the oil phase and the surfactant exists as monomer at small concentration. In Winsor

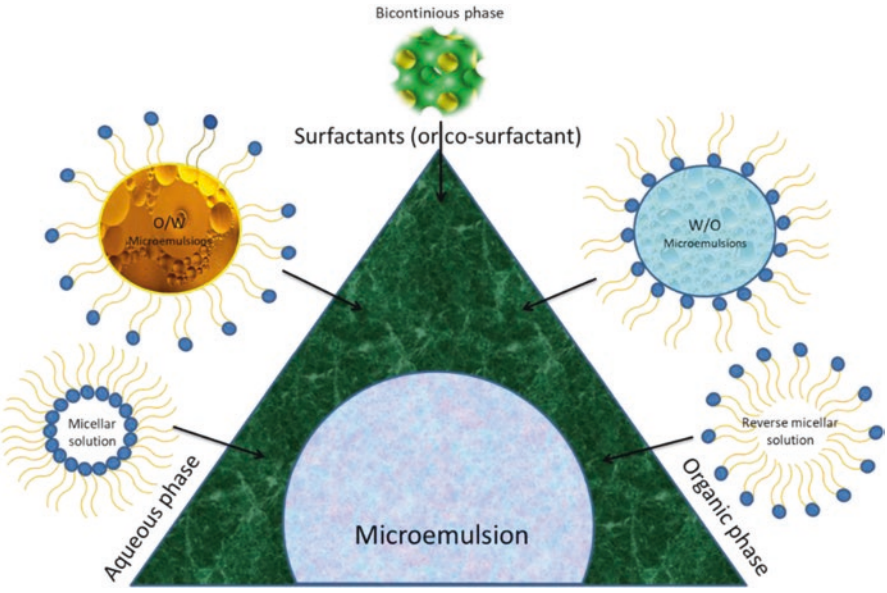

Fig. 12.1 Categorization of MEs (Jalali-Jivan et al. 2020)

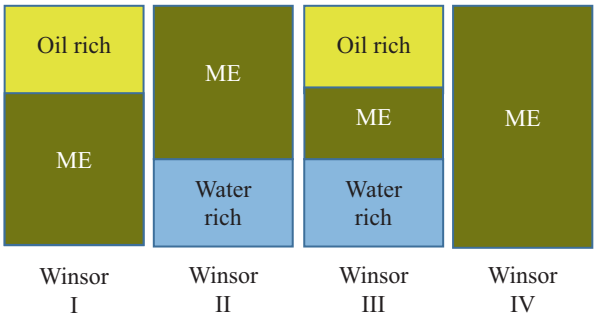

Fig. 12.2 Categorization of Winsor microemulsions

II system, surfactant solubilization preference is in the oil phase and form W/O MEs and the oil phase with surfactants unite with the water phase which contains lower amounts of surfactant. In Winsor III, an intermediate phase forms by surfactant and combines with the two other phases making a ME of three phases. For this type of ME, there are very low amounts of surfactant for the water and oil phases. When a higher amount of surfactant and co-surfactant is added to Winsor III type of ME, the intermediate phase extends to the whole liquid and forms a single phase which is called Winsor IV, an isotropic dispersion (single micellar) (Fig. 12.2).

Surfactants are typically amphiphilic molecules containing both hydrophilic and lipophilic groups for which measurement of the molar ratio of these groups, the hydrophilic-lipophilic balance (HLB) number, is defined. In this base, surfactants with low HLB (<10) are used to fabricate reverse MEs whereas those with higher HLB (>10) is suitable for direct micelles (Gadhave 2014). Surfactants decrease the interfacial tension resulting in the droplets to disperse easier and prepares a proper curvature at the interfacial area. In addition, high concentrations of surfactants, enable MEs as "super solvents" to solubilize and extract a diverse range of water and oil soluble bioactive agro-chemical compounds with favorable attributes like high stability, low viscosity, and large extraction capacity (Jalali-Jivan and Abbasi 2020; Jalali-Jivan et al. 2019). Therefore, in the past two decades, MEs gained very much attention for their ability to separate beneficial bioactive compounds like vitamins, phenolics, carotenoids and colorants, proteins, peptides and amino acids, besides different herbal and essential oils (Dimitrova and Bart 2009) Hayes et al. 2017; Jalali-Jivan et al. 2020). The preset study aimed to comprehensively review the relevant publications which are focused on application of MEs in extraction, separation and purification of these compounds.

2 Preparation, Specification and Characterization of Microemulsions

Only by combination of specific ratios of ingredients, MEs can be constructed. Hence, the phase diagrams must be constructed to determine the monophasic ME area from other emulsion types like biphasic or multiphasic dispersions and gels (Fig. 12.3). Since ME type is a key factor affecting the extraction capability, importance of using these diargrams is undeniable. In this context, beside the importance of phase diagrams, other methodologies such as conductivity measurement are also might be useful to characterize the ME type. Conductivity is defined as capability of a system to ease the transportation of electrical current and assists to deduce different ME zones. In detail, due to formation of W/O ME the conductivity initially show increase and gradually is fixed under bicontinueous structures followed by a remarkable decrease confirming formation of direct (O/W) ME (Amiri-Rigi and Abbasi 2016). Best knowledge to the obtained results, bicontinuous MEs are highly applicable systems of biomolecules separation, suitable for multiphasic biochemical reactions, and also could be applied as a template medium for nanomaterials preparation.

MEs formation might be hypothesized under three famous theories including "Interfacial Theory", "Solubilization Theory" and "Thermodynamic Theory". The

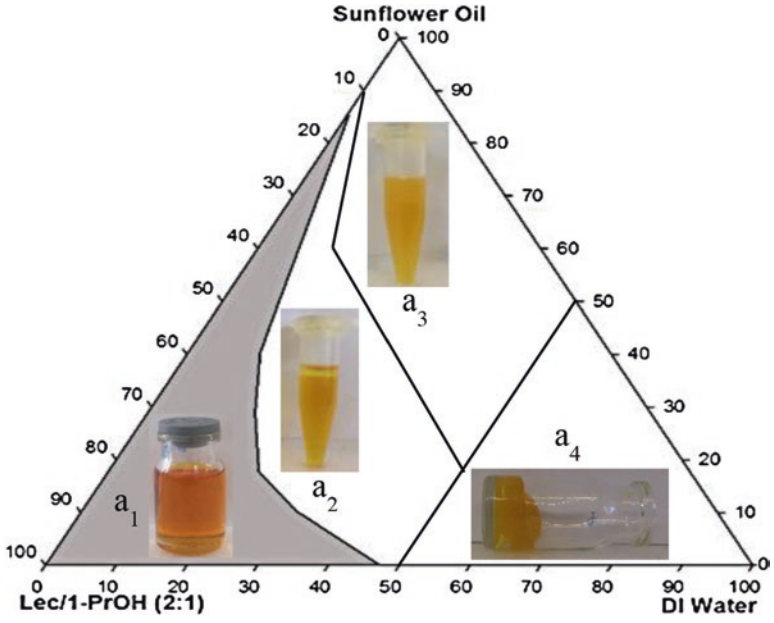

Fig. 12.3 Pseudo-ternary phase diagrams of lecithin: 1-propanol (2:1) represent microemulsion area (gray color; a_1) and multiphase region (white color; a_2: phase separated emulsion, a_3: turbid emulsion, a_4: gel structure) (Jalali-Jivan and Abbasi, 2020)

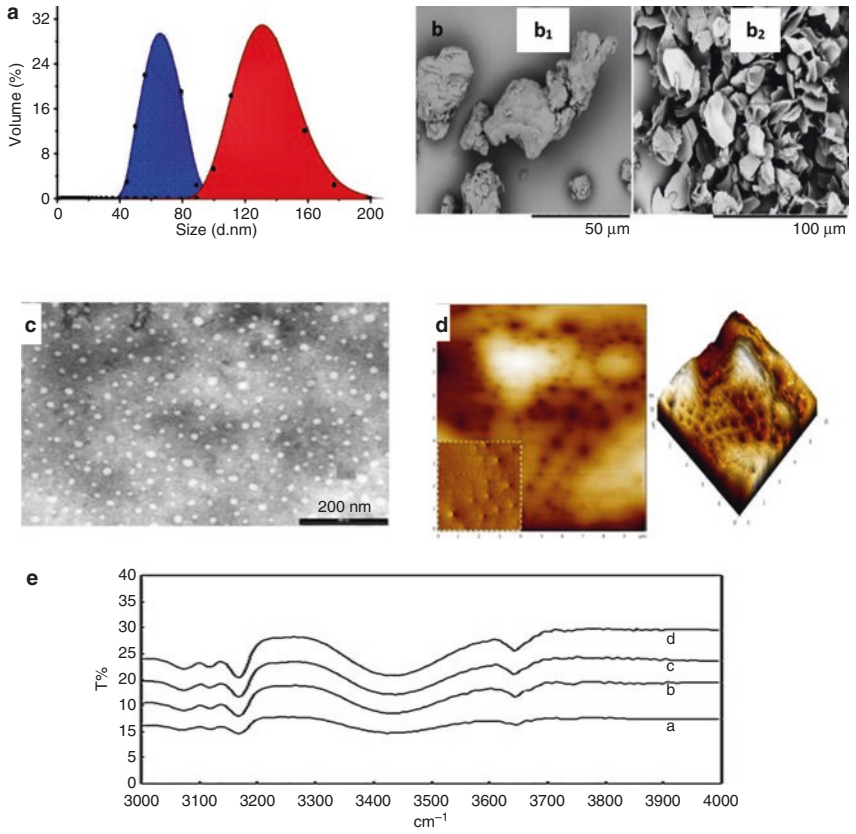

Fig. 12.4 Characterization of MEs; (**a**) Size distribution of levofloxacin free (blue) and loaded (red) ME analyzed by DLS (Nazar et al. 2017), (**b**) SEM illustration of coenzyme Q10 (b_1) and freeze-dried CoQ10-loaded ME with mannitol (b_2) (Uchiyama et al. 2019), (**c**) TEM images of curcumin loaded ME based on tween 20 (Bergonzi et al. 2014), (**d**) AFM images of food grade ME based on sucrose laurate, and (**e**) FTIR-spectra of the ionic liquid ME based on 1-octyl-3-methylimidazolium chloride with different water contents (Safavi et al. 2010)

"Interfacial Theory" which is also called the mixed/ dual film theory is about when a complex film formation on the interface of the two phases takes place due to the mixture of surfactants and co-surfactants, resulting in the creation of fine droplets. In the second theory, the solubilization of nonpolar and polar phases occur by the formation of direct and reverse-micelle respectively,:and fine droplets are formed by inflated micelle arrangements. "Thermodynamic Theory" describes how a stable ME system form through the interfacial tension reduction between dual phases facilitating spontaneous micellation of ME droplets (Jalali-Jivan et al. 2020).

The other aspect for MEs characterization is determination of their dimension and droplet size which could be conducted by application of some methods like dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM) (Fig. 12.4). Another

point that must be highlighted for MEs applications is their interaction with other ingredients such as cored materials or the extracted biomolecules. Diverse spectroscopy for instance, Fourier transform infrared (FTIR) spectroscopy, Chemiluminescence spectroscopy (CLS), ultrafast IR (UIR) spectroscopy and fluorescence correlation (FSC) spectroscopy are considered to be the common methods to monitor transitions behaviors (chemical interactions or physical entrapment) and structural proprieties of MEs (Fig. 12.4). The other techniques to interpret structural and morphological properties of MEs are field emission SEM (FE-SEM), cryo-TEM, polarized light microscopy, and freeze fracture electron microscopy (FFEM), small angle x-ray scattering (SAXS), low angle x-ray scattering (LAXRD), small angle neutron scattering (SANS), time resolved SAXS (TR-SAXS), and generalized indirect Fourier transformation (GIFT) that are of great interest in the related studies.

3 Application of Microemulsions

MEs have been mostly used in chemical, detergents and petroleum processes. However, their application in food and drug industry and nutraceuticals is facing both technical and safety limitations. First of all, health concerns regard to surfactants toxicity have limited MEs wide application for oral purposes (McClements and Jafari 2018). Wherein, only food origin natural surfactants which were generally recognized as safe (GRAS) like lecithin, saponin, rhamnolipids, mono and diesters of sucrose are accepted by international authorities like European Food and Safety Authority (EFSA) and US Food and Drug Administration (FDA). While others are either thoroughly inhibited or limited to be used at very low concentration. Table 12.1 summarizes a brief list of surfactants commonly used for food grade ME formulations. Alongside the above mentioned limitation for preparation of food grade MEs, the short and medium chain oils have higher tendency to join the surfactant's tail groups, without negative effect on interface membrane curvature (Chatzidaki et al. 2019; Ghosh and Murthy 2006). While for non-food industries (chemical, petroleum, detergent) a variety of organic phases like alkanes, mineral oils and hydrocarbons can be used. Furthermore, only short chain alcohols (1-propanol and ethanol) are allowed to be used for food, drug and nutraceutical (Jalali-Jivan and Abbasi 2020).

Besides the mentioned limitations, these delivery systems are widely paid attention scientifically and technologically owning to their capability to extract and involve a variety of bioactive compounds (hydrophilic and hydrophobic) considering whether lipophilic and hydrophilic domains are present or not. Furthermore, their ability to protect the intended bioactives from oxidation, enzymolysis and help the lipophilic bioactive compounds to solubilize resulting in a higher bioavailability are considered as advantage (Jalali-Jivan et al. 2019). Therefore, among the various capabilities of MEs including; reaction medium of detergents and petroleum

Table 12.1 Summarizing list of surfactants commonly used in food (Flanagan and Singh 2006)

Main class	examples	US 21 CFR	EU no
Lecithin and lecithin derivatives	Pure phospholipid (e.g. phosphatidyl choline) and mixed phospholipids	184.1400	E322
	Hydroxylated phospholipids/lecithin	172.814	E322
Lactylated esters	Lactylic esters of fatty acids	172.848	
	Lactylated fatty acid esters of glycerol and propylene glycol	172.850	
	Calcium stearoyl-2-lactylate	172.844	E482
	Sodium stearoyl-2-lactylate,	172.846	E481
Glycerol fatty acid esters	Polyglycerol fatty acid esters	172.854	E475
	Polyglycerol polyricinoleate		E476
	Propylene glycol fatty acid esters (Propane-1, 2-diol esters of fatty acids)	172.856	E477
Partial glycerides and derivatives	Mono- and di-glycerides	184.1505	E471
	Monosodium phosphate derivatives of mono- and diglycerides	184.1521	
	Acetic acid esters of mono- and diglycerides	172.828	E472
	Lactic acid esters of mono- and diglycerides	172.852	E472
	Citric acid esters of mono- and diglycerides		E472
	Stearyl citrate (mixture of mono-, di- and tri-stearyl esters of citric acid)	184.1851	E484
	Diacetyl tartaric acid esters of mono- and di-glycerides (DATEMS)	184.1101	
	Succinylated monoglycerides	172.830	E472
	Ethoxylated mono- and di-glycerides	172.834	
Sucrose esters	Mono-, di-, and tri-esters of sucrose with fatty acids	172.859	E473
Sorbitan fatty acid esters	Sorbitan monostearate	172.842	E491
	Sorbitan tristearate		E492
	Sorbitan monolaurate		E493
	Sorbitan monooleate		E494
Polyoxyethylene sorbitan fatty acid esters	Polyoxyethylene (20) sorbitan monostearate (Polysorbate 60)	172.836	E435
	Polyoxyethylene (20) sorbitan tristearate (Polysorbate 65)	172.838	E436
	Polyoxyethylene (20) sorbitan monooleate (Polysorbate 80)	172.840	E433
Others	Ox bile extract	184.1560	
	Propylene glycol	184.1666	
	Sodium lauryl sulfate	172.822	

process, development of nano-metric antimicrobial systems, synthesis of nanoparticles and nano-droplets from different agro-food phytochemicals, liquid vehicles for encapsulation of different nutraceuticals and drugs, and designing of intelligent

food based delivery systems, the present chapter deals with the capacity of MEs for separation purposes such as extraction, solubilization and protection of diverse bioactive nutraceuticals (proteins, phenolics, carotenoids, colorants, essential and herbal oils and vitamins) and also purification of nutrient inhibitors (trypsin and glucosinolate) as will be discussed in the following sections.

3.1 Microemulsions for Separation of Bioactive Compounds

The presence of remarkable ratio of surfactants in the structure of MEs make them as applicable potential vehicles for solubilization, purification and separation of a vast range of hydrophilic to lipophilic phytochemicals, nutraceuticals and food ingredients. However, the majority of research available in the literature is focused on solubilization than extraction and purification approaches. MEs are therefore inexpensive and efficient alternatives for current methods in which organic solvents are used. These types of emulsions have been previously applied to selectively extract metal ions and DNA (Budker et al. 2002; Cortez et al. 2004). An overview of most related studies of extraction via MEs is summarized in Table 12.2. Also, a comprehensive list of MEs application for extraction, separation and purification of various food ingredients are presented in Table 12.3.

3.1.1 Phenolics

Phenolics are widely recognized for their antimicrobial and antioxidant activities making them suitable agrochemicals to be used as ingredients of health related food. On the other side, phenolics might remain in wastewater of processing industries for fruits and vegetables, transmitting through surface and groundwater to farms and orchards, therefore contaminating biological resources due to their higher biochemical oxygen demand. Extracting these compounds from wastewater of the mentioned industries is advantageous due to reduction or elimination of oxygen demanding species and inhibiting them to enter the environment while obtaining valuable bioactive compounds which are applicable in nutrition related industries. In this regard, different procedures such as solvent extraction, ozonation, precipitation, electro coagulation, distillation, membrane technology, ion exchange, electrodialysis, liquid–liquid extraction and emulsion liquid membrane (ELM) are employed to remove pollutants from the wastes.

As a novel approach, phenolics found in pistachio peeling wastewater were successfully extracted by a W/O ME liquid membrane (MLM) (Garavand and Madadlou 2014). In the MLM, target molecules are transferred between exterior and internal phases through a membrane which is located at the interface of the two phases. This methodology has several unique features such as rapid extraction, high efficiency and selectivity, solute transfer flux across the membrane, ability to be scaled, free toxic organic solvents, ability to recycle membrane components, ability to treat

Table 12.2 Application of ME for solubilizing of diverse nutraceuticals and pharmaceuticals

ME type	ME ingredient	Solubilized molecules	Conclusion	References
O/W	Tween 60/ Ethanol (EtOH)/ Propylene Glycol (PG)	Limonene	Dramatically increasing of limonene solubility using direct ME containing EtOH and PG	Garti et al. (2001)
W/O, Bicontinuous, O/W	Tween 60/ Propylene glycol/ Ethanol	Lycopene	High solubility (up to 10 times) of lycopene in ME than limonene	Spernath et al. (2002)
O/W and W/O	Tween 80/ Ethanol/ Glycerol	Lutein/lutein Ester	High capability of W/O to solubilized both lutein Positive effect of glycerol and ethanol to solubilize both lutein	Amar et al. (2003)
O/W	Tween 60/ Ethanol	Lycopene	Designing a new vehicle with a very significant solubilization capacity and applicable in aqueous media	Garti et al. (2003b)
W/O	Tween 60 and 80/Ethanol/ Glycerol	Lutein/ Phytosterol	Maximum solubility of both molecules in the reverse micelles Inducing the structural transitions of W/O to bicontinuous ME by the guest molecules.	Garti et al. (2003a)
W/O	Tween 80/ Propylene Glycol	Omega-3 fatty acid esters and coenzyme Q10	Synergistic capacity of ME for both emulsified compound	Deutch-Kolevzon et al. (2011)
W/O	Tween 80/ Ethanol/ Isopropanol/ Propylene Glycol	Curcumin	High curcumin permeation rates of limonene ME than 1,8-cineole and α-terpineol MEs Introducing of limonene ME as promising vahicles for the percutaneous delivery of curcumin	Liu et al. (2011)
W/O	Tween 20/ Ethanol/ Isopropanol/ Propylene Glycol	Essential oils (EO)	Preparation a EO loadind ME with droplet size of 6-17 nm	Edris and Malone (2012)

(continued)

Table 12.2 (continued)

ME type	ME ingredient	Solubilized molecules	Conclusion	References
O/W	Tween 20/ ethanol	Curcumin	Maximum 1.5% of curcumin solubility	Bergonzi et al. (2014)
O/W	Tween 80	β-Carotene	Solubilizing 0.4% of β-carotene in ME	Roohinejad et al. (2015)
W/O	Tween 80/ Span 80/ Ethanol	Tea polyphenols	Construction a stable ME with 8.40 nm droplet size	Sun et al. (2015)
W/O, Bicontinuous, O/W	Tween 20/ Ethanol	Tea seed oil (TSO)	A maximum solubilization of 1.5% TSO	Deng et al. (2015)
O/W	Tween 80/ Propylene Glycol (PG)	Essential oils (EOs)	Long time stable (90 days) stable dilutable ME with high potential to deliver hydrophobic EOs for various applications	Ma and Zhong (2015)
W/O	Lecithin/ Ethanol/ Glycerol	Gallic acid, P-hydroxybenzoic acid, Protocatechuic acid and Tyrosol	The highest antioxidant activity of encapsulated gallic acid as compared to other antioxidants	Chatzidaki et al. (2015)
O/W	Propylene Glycol/ Glycerol	Riboflavin phosphate (RFP)	Solubilizing a maximum 4.25% RFP in ME with 14 nm droplet size	Lidich et al. (2016)
O/W	Glycerol	α-Tocopherol	Radical scavenging activity slightly increased within a slow release of the αToc	Aboudzadeh et al. (2018)

secondary and ternary mixtures in the wastewater, low-energy consumption and higher stability. MLM was more efficient (64%) compared to the corresponding emulsion liquid membrane (ELM. 46%). Decreased droplet sizes and increased in nano-sized droplets in the interior aqueous phase, low viscosity and surface tension, and higher numbers of formed reverse micelles in the membrane that eventually provided greater potential of mass transferring and consequently higher extraction efficiency with MLM are considered to be the unique features of ME. In this study, smaller droplets (136 nm) due to higher specific surface area provided an increased area to transport phenolics from the exterior aqueous phase into the interiors. Previous study confirmed the significant effect of surfactant concentration on decreasing droplet size of the emulsion, which resulted in a faster transferring of bioactives from the exterior aqueous phase into the interior one (Ahmad et al. 2012).

Light microscopy confirmed the hyper-droplets are made up of microdroplets which come from clustered nano sized droplets originally. Surfactant molecules

Table 12.3 Application of ME for recovery of diverse nutraceuticals and pharmaceuticals

ME type	ME ingredient	Guest molecules	Conclusion	References
W/O	Tween 85/ Isopropanol	Cytochrome C	Solubilizing a large amount of protein in stable ME Tween 85 did not denature the protein A careful choice of ionic strength will enable protein purification after optimization	Ayala et al. (1992)
W/O	Sodium Bis[2-Ethylhexyl] Sulfosuccinate (AOT)	Bovine serum albumin/ a-chymotrypsin/ lysozyme	Linear behavior between protein concentration and extraction efficiency The driving force behind adsorption is either AOT–protein interactions or the protein's affinity for microemulsified water	Hayes (1997)
W/O	Bis(2-Ethylhexyl) sodium sulfosuccinate (AOT)/ ethanol	Ginsenosides	Ultrasound assisted ME extraction of ginsenosides	Luo et al. (2007)
W/ ionic liquid	Sodium Bis(2-Ethylhexyl) sulfosuccinate (AOT)	Hemoglobin (HG)	A 96% OF HG extraction based on electrostatic interaction	Shu et al. (2008)
W/O	Sodium linear alkyl Polypropoxylated Polyethoxylated sulfates	Corn germ oil	83% recovery of corn germ oil using ME with similar chemical composition to oil extracted with hexane	Kadioglu et al. (2011)

(continued)

Table 12.3 (continued)

ME type	ME ingredient	Guest molecules	Conclusion	References
O/W	Lecithin/propanol	Canola oil	82% oil separation with similar quality to hexane based extraction sample	Radi et al. (2013)
Dual-IL ME	1-Decyl-3-Methylimidazolium Bromide (DmimBr)	Hemoglobin (HG)	A successful extraction of HG with 56% recovery	Mao et al. (2014)
O/W	Tween 80	B-carotene	The transparent ME as promising vehicle for fortification of food product	Roohinejad et al. (2014)
Bicontinuous ME	Decyl tetraethy leneglycol ether	Haem	Maximum 98% separation of Haem from initial peptide hydrolysate using ME containing 5% surfactant	Ontiveros et al. (2014)
O/W	Genapol X-080/ n-Butanol	Flavonoids (rutin, hyperoside, quercetin-3-O-sophoroside, isoquercitrin, astragalin and quercetin)	Construction a ME as mobile phase of chromatography to separation of flavonoids	Juan Song and Zhou (2015)
O/W	Saponin / Glycerol	Lycopene	A 39% efficiency of ME combined with sonication and enzymatic hydrolysis	Amiri-Rigi et al. (2016)
Bicontinuous ME	SDS/ Pentanol	Bovine serum albumin	Extracting of 4.4% protein via protein-surfactant complex	Hayes et al. (2017)
O/W	Lecithin /Propanol	Canola seed oil	Extraction efficiency of ~83% at optimum condition	Radi and Abbasi (2018)

(continued)

Table 12.3 (continued)

ME type	ME ingredient	Guest molecules	Conclusion	References
O/W	Bis (2-ethylhexyl) succinate sulfonate (AOT)	Low density lipoprotein (LDL)	Maximum 96% extraction pf LDL from phosphate buffer solution	Cao et al. (2019)
O/W	Lecithin/ 1-Propanol	Lycopene	Maximum 88% efficiency for 4-cycle extraction with ME	Amiri-Rigi and abbasi (2019)
O/W	SDS/ Ethanol	Lutein	Extraction of lutein with 85% efficiency High protection of ME on lutein regard to thermal treatment and UV-radiation	Jalali-Jivan and Abbasi (2019)
O/W	Sucrose Monopalmitate/ 1-Propanol	Lutein	Highlighting the effect of surfactant type on formation of monophasic ME based on pseudoternary Remarkable effect of co-surfactant on extraction process efficiency	Jalali-Jivan et al. (2019)

have both hydrophilic and lipophilic parts. The steric hindrance by the long hydrophobic tails of surfactants located at the droplet surface acting as a steric barrier is capable of preventing agglomeration of the nano sized droplets to occur (Mingzheng et al. 2012). However, the presence of alkaline agent could partially hydrolyze a number of surfactant molecules (Abou-Nemeh and Van Peteghem 1992) and as a result, the fatty acid sodium carboxylate salt is formed causing sorbitan molecules to get released to the aqueous phase at which it gets deprotonated and consequently being capable of making electrostatic interactions with sodium ions. Because of the destruction of hydrophobic chains of salted fatty acids, the steric barrier gets eliminated causing the nano sized droplets get close to each other making them create clusters. Previous study (Mehta and Kaur 2011) demonstrated that higher diffusions of ions or changes in droplet contents results in a consistent occurrence of clustering. This clarifies the reason of a more efficient extraction seen in MLM having clusters of nano sized droplets than ELM having individual micro sized droplets. By

using volume fraction of the dispersed phase at percolation threshold, the process of droplet clusters formation can be calculated (Alexandridis et al. 1995). X-ray scattering suggested the more ordered surfactant molecules with phenolic compound in the membrane of the MLM than of the ELM.

Curcumin, the pharmacologically safe phenolic compound of curcuma is suffering from its low water solubility, poor bioavailability, rapid hydrolysis in alkaline condition and photochemical degradation despite its remarkable biological activities such as antioxidant, anticancer, anti-inflammatory and hypocholesterolemic attributes (Kunnumakkara et al. 2008). Hereupon, it is necessary to develop novel vehicles for its carrying into water containing foods, drugs and nutraceuticals. MEs have taken more interest in recent years for these purposes because of both solubilization and stabilizing capacity is ameliorating oral absorption of this compound using food ingredients. Many formulations of MEs were therefore tried based on various pseudo-ternary phase diagrams using different surfactants mostly non-ionic (e.g. Tweens and Spans) and Zwitterion (e.g. lecithin) surfactants (Bergonzi et al. 2014). In this regard, natural lecithin based food grade reverse ME was constructed as novel carrier of natural food antioxidant agents including tyrosol, *p*-hydroxybenzoic acid, gallic acid, and protocatechuic acid (Chatzidaki et al. 2015). In this work, the presence of nano size (<10 nm) swollen reverse micelles monitored by DLS technique and confirmed using cryogenic transmission electron microscopy micrographs. In addition, the capability of prepared MEs regard to antioxidant activity of encapsulated phenolic compounds was established using an electron paramagnetic resonance method based on free radicals where microemulsified gallic acid exhibited the highest antioxidant potential (0.93 mM trolox equivalents).

It is worth to mention that, besides the effects on sensory properties, antioxidant-loaded MEs are also prevent oxidative deterioration of food products as well as protect human body against probable risks of free radicals. In other study, the solubility of natural tea polyphenols was increased using food- grade ME system composed of Tween 80 and Span 80 surfactants in the presence of ethanol as co-surfactant, and soybean oil and water as organic and aqueous phases, respectively (Sun et al. 2015). The results showed that a reverse stable ME over 45 days possessing smallest droplet size (~10 nm) was only generated in the water content above 30% of mass ratio. The results of this study showed a viewpoint to solubilize natural phenolic compounds as appropriate substitutions instead of common artificial antioxidant agents such as tertiary butylhydroquinone, butylated hydroxyanisole and butylated hydroxytoluene, to inhibit rancidity chain reactions. In a comparable study, a food grade ME system based on Tween 20, ethanol: oleic acid (3:1, as oil phase) and water was applied to solubilize tea seed oil (Deng et al. 2015). The solubilizing yield of the prepared ME was assessed at surfactant: organic phase mass ratio of 70:30 wherein, up to 1.5% of tea seed oil was solubilized into optimized ME system without changing the microstructural characteristics of ME assembly throughout dilution and phase separation. In addition, based on differential scanning calorimetry measurements, the microstructure of reverse micelles (<35% water) was translated to bicontinuous (40-45% water) followed by conversion to oil/water system (>45% water) along with the dilution line. The other investigation was constructed

pseudo-ternary phase diagrams of Tween 20/propylene glycol: water (1:1)/essential oil: ethanol (3:1) to prepare a thermodynamically stable isotropic micellar carrier with homogeneous droplet size (~6-17 nm). It can be an useful system to scale up the production of thermodynamically stable aqueous system loading bioactive compounds for various applications in food, personal care, supplement, and other nutraceutical products (Edris and Malone 2012).

In line with the reviewed study, recently a successful extraction of curcumin from *Curcuma Longa* by the use of a food-grade surfactant-free ME (SFME) based on water, ethanol, and triacetin was conducted (Degot et al. 2020). The developed SFME system had high solubility of curcumin which make possible the production of highly concentrated tinctures (~130 mg/mL) by multi-cycle extraction. The extent of water was a key factor on the number of cycles needed to be conducted and on the extracting different types of curcuminoids. Moreover, vacuum distilled and freeze dried extracts as examples of purification steps can dramatically improve (94%) the purity of single extracts. Also, in order to permanently solubilize curcumin extract in water, application of a purification step is helpful before extraction. And finally stability tests confirmed the long term (150 days) stability of solutions of curcumin when concealed from natural light.

Ginsenosides are other antioxidant agents which extracted using reverse ME from Panax ginseng, the Chinese medicine plant (Luo et al. 2007). Based on the result of this study, short sonication of soaked plant led to 2.6 times more extraction improvement using a ME system based AOT and ethanol as surfactant and co-surfactant, respectively. However, the intense sonication was less affective in lower content of surfactant, while as surfactant increased the effect of higher intensity of sonication was increased, implying the necessity of entrapped pools formed by surfactants to load the molecules of interest. Besides this, considering the solubility of ginsenosides in water pools of reverse phase ME, its extraction is significantly depending on droplet size, polarity and pools number of reverse MEs.

Date palm pit is another polyphenol-enriched substance displayed suitable antioxidant, antimicrobial and antimutagenes attributes. Further applications of this bioactive compound is limited for industrial applications due to the sensitivity to some operational conditions like high temperature, acidic conditions etc. In view of that, a ME system has been applied to encapsulate date palm pit extract using span 80 as surfactant, sodium hexametaphosphate as cross-linker agent, sunflower oil as oil phase and starch nanocrystals as wall material, providing a stable construction against the effects of mouth amylases and acidic condition of human gastric (Jalali-Jivan et al. 2014). Based on dynamic light spectroscopy results, particulation of emulsified aqueous droplets of starch nanocrystals led to the formation of nano-size particles (83–326 nm). In addition, pit extract loaded ME droplets have size distribution range between 105–376 nm and polydispersity index of 0.16, indicating the homogeneous distribution of the manufactured droplets. The analogous FTIR pattern of core-free particles and polyphenol-loaded droplets confirmed the physical entrapment of phenolic compounds into the particulated cross-linked starch nanocrystals, and probably no interaction between core and sphere interface. Moreover, the encapsulation efficiency of phenolic compounds in the emulsified aqueous

phase was about 63%, and the rest of phenolic compounds most likely transferred into ME micelles and vanished over the organic phase separation.

In another study the major flavonoids of *Apocynum venetum* L. leaf extract (i.e. quercetin, rutin, quercetin-3-O-sophoroside, astragalin, isoquercitrin and hyperoside) were separated by using a C18 reversed-phase high performance liquid chromatography (HPLC) using an O/W ME as the mobile phase, Genapol X-080 as surfactant and n-butanol as co-surfactant (Juan Song and Zhou 2015). O/W MEs are very well-matched substances with reversed-phase HPLC due to their high water content. The mobile phase was assembled by 2.5% (v/v) co-surfactant, 1.2% (v/v) surfactant, 0.5% (v/v) ethyl acetate and 95.8% (w/v) phosphoric acid solution (20 mM) at pH 6.0 with plus 0.3% trimethylamine for better separation of flavonoids. Results showed that ME mobile phase required less organic solvent and shorter separation and determination time compared to the traditional mobile phases under the same experimental conditions, representing stronger elution capacity of ME. Another valuable phenolic compound is tannic acid (TA), which was extracted by ME (Ghouas et al. 2016) by application of nonionic surfactants which are used commercially in separate experiments: Lutensol ON 30 and Triton X-114 (TX-114). Under optimum conditions, the extraction yield of TA calculated to be 95 and 87% by the use of TX-114 and Lutensol ON 30, respectively.

According to the discussed results, it can be concluded that MEs have high capability for solubilization, separation, purification, encapsulation and determination of various phenolic compounds.

3.1.2 Essential and Herbal Oils

Extraction of herbal oils can be conducted by various methods like mechanical press and diffusion based techniques. Also, various seed oils can be extracted by solvents as a conventional method mostly in mass productions. The most common solvent applied for oil extraction is hexane which has volatile nature and needs expensive equipment to process. In addition, the US Environmental Protection Agency (EPA) categorized hexane into hazardous air pollutants (Naksuk et al. 2009). Therefore, oil industry call for a safer alternative could be remove oil without toxic carriers. Among reported studies were aqueous-based extraction such as enzyme-assisted aqueous extraction and emulsion based extraction (Wu et al. 2009). Another attractive method was suggested for oil recovery was ME based extraction. ME structures exhibited a great potential in enhancing efficiency of oil recovery systems of food grade oils.

During the conventional solvent extraction, a part of oil entrapped in plant cell walls due to higher interface tension between plant cells and extraction solvent, while a substantial fraction of the stuck residual oil could be released into ME extraction solvent due to their significantly lower interface tension because of the presence of bipolar ingredients (i.e. surfactants) (Radi and Abbasi 2018). However, the interface properties of ME extraction media is affected by different factors like type of both head and tail groups and number and length of tail groups (Spernath

et al. 2006). Moreover, throughout the flooding of surfactant droplets into plant cell walls, the entrapped oil molecules can generate complexes with tails of surfactants, leading to construction of ME bicontinuous phase with lower viscosity and higher mobility characteristics, facilitating the extraction of oil droplets (Radi and Abbasi 2018). All in all, the advantages of ME systems over other oil extraction methods could be summarized as follow: green approach due to the elimination of hazardous solvents, high efficiency even at ambient temperatures, short extraction time, one-pot extraction of oils and proteins, using evaporation instead of centrifugation process to separate oil-solvent phase and cost-effectiveness (Gadhave and Waghmare 2014).

As it was mentioned, ME technique is considered to be a clean technology due to the use of biodegradable and non-toxic surfactants. Over extraction with ME, surfactant plays an important role by reducing the interfacial tension between the aqueous carrier phase and the oil phase of seeds. Several studies investigated the feasibility of ME creation in the presence of herbal oil (Ab Raman et al. 2003). For herbal oils containing triglycerides because of the high molecular weight, it is the most difficult to form a ME system, therefore choosing a proper surfactant is a serious step for ME preparation. The capability of mixing non-ionic surfactant (Brij 35) with anionic one (AOT) on emulsification of eucalyptus oil was successfully evaluated in the presence of butanol as co-surfactant (Mitra and Paul 2005). Regarding to the oil extraction with ME system, non-ionic surfactant (Comperlan KD) was used to extract soybean oil (Klongklaew 2005). In line with this work, ME technique was successfully applied for recovery of palm kernel oil using mixed (3 wt% Comperlan KD and either 0.1 wt% Alfoterra145-5PO or 145-8PO) surfactant system (Naksuk et al. 2009). Both of these systems could extract with efficiency more than 90% with oil quality (remained water, color and fatty acid profile) of similar or ever better than of counterpart extracted by hexane through solid-liquid extraction procedure.

A ME based extraction system based on anionic sodium linear-alkyl polypropoxylated and polyethoxylated sulfates ($C_{12,14}P_{10}E_2SO_4Na$ and $C_{10}P_{18}E_2SO_4Na$, respectively) as surfactants, was employed to extract corn germ oil (Kadioglu et al. 2011). A high oil extraction efficiency of about 83% obtained using 0.4% polypropoxylated surfactant and 1% NaCl. They found comparable chemical composition of corn germ oil in both ME system and reference organic oil extraction system (hexane). Concluding from the result of this study, aqueous-based surfactant ME oilseed extraction is an encouraging alternative approach for conventional oil extraction using hazardous solvents. Furthermore, simultaneous recovery of protein and oil from soy bean powder was established using ME system based on sodium bis (2-ethylhexyl) sulphosuccinate (AOT) and AOT-Tween reverse micelles (Bu et al. 2014). They reported that the extraction yield of the obtained oils by AOT-Tween reverse micelles was comparable with those recorded by traditional solvent extraction method from both cost and ingredient points of view. In another study one-pot extraction of protein and oil from soybean powder was investigated using ME systems based on AOT reverse micelle procedure (Zhang et al. 2018). The obtained proteins and oils were comparable with those extracted by alkaline-acid and organic solvent methods, respectively. Peroxide value and acid value of ME extracted oils

were even better than those obtained from Soxhlet method, which is an interesting matter for industrial applications since oxidation process adversely affects the quality of oils and oil-containing products.

Another study is extraction of canola seed oil by ME based on soy lecithin (Radi et al. 2013, Radi and Abbasi 2018). In this study, based on temperature sensitive pseudoternary phase diagrams the suitable ratio of surfactant: co-surfactant: aqueous phase (2:1:3) was applied to oil recovery. According to reported result, the highest efficiency (>82%) achieved at 60 °C for 60 min and with the ratio of 6:1 premix:canola seeds and no agitation. Furthermore, the oil obtained through ME extraction showed less amount of peroxide value, more total acidity, less phosphorus and lecithin contents comparing to samples obtained from hexane extraction. Besides, temperature was discovered to be the main factor for the simple emulsification (oil extraction) and de-emulsification (oil separation) which reduced the downstream processing. This results confirms ME's simultaneous solubilizing and extraction abilities which can be used for oil extraction and introducing of oil into food formulation. Furthermore, (Naksuk et al. 2009) designed a ME-based extraction system to extract palm kernel oil. They used tow surfactants namely Comperlan KD and Alfoterra145-5PO at 3.0% and 0.1% levels, respectively to minimize palm kernel oil interfacial tension ranging from 0.0197 to 0.0359 $mN.m^{-1}$, providing smoothed liberation of oil from the entrapped matrix. Extraction efficiency of about 94% stated for both surfactants by exposure time of 30 min and seed to solution ratio of 1:10 (g/mL). The quality characteristics of the obtained oil was also comparable or even better that hexane-extracted oil in light of moisture content, fatty acid profile and presence of surfactant residues in oil phase. Several efforts have been made to separate different oils by ME systems including mustard oil using Cetyltrimethylammonium bromide (CTAB) as surfactant (Ugolini et al. 2008), peanut and canola oil using C10-18PO-2EO sulfate as surfactant (Do and Sabatini 2010) and tea seed oil using Tween 20 as surfactant (Deng et al. 2015). These results introduced a novel approach to solubilize and recovery of edible oils by ME systems as high efficiency approaches compared to the traditional solvent-based extraction systems.

Another significant oil-soluble ingredient is coenzyme Q_{10} (COQ_{10}) which is mostly found in the plants mitochondrial membrane and has an important antioxidant role and takes an imperative role in inhibition or treatment of cardiovascular and neurodegenerative diseases (Dighe et al. 2010). Its hydrophobic nature is considered as a main challenge in their implementation for food and nutraceutical applications. Therefore, among many attempts conducted for improving its solubility and consequently bioavailability, a fully dilute-able ME system based on propylene glycol and Tween 80 which showed synergistic behavior for solubilizing of Q_{10} with essential fatty acid, was efficiently worked (Deutch-Kolevzon et al. 2011).

Considering the reviewed studies, it can be concluded that replacement of organic solvents like hexane with MEs possess several advantages as bellow. First of all, due to not utilizing such solvents in the system, the amount of toxics entering the ecosystem will be reduced. In addition, since MEs have simple preparation methods, can be conducted at moderate temperature and totally low energies are required

comparing to high energy consumption of systems like evaporators or distillatory. Generally, as it was mentioned, due to less energy consuming systems and less toxic solvents entrance to the environment, also less pollution emission and waste production, MEs are considered as cost worthy and eco-friendly methods of extraction.

3.1.3 Proteins, Peptides and Amino Acids

The alkaline-assisted extraction and isoelectric precipitation method are mentioned as the most common protein separation approaches (Zhu et al. 2006). The use of organic solvents in conventional extraction systems may adversely affected of protein structure and property. While the aqueous core of ME facilitated of proteins extraction with maintained activity (Noritomi et al. 2006). ME technique is considered as an emerging alternative method for protein purification with relatively compact conformation, better functionality such as pH-independent, water solubility and suitable emulsifying capacity and stability, and also improved sensory and nutritional attributes in comparison with conventional alkaline extraction methods (Zhao et al. 2018; Zhu et al. 2009).

A Winsor III ME based on sodium dodecyl sulfate (SDS, surfactant), 1-pentanol (1-PrOH, co-surfactant) and dodecane (oil phase) was applied to proteins (bovine serum albumin (BSA) and cytochrome c (CC)) co-extraction into the middle phase (Hayes et al. 2017). The bicontinuous ME showed remarkable efficiency in separation of both BSA (64%) and CC (81%) with highly concentrated protein solutions (3.2 and 4.4% (w/v) respectively) by releasing water and oil from ME. Circular dichroism spectroscopic analysis showed little secondary changes in the structure of BSA because of the participation in bicontinuous ME, in contrast to major changes in secondary structure of CC and pepsin and also partial unfolding of BSA in SDS and AOT based reverse MEs reported by others (Ding et al. 2007; Takeda et al. 1994). In addition, X-ray scattering highlighted the enhanced both interface membrane fluidity and specific surface area due to proteins incorporation into ME which may be resulted from the increased lipophilicity of the Winsor III and the release of water and oil from the bicontinuous ME, creating MEs with increased surface area per volume and interfacial fluidity for the surfactant monolayers. Moreover, proteins individually changed the self-assembly occurring in the Winsor III systems. Electrostatic interaction is the major possible mechanism to bonding of CC with negatively charged SDS. Wherein, regard to BSA both hydrophobic complexation and electrostatic interaction respectively with SDS and oil phase are the main incorporation motivations.

Previously, precipitation of complexes which are created by electrostatic isolation of lysozyme by SDS causes the lysozyme to denature (Behbehani et al. 2008; Stenstam et al. 2001). The ME of SDS and 1-PrOH provided superior interface fluidity, surfactant concentration, and salinity in comparison with the application AOT/CK-2,13 (Hayes et al. 2015). Therefore, the higher capability of this system better demonstrates the importance of interfacial fluidity on the capacity of the extraction. The attraction of proteins with positive charges on AOT decreased its

surface activity disrupting Winsor III structure and lowering protein isolation capacity of bicontinuous MEs. Further, SDS is served as inactivation agent of α-chymotrypsin in water and MEs due to non-competitive inhibition mechanism (Schomaecker et al. 1988).

As it was reported in previous studies, MEs containing 1-dodecyl-3 methylimidazolium hydrogen sulfate ([C12mim]HSO4), 1-vinyl-3-methylimidazolium hexafluorophosphate\ ([C6mim] PF6) and water were more efficient in extracting hydrophilics and lipophilics comparing to the conventional organic solvents (Chen et al. 2013). Also, using [C4mim]PF6 as non-polar phase in ME extracted the lipoprotein with low density at 96% efficiency (Cao et al. 2019).

Methods involving extractions are interesting for bio-separations because of their potential to be used at larger scales. The extraction method for other proteins was Winsor-III conducted by mixing protein containing aqueous phase with organic phase of surfactant like Aerosol-OT (AOT) and a two-tailed cyclic ketal alkyl ethoxylate, CK-2,13 (Gomez del Rio and Hayes 2011). Winsor III type ME, is made up of two phases of oil and aqueous in balance with ME phase in the middle led to remarkable extraction efficiency (>80%) due to the ability of AOT to electrostatically act as a driving force when pH < pI. Also, in case of molecules with negative charges like bovine serum albumin (BSA) with pH = 7, hydrophobic interactions are the main mechanisms. Small-angle neutron scattering (SANS) highlighted that proteins like cytochrome c and lysozyme which have higher pI values (which create the strongest electrostatic attractive driving force), when at a concentration > 1 g L^{-1} in the MEs, made considerable changes in the structure of surfactants specially a more dense packing at the interface (Hayes et al. 2015).

Owning to their insignificant vapor pressure, high chemical/ thermal stability and non-flammability, ionic liquid (IL) containing MEs (ILMEs) showed desirable biocompatibility and considered as an ecofriendly approach for the separation of biomolecules named proteins. Considering the amphiphilic nature of their cations or anions, long chain ionic liquids are capable of acting as modern surfactants. The adjustable structure of ILMEs make it possible to give them specific properties such as pH, IP and so on. For example, alterations in parameters of length in alkyl chain, and cationic or anionic structure creates special structures of ILMEs assembled by itself (Wang et al. 2014). ILME containing 1-butyl-3-methylimidazolium hexaflourophosphate (BmimPF6, oil phase) and 1-decyl-3-methylimidazolium bromine (DmimBr, surfactant) prepared to form a water/1-decyl-3-methylimidazolium bromine (DmimBr)/1-butyl-3-methylimidazolium hexaflourophosphate (BmimPF6) (water/ DmimBr/ BmimPF6) dual IL ME system that had great hemoglobin separation selectivity when extracting different protein molecules (Mao et al. 2014). The interaction between heme group of hemoglobin and the imidazolium cationic part can explain the phenomenon. The extracted hemoglobin successfully recovered (>55%) by back extraction with pH adjusting (12) using Britton–Robinson buffer. This system could introduce to the isolation of hemoglobin and other proteins from whole protein solutions. Extraction of cytochrome c with ME containing sucrose fatty acid esters (mono and polyester of stearic acid, DK-F-110) was conducted (Noritomi et al. 2006). The result showed that by simple adjusting of pH and ionic

strength, this protein could be separated with forward or back extraction. In other words, when moderate alkalinity and low ionic strength exists, higher ratio of forward extraction was preferred, while at conditions of acidity in pH or higher ionic strength, high backward extraction ratio was obtained. Moreover, cytochrome c recovery from the ME was remarkably active.

Another compound extracted with reverse micelles is xylitol dehydrogenase (Cortez et al. 2004). This enzyme was separated from *Candida guilliermondii* by reversed micelles of cationic surfactant named BDBAC [N-benzyl-N-dodecyl-N--bis (2-hydroxyethyl) ammonium chloride]. The target enzyme was recovered with total activity of almost 121% and 2.3-times higher purity after optimization of conditions. Beside proteins, amino acids have also been separated through reverse MEs according to their hydro-solubility natures (Dimitrova and bart 2009). For this types of extraction, the electrostatic and hydrophobic interactions as well as the free energy of amino acid transferring between water and carrier liquid (i.e., surfactant molecules) are considered as main driving forces of extraction process. Further, the droplets size plays a critical role due to controlling the hydrophilicity of ME droplet core and the interfacial hydrophobicity. In other words, as droplet size decreased the solubilized amino acids in the shell of reverse micelles can be expelled from the interface. Another protein which was successfully extracted with ME is tannase (Gaikaiwari et al. 2012). In this study, the effect of various factors like surfactant type and concentration, extraction time, organic to aqueous phase ratio, ionic strength and pH was investigated on enzyme purification fold and enzyme recovery. Wherein, the highest recovery (81%) was obtained after 13-fold purification using CTAB-isooctane mixture as surfactant. Compared with conventional methods, ME is considered as convenient enzyme purification approach capable of maintaining desire enzymatic activity and stability along with high efficiency and scale-up ability (Yin et al. 2011).

A dual ionic liquid ME system based on 1-butyl-3-methylimidazolium hexaflourophosphate (BmimPF6) and 1-decyl-3-methylimidazolium bromide (DmimBr) as organic phase and surfactant, respectively, was applied to extract hemoglobin (Mao et al. 2014). They reported that such ME systems is able to selectively recover hemoglobin from human blood stream which containing different proteins and undesired compounds, most probably due to the interaction between imidazolium group of ionic liquids (from surfactant and organic phase) and heme group of hemoglobin. As a result, this approach might provide potential alternative for purification of biomolecules from complex biological matrices.

(Shu et al. 2008) constructed a similar reverse ionic ME based on AOT as surfactant and BmimPF6 as ionic liquid for selective extraction of hemoglobin from aqueous solution. The results showed that under optimal condition (i.e. pH = 6.3, surfactant dosage of 50 mmol. L^{-1}, and water/AOT/BmimPF6 ratio of 6/50/5) significantly high extraction efficiency (96%) could be achieved. Following these studies, haem extraction from bovine hemoglobin hydrolysis (15% hydrolysis degree) was conducted via temperature sensitive tetraethyleneglycol decyl ether (C10E4)/O/W ME (Ontiveros et al. 2014). Results showed that under optimum condition (T: 27 °C, surfactant: hydrolysates (5:1)) a 98% of starting haem was transferred into

middle ME phase, while the 94% of the starting peptide reminded into the aqueous phase. Unlike this, at the same condition and for the peptide solution with hydrolysis degree of 3%, approximately all of haem (>99%) was separated from the initial peptide hydrolysate into the ME system and 90% of the peptides are recovered.

The application of micellar systems to protein extraction and purification can be established either for separation of proteins for fortification and enriching of various functional products or removing some proteins with adverse health effects from food and plant matrices. One of these proteins is low density lipoprotein (LDL) which its higher amounts in blood is strongly related to atherosclerosis, considered as one of the serious concerns leading to coronary artery disease and myocardial infarction. As a result, discarding LDL from processed diets can be a potentially effective step in prevention of atherosclerosis. Unfortunately, there are not many publications about removing these undesirable compounds. However, most recently LDL extraction using an ionic liquid ME model system was conducted using AOT as surfactant, BmimPF6 as organic liquid phase and sodium alginate sulfate as aqueous phase (Cao et al. 2019). The prepared ME could successfully extract ca. 96% of LDL from initial phosphate buffer solution. It is worth mentioning that, about 83% of the encapsulated LDL has been back-extracted through sodium dodecyl sulfate as stripping agent. From practical pint of view, they also investigate the selective LDL separation from human serum using this ME conformation as confirmed by SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) and ELISA (enzyme linked immunosorbent assay) tests.

3.1.4 Carotenoids

Carotenoids, the natural pigments with great importance for food industry, gained more attention to replace artificial dyes alongside to their nutritional future (Jalali-Jivan et al., 2021b). On the other hand, due to public awareness of consuming natural ingredients rather than synthetic ones and making difference between these two, more researches have been focused on their extraction methodology (Passos et al. 2014). Conventionally in order to extract lipophilic ingredients like carotenoids from cells, organic solvents are used along with physical methods to enhance mass transfer. These methods need a lot of costly solvents with potential of diverse effects on environment due to higher volatility beside the operationally hazardous and residues of the organic solvent as well as loss of carotenoids during solvent evaporation (Soares et al. 2016).

In recent decades, the term “Green Chemistry” was introduced due to the increased environmental concerns and sustainable development resulting in alterations in the designs of chemical processes academically and industrially. One of the priorities of today’s life is to reduce the negative effects of solvent utilization on health and ecosystem, leading to the presentation of novel alternatives which are safer and less pollutant (Passos et al. 2014). Regarding to this, developing “green” and sustainable extraction methods has become popular in recent years. Due to its

benefits, Ionic liquid membrane MEs have shown to be a suitable alternative for conventional methods (Ullah et al. 2019).

Another study was performed to investigate of the effects of organic phase type and fatty acid chain length on construction of a ME system to extract β-carotene (Roohinejad et al. 2015). Results showed that for preparation of a ME using Tween 80 as surfactant, the monophasic area of ternary phase diagram composed of short chain monoglycerides was bigger than those plotted for diglycerides and specially triglycerides. In addition, it is difficult to prepare ME with long chain triglycerides (e.g. soybean oil), while monoglycerides are able to formulate ME and reverse ME systems. The outstanding output of this study was development of β-carotene loaded O/W ME with Capmul oil using medium chain monoglycerides as surfactants to encapsulate and stabilize β-carotene for implementation in food and beverage formulations. To complete this study, β-carotene in carrot pomace was extracted by the pulse electric field (PEF) method by application of O/W ME (Roohinejad et al. 2014). Factors investigated in this study were the time and temperature of extraction and proportion of pomace/ME on extraction efficiency, polydispersity index (PDI) and micelles droplet diameter was investigated based on a three-level Box–Behnken designing. PEF increase the efficiency of β-carotene extraction compared to untreated pomace. In addition, β-carotene extracted using ME was more efficient than 100% of organic solvents named hexane and glycerol monocaprylocaprate oil. The mathematical model predicted optimum extraction condition (49.4 min at 52.2 °C and pomace/ME (w/w) ratio of 1:70) which resulted to the highest β-carotene loading (19.6 ppm), lowest PDI (0.27) and droplet size (74 nm). Lycopene extraction from industrial by-products is another novel establishment for ME application to bioactive molecules separation.

Lycopene, the essential lipophilic carotenoid of tomato, has important role in reducing risk factors of cardiovascular diseases, various cancers and aging process. It is worth to mention that functionality of lycopene is highly related to its bioavailability, which is affected by factors like solubility. In general, lycopene is water insoluble substance, which its application is paled in water containing formulations. Therefore, the solubilization methods are more requested for its further applications. In this regards, lycopene was successfully solubilized into Tween 60/ propylene glycol: water (1:1)/ limonene: ethanol (1:1) W/O, O/W and bicontinuous ME up to 10 times compared to its solubility in the limonene as organic phase (Spernath et al. 2002). In line with this study, (Amiri-Rigi and Abbasi 2016) extracted lycopene from tomato pomace via saponin/glycerol/water bicontinuous ME system leading to efficiency of about 35%. In addition, the sonication process (power 37 W and amplitude 90% at 10 °C for 15 min) followed by enzymatic hydrolysis (0.2 ml enzyme solution/kg of pomace for 30 min at 35 °C and pH = 4) caused higher extraction efficiency in ME system (ca. 39% lycopene recovery), with suitable stability against freeze-thaw cycles, thermal treatments (e.g. pasteurization, sterilization and etc.), and UV-irradiation (Amiri-Rigi and Abbasi 2017).

Such ME systems can introduce a low-cost natural method for separation of lycopene (Jalali-Jivan and Abbasi 2019; Jalali-Jivan et al. 2019). Besides, lycopene extraction with ME technique was also conducted based on food grade

lecithin-olive oil micellar system (Amiri-Rigi and Abbasi 2019). In this study, 88% of lycopene was extracted from tomato pomace with fourth extraction cycles using a ME system composed of lecithin: 1-propanol (2:1), olive oil and distilled water. It is worth to mention that 1-propanol has been generally recognized as a safe solvent for food flavoring and coloring application by FDA (Patel et al. 2006). This achievement can improve the health promoting properties of lycopene due to the increasing solubility and consequently bioavailability in both aqueous and lyophilic formulations. A related study used non-ionic surfactants (Spans 20, 40, 60 and 85; Tweens 20, 80 and 85 and Triton X100) to extract lycopene from tomato peel. This ME system led to 25% recovery of lycopene in tandem with enzymatic pretreatment with Citrozym® CEO for 30 min followed by Span 20 assisted extraction for 30 min as the optimum conditions for improving the extraction efficiency (Papaioannou and Karabelas 2012). Extraction of lycopene using natural (e.g. saponin and lecithin), synthetic (e.g. Tweens and Spans), and microbial (e.g. sucrose monopalmitate and rhamnolipid) surfactants and various co-surfactant agents (e.g. propylene glycol, glycerol, ethanol and 1- propanol) was also scrutinized from tomato pomace substrates (Amiri-Rigi et al. 2019).

Lutein is another example of carotenoid, which 6 mg daily intake of this xanthophyll has an remarkable antioxidant activity with significant effects in treatment of cataracts, age-related macular degeneration, and other ocular diseases (Amar et al. 2003; Jalali-Jivan et al. 2019). Amar et al. solubilized both lutein and lutein esters into non-ionic food grade surfactant based U-type ME droplets than its solubility in each of the ME separate phase (Amar et al. 2003). Their results showed that both esterified and free lutein has been better solubilized into reverse micelles droplets of Tween 80, glycerol, limonene, and ethanol compared to O/W ME system. The maximum capability for solubilization is obtained from bicontinuous system. In addition, their study was confirmed the facilitative effect of co-surfactants (i.e., ethanol and glycerol) in solubilizing of lutein and lutein esters. However, the exact mechanism of the co-surfactant molecules still remains vague, it was proposed that co-surfactant might be located between the surfactant molecules, leading to the moderation of surfactant hydrophilicity and loosening the arrangement of surfactant molecules in the solvent which might be facilitate to overwhelmed the steric exertion which result in flexibility improvement of interface layer. Moreover, the addition of co-surfactant to the aqueous phase is essential to reduce its hydrophilicity and simplify the penetration of lipophilic bioactive molecules (such as lutein) into the interface layer. This indicates that the surfactant-enriched interface can solubilize more lutein content under these conditions, which showed less solubility in the continuous phase. However, employing higher content of co-surfactant can moderate the extraction efficiency of lutein from the entrapped matrix that can be associated to the competitive adsorption behavior between co-surfactant and lutein.

The ability of various surfactants (e.g. Tween 20, Tween 80, Span 20, lecithin, SDS, saponin, rhamnolipid and sucrose monopalmitate) in combination with various ratios of co-surfactants (e.g. propylene glycol, ethanol, 1-propanol and glycerol) was investigated to extract lutein from Marigold petals powder (MPP) (Jalali-Jivan and Abbasi 2019). In this study first, the pseudo-ternary phase diagram

for each surfactant based ME was plotted to figure out the monophasic ME area for lutein extraction. After that, the effect of surfactant: lutein ratio (SLR) (100:1, 200:1, 500:1, 1000:1, 2000:1 and 5000:1) was optimized (SLR_{max}) for each surfactant followed by investigation of the effect of various co-surfactant: surfactant of ratio (CSR) (2:1, 1:1, 1:2, 1:5, 1:10, 1:20 and 1:50) at CSR_{max}. The poor extraction capability (3-13%) of basic MEs (without co-surfactants) was improved as MPP was exposed to co-surfactants wherein, the ME based on Tween 80: 1-propanol (2:1) was the most capable formula (~28%) to extract lutein under the SLR_{max} (2000:1). In addition, the preparation method was also affected the extraction efficiency so that when MPP was exposed to co-surfactant prior to mixing with surfactant: water dispersion, the efficiency more affected by co-surfactant, which is led to high extraction efficiency (up to 40%) in Tween 80 based ME construction. It may be due to enhanced flexibility of amphiphilic monolayer as a result of MPP hydration which could facilitated its interaction with surfactant in ME solution (Jalali-Jivan and Abbasi 2019).

In addition to this formula, another food grade ME system based on saponin:1-propanol (1:2) at SLR_{max} (200:1) showed significantly high extraction efficiency (ca. 33%), representing a ME assembly to extract and solubilize lipophilic bioactive compounds for food industry applications. It also should be noted that saponin could synergistically strengthen the antioxidant potential of extracted lutein because of the presence of some hydrophobic phenolic moieties within saponin structure. According to the results of this investigation, it is possible to design ME systems to load lutein-enriched fractions for functional foods and supplements. Furthermore, employing some strategies like sonication pretreatment can improve the extraction efficiency, leading to obtain lutein-enriched products as appropriate candidates for commercializing functional foods and nutraceuticals.

The optimization of ultrasound pretreatment was therefore performed for lutein extraction of MPP using a ME system based on various surfactants under the above-mentioned optimum SLRs and CSRs (Jalali-Jivan et al. 2019). The optimized sonication condition (i.e. amplitude 100% for 2 min at 25 °C) increased the lutein extraction efficiency using a ME system composed of SDS: ethanol (1:2) up to 85%, in comparison with acetone extraction as reference method. This is most probably related to the mechanical disintegration of plant cell wall membrane caused more penetration of surfactant to interact with intercellular lutein. Moreover, ultrasound can generate smaller droplets (12–163 nm) and thermodynamically stable ME systems. In addition, the microemulsified lutein was relatively stable against thermal treatment (80 °C for 21 h) and UV radiation in comparison with acetone and ethanol lutein extracts, indicating the high sensitivity of lutein to operational parameters, most probably due to the oxidative degradation of lutein affecting its health-promoting attributes (Weigel et al. 2018). It is also found that co-surfactant could be excluded from ME assembly when sonication pretreatment applied.

Most recently, the biologically active astaxanthin was efficiently (99%) recovered from shrimp waste with application of an sonication aassisted ME (Gao et al. 2020). ME containing tributyloctylphosphonium bromide ([P4448] Br), tributyloctylphosphonium trifluoroacetate ([P4448]CF3COO), or tetrabutylphosphonium

trifluoroacetate ([P4444]CF3COO) extracted astaxanthin more efficiently comparing to the application of organic solvents. This is most probably because of the stronger electrostatic and hydrogen interactions. Astaxanthin is more biologically active because of conjugated double bonds and hydroxyl groups in comparison with those antioxidants which are capable of reacting with free radicals in or out of the cell (Dose et al. 2016). Routinely, astaxanthin was recovered with solid–liquid extraction utilizing edible oils or volatile organic compounds (Handayani et al. 2008; Irna et al. 2018). However, the lower extraction yield of oils required a combination with organic solvents (Silva et al. 2018). With this regard, the high viscosity of vegetable oils could affect the penetration phenomena and intracellular transferring rate, also as organic solvents are toxic, highly volatile and not able to be renewed, they are not considered as eco-friendly (Rammuni et al. 2019). Worth noting that, by taking into account of safety aspects, supercritical fluid extraction (SFE) as environmentally friendly with no use of toxic solvents has recently become a significant method for separation of food ingredients. Nevertheless, in comparison with organic extraction, SFE is less efficient and more costly (Parjikolaei et al. 2017).

3.1.5 Other Bioactive Compounds

The two major glycosides of steviol (stevioside and rebaudioside A) are sweet taste secondary metabolites of stevia leaves. These calorie free compounds are the most popular substitute for the traditional sucrose (Lemus-Mondaca et al. 2012) and extracted by water-in supercritical carbon dioxide ($scCO_2$) ME in the presence of polyethylene glycol trimethylnonyl ether (TMN) surfactants (Cui et al. 2019). A CO_2-water-TMN 10 mixture (35 °C, 30.0 MPa) has the ability to extract 7 mg of the intended ingredient per gram of dry leaves. Water-/$scCO_2$ MEs are reversed micelles with a high polarity aqueous core to extract the guest molecules.

3.2 Back-Extraction of Bioactive Compounds from Microemulsions

Bioactive loaded MEs may be used as a novel product or be directly added into foods and pharmaceuticals. However, in some types especially for those extracted with non-edible surfactants to further applications of bioactive compounds, back extraction of guest molecules from the MEs is preferred. For example, to successful separation of protein using ME technique, the possibility of both forward and backward extraction procedures must be investigated. To achieve this, several issues such as protein purification, protein integrity attributes like hydrophilicity and surface charge, practical conditions such as temperature and water content, operational factors like type and dosage of surfactant, co-surfactant and protein, the ionic strength as well as pH of aqueous phase must be addressed (Serrano et al. 2018).

However, almost in all protein extraction protocols, the pH value and salt content are not affected by backward extraction (Goto et al. 1998) indicating the poor functionality effects of electrostatic repulsion on driving of backward transferring.

For back-extraction process, the anti-solvent precipitation with food grade alkaline or organic acids as well as thermo-ionic titration is applied for disintegration of MEs and separation of bioactives. Moreover, the target compounds were back extracted by the use of organic solvents, evaporating solvents or compounds (for volatile samples), precipitation with anti-solvents, and less popular, application of a microporous material and anion-exchange resins (Passos et al. 2014). Back-extraction of carotenoids from the IL was conducted using adsorbent polymer resin Amberlite XAD-7HP which was modified with ethanol followed by packing a glass column with deionized water (Murador et al. 2019). In this study, by the application of XAD-7HP resin with a peristaltic pump in a columnar structure, rinsing the [BMIM][Cl], primarily, followed by the carotenoids, both in ethanolic phase. [BMIM][Cl] and carotenoids were recovered 59–64% and 52–59%, respectively. In line with this study, extraction of tannins from *Galla chinensis* was conducted by [BMIM][Br] and in order to purify them and removing the IL XAD-6 resin was used resulting in a recovery of 99%.

Another study was conducted on tomatoes to recover carotenoids and IL after extraction by the application of [BMIM][Cl]. Physical separation after the time that IL precipitated at −40 °C, caused the carotenoid extract stay in the ethanol liquid phase (Martins et al. 2017). At −80 °C temperature, the precipitation of IL ([BMIM][BF4]) occurred when *Bactris gasipaes* fruits were the matrix and then, IL 94% recovered in separation from the ethanol supernatant enriched in carotenoids (de Souza Mesquita et al. 2019). Although there was some carotenoid loss during back-extraction. (Passos et al. 2014) stated that there are still challenges in isolation/purification of ingredients from solvents with ILs; less than 50% of studies on extraction by ILs, investigated the procedure of the isolation of the intended compound from the mixture or solution which is IL-based. In a review by (Ventura et al. 2017) in which a presentation of results from studies on the extraction of carotenoids by IL was concerned, no recovery levels were reported.

Back extraction of proteins from the ME was successfully performed by replacing the bottom phase with an aqueous stripping phase making the electrostatic attractive driving force into negative by pH or salinity justification. The use of Winsor III for protein isolation compensates the limitations of the application of commonly studied approaches: Winsor III (water-in-oil MEs in equilibrium with an oil excess phase), since it has the higher capacity to solubilize proteins using bicontinuous ME and complete recovery with higher rates via back-extraction. For instance, (Sun et al. 2008) were extracted wheat germ protein by W/O ME based on AOT, isooctane and KCl solution and highlighted the significant effects of surfactant, KCl concentration, pH, defatted wheat germ flour to AOT ratio, and extraction time and temperature on optimum extraction efficiency (37%). Subsequently, (Zhu et al. 2009) surprisingly enhanced the protein extraction efficiency up to 57% in the presence of sonication process (sonication time of 24 min, output power of 363 W, and pulse period of 2.4/2.0 s on/off). (Zhang et al. 2017) extracted grape seeds

protein with reverse micelles using CTAB, methenyl trichoride and butyl alcohol with extraction efficiency of 82%. Also it is noted that the mass transferring kinetic of protein into aqueous carrier phase was well investigated wherein, temperature, pH and ionic strength strongly affected the mass transfer coefficient which is Microemulsions (ME)back-extraction processvery important to optimize the entrapped protein transformation into ME micelles (Liu et al. 2004). In this method, interfacial resistance between ME phases and diffusion resistance cause poor recovery of protein from reverse micelles (Guo et al. 2015; Sun et al. 2009). However, it is possible to collapse ME droplet by electrostatic interaction of positively charged surfactants like dodecyl trimethyl ammonium bromide and methyl trioctyl ammonium chloride with negatively charged surfactant like AOT, leading to successful protein recovery (Jarudilokkul et al. 1999).

For instance, (Sun et al. 2008) were extracted wheat germ protein by W/O ME based on AOT, isooctane and KCl solution and highlighted the significant effects of surfactant, KCl concentration, pH, defatted wheat germ flour to AOT ratio, and extraction time and temperature on optimum extraction efficiency (37%). Subsequently, (Zhu et al. 2009) surprisingly enhanced the protein extraction efficiency up to 57% in the presence of sonication process (sonication time of 24 min, output power of 363 W, and pulse period of 2.4/2.0 s on/off). (Zhang et al. 2017) extracted grape seeds protein with reverse micelles using CTAB, methenyl trichoride and butyl alcohol with extraction efficiency of 82%. Also it is noted that the mass transferring kinetic of protein into aqueous carrier phase was well investigated wherein, temperature, pH and ionic strength strongly affected the mass transfer coefficient which is very important to optimize the entrapped protein transformation into ME micelles (Liu et al. 2004). In this method, interfacial resistance between ME phases and diffusion resistance cause poor recovery of protein from reverse micelles (Guo et al. 2015; Sun et al. 2009). However, it is possible to collapse ME droplet by electrostatic interaction of positively charged surfactants like dodecyl trimethyl ammonium bromide and methyl trioctyl ammonium chloride with negatively charged surfactant like AOT, leading to successful protein recovery (Jarudilokkul et al. 1999).

In addition, it may possible to achieve the higher efficiency with superior purity of protein (surfactant free) by selecting the correct ratios of suitable solvents in the backward extraction of obtained protein from reverse micelles (X.-H. Sun et al. 2009). This approach is able to overcome one of the major concerns regarding ME based extraction systems (i.e., surfactant residual). Furthermore, considering the protein nature, gemini surfactant (C_{12}-8-C_{12}.2Br) showed higher capability of bromelain protein extraction from pineapple peel compare to DTAB surfactant as one of the common surfactants in ME systems, most probably due to higher density of their head group charges which facilitate their effective interactions with the protein of interest (Wan et al. 2016). Similarly, (Ding et al. 2016) reported more than 90% extraction of ovalbumin protein from a model aqueous solution into the reverse micelles by a ME system based on different gemini compounds as surfactants. They pointed out that C_{12}-2-C_{12}.2Br and C_{16}-8-C_{16}.2Br and C_{16}-5-C_{16}.2Br gemini surfactants are more efficient in backward extraction compared to other tested gemini

compounds, in which intact proteins with considerable functional properties obtained. In addition, a successful extraction of different proteins including lysozyme, ribonuclease-a, and cytochrome-c could be achieved by reverse ME assemblies (Goklen and Hatton 1987). The results showed that employing some strategies like picking optimum pH values (i.e. pHs lower than isoelectric point) and suitable salt concentrations (1-2% depending on the type of protein), causing formation of strong electrostatic protein-surfactant interactions and changes in ionic strength of protein solutions, respectively.

3.3 Stability of Bioactive Compounds Extracted by Microemulsions

In order to understand the behavior of bioactive ingredients in industry, study of their reaction to heat and thermal degradation is of great importance. Various studies found that nutraceuticals especially unsaturated structural compounds are unstable under processing condition (Fratianni et al. 2010; Lee and Coates 2003). For example, stability of carotenoids has shown to follow a similar behavior in various temperatures, and among them violaxanthin and lutein are considered as the most sensitive carotenoid and most stable xanthophyll, respectively along with the carotenes. The physicochemical stability of bioactive compounds under different thermal processes, various pH condition, UV radiation and shelf stability are of great interest from commercial perspective. Unfortunately, the conjugated nature of most of these compounds makes them susceptible to degradation. However, there is evidence confirming the capability of MEs to protect bioactive compounds (Jalali-Jivan et al. 2019). In our previous work, the lutein stability of Span 20 based lutein MEs (LME) is compared with marigold ethanol extract (MEE) under the same conditions (Jalali-Jivan et al., 2021a). Results confirmed the valuable stability of lutein as LME than of organic solvent extract under thermal processing, pasteurization (85 °C for 25 s, HTST), sterilization (121.5 °C for 15 min), storage stability and pH resistance. The most probable reasoning behind this phenomenon is that the microemulsification formed micelle constructions which entrapped lutein into reverse membranes and consequently protected the sensitive lutein from unfavorable interactions (Weigel et al. 2018).

The fading of carotenoids under thermal processing depended on their composition and storage conditions, here in various interactions such as oxidation and isomerization may occur leading to carotenoids deterioration (Boon et al. 2010). Moreover, specific interaction between phytochemicals and surfactants under stresses might be has a key role on stabilization mechanism. For example, heating may be dehydrated the hydrophilic head groups of nonionic surfactant (Azarikia and Abbasi 2016) which could facilitate the packing of bioactives into core of nanomicelles and consequently protected them. Furthermore, the conformational changes of surfactants should not be neglected (Davidov-Pardo et al. 2016).

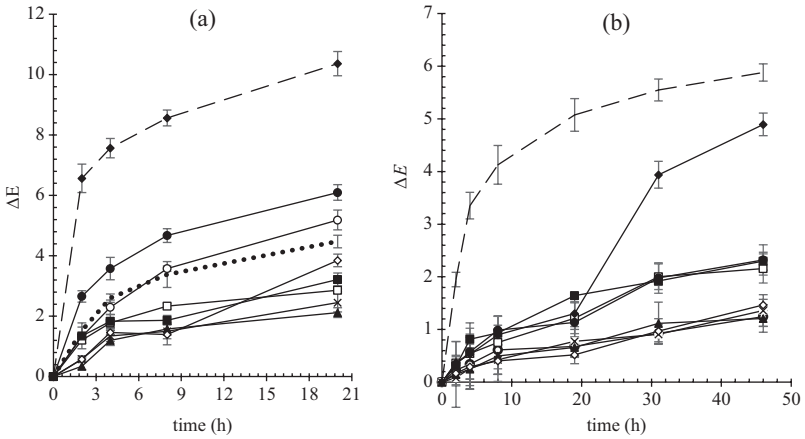

Fig. 12.5 Effect of (**a**) heating (80 °C) and, (**b**) UV-radiation (λ = 254 nm, x = 15 cm, T = 25 °C) on Δ*E* of marigold acetone extract (---MAE) and lutein MEs based on different surfactants (○ Lec, ● Sap, □ Rhl, ■ SMP, × T20, ▲ T80, ◇ S20, ◆ SDS,) (Jalali-Jivan et al. 2019)

In carotenoids containing functional foods, the photo-oxidation could result in faint of organoleptic (color loss, rancidity) and nutritional (bioactivity) quality. Our previous study (Jalali-Jivan et al. 2019) confirmed the high potential of ME to protect lutein under UV-radiation and thermal treatment (Fig. 12.5). With regard to marigold acetone extract (MAE), the conjugated structure of lutein is likely oxidized in the presence of pro-oxidant (UV light) and produced mono and di-epoxides, carbonyls, alcohols and even under extensive oxidation could result in bleached xanthophylls (Sowbhagya et al. 2004). With reference to MEs, the physicochemical interactions are governed by different factors considering the nano-micelles interfaces arrangement. In other words, the superior stability of lutein is due to its lyophilic interactions with surfactant molecules and entrapment and at the same time the hydrophilic interactions of surfactant and co-surfactant with surrounding polar molecules which improve its stability because of formation of interface membranes with tightly packed surfactant molecules which could remarkably protect the core materials (*i.e.*, lutein). Regarding to these results, it can be concluded that free lutein is very sensitive to environmental and processing stresses. Besides, these stability results provided useful information to assess the initial lutein content for enrichment purposes and established stable lutein loading possibility as LME into functional products which have to be processed as above.

4 Challenges and Future Trends

Besides the lab-scale application of MEs, there are some questions must be addressed in the future studies. First of all, the fate of MES and specially ingredient named surfactants and co-surfactants after oral administration is of drastic concern.

Although, this problem was overcoming to some extend by substitution of pharmalogical grade surfactants by food grade ones like soy lecithin, proteins and rhamnolipids (Jalali-Jivan and Abbasi 2019). By application them, it is logical think that there should not raise safety concerns as they are likely to be digested in the gastrointestinal tract. Furthermore, with the best knowledge of different investigations have been conducted about worthwhile and concerns of nanotechnology approaches, there has been no conclusive report regard to the undesirable effects of nanotechnology on biological systems is called to further research in this area wherein authorities responsible for regulations such as FDA and Codex must classification of various nano-carriers and make clear statements about using the nanotechnological instruments including MEs and nano-micelles.

5 Conclusion

MEs have been vast applications in solubilizing and extraction of various phytochemicals, bioactive compounds and pharmaceuticals. Formulation of effective MEs based on biocompatible and edible surfactants (e.g. sugar esters and lecithin) and apolar solvents (e.g. essential oils and/or vegetable oils) is critical for further application of the ME systems in the health-related products. For successful extraction with MEs, different operational factors like different temperatures, pH values, ionic strength and the interaction of other compounds have key roles. Extraction of food ingredients (carotenoids, proteins, phenolics, and herbal oils) using MEs has been mostly carried out at the laboratory scale, although the scale-up of such processes is possible by overwhelming some practical challenges to design continuous extraction and/or encapsulation processes for the bioactives using ME systems. All in all, MEs are increasingly attracting the attention of scientists and industries owning to their ability for selective extraction, purification and synchronized stabilizing of phytochemicals.

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Chapter 13
Modelling in Membrane Separation of Bioactives

Krishnasri V. Kurada, Sourav Mondal, and Sirshendu De

Abstract Membrane based systems have become integral parts of the processing of bioactive compounds from the plant extract or fruit/vegetable juice. The technical feasibility of the process is generally established experimentally in small scale laboratory set ups. The results in the lab scale experimental data are generally used to scale up the process to the industrial level. To achieve this, a suitable model is needed. The major aspects of modelling the membrane-based systems are the prediction of the permeate flux and permeate concentration of the target species. These two parameters are related to the process throughput and quality of the product stream. The actual extract or juice is a complex fluid with an assortment of various components. Therefore, it is quite difficult to estimate the physico-chemical and transport properties of the extract/juice making the formulation of a physical model almost untenable. In this context, the popular models for tracing the behavior of the membrane-based systems are classified into three categories, namely, empirical, semi-empirical and transport phenomena based models from first principles. These three classes of the models are discussed in depth in this book chapter in relevance to the processing of the bioactive components. The assumptions, underlying physical principles, advantages, limitations and applicability of various models are discussed with great details. The models are also demonstrated with the practical case studies. It is envisaged that the presentation in this chapter would be of immense help to the design engineers to model and subsequent scaling up of the membrane processing of the production of bioactive components from the plant extract or the fruit/vegetable juices.

Keywords Bio-actives · Membranes · Modelling · Permeate flux · Fouling · Scale-up

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Nomenclature

A_m	Effective area of the membrane (m^2)
a and b	Pressure dependency parameters of mass transfer coefficient
B_1	Phenomenological membrane transport coefficients of permeation ($m^3/m^2.s$)
C_{0i}	Initial concentration of ith component (kg/m^3)
C_{ib}	Bulk concentration of ith component (kg/m^3)
C_{ig}	Concentration of ith component in gel layer (kg/m^3)
C_{pi}	Permeate concentration of ith component (kg/m^3)
d_e	Effective diameter of the channel (μm)
D_i	Diffusivity of ith component (m^2/s)
G_1 and G_2	Dimensionless parameters
J	Permeate flux (m^3/m^2 s)
J_0	Permeate flux at $t = 0$ (m^3/m^2 s)
J_w	Permeate flux using pure distilled water (m^3/m^2 s)
k and n	System specific parameters of Hermia's model
k' and m	System specific parameters of Field's model
k_1	Complete pore blocking constant
k_2	Intermediate pore blocking constant
k_c	Cake filtration constant
k_f	Mass transfer coefficient (m/s)
k_{f1}	Pressure dependent mass transfer coefficient
k_g	The parameter responsible for the rapid or slow growth of the fouling layer
L	Gel layer thickness (μm)
M_w	Molecular weight (kDa)
N	No. of experiments
n_1	Exponent in the pressure dependency expression of ε and α
ΔP	Transmembrane pressure drop (kPa)
Q	Volumetric flow rate (m^3/s)
R_{bl}	Resistance due to boundary layer (m^{-1})
R_F	Fouling layer resistance (m^{-1})
R_g	Gel layer resistance (m^{-1})
R_m	Membrane hydraulic resistance (m^{-1})
R_p	Pore blocking resistance (m^{-1})
Rr	Real retention
R_T	Total resistance (m^{-1})
S_0 and S	Square of errors
T	Temperature (K)
t	Time (s)
t_{PB}	The time up to which the pore blocking prevails (s)
u	Cross flow velocity (m/s)
V	*V*olume (m^3)

v_1, v_2 and v_3	Dimensionless parameters
w	Width of the filtration cell (cm)

Greek Letters

α	*S*pecific gel resistance (m/kg)
α_0	Pressure independent specific gel resistance (m/kg)
β	Gel layer resistance per unit length (m^{-1} kg^{-1})
δ	Thickness of the concentration boundary layer (μm)
ε_g	Porosity of the gel layer
ε_0	Pressure independent porosity of the gel layer
γ_g	Partition coefficient
ϕ	Standard pore blocking constant
μ	Viscosity of the permeating solution (kg/m s)
μ_w	Viscosity of water (kg/m s)
π	Osmotic pressure (kPa)
ρ_g	Density of the gel layer (kg/m^3)
ρ_f	Density of the feed stream (kg/m^3)
ρ_p	Density of the permeate stream (kg/m^3)
σ_1	Phenomenological membrane transport coefficients of reflection
τ	Non-dimensional parameter

Abbreviations

CFR	Cross flow rate
EGCG	Epigallochatechin gallate
HMW	High molecular weight
LMW	Low molecular weight
MWCO	Molecular weight cut-off
PSf	Polysulfone
TMP	Transmembrane pressure drop
TDS	Total dissolved solids

1 Introduction

Extraction of bioactive compounds from plant extracts is a sequential process of five distinct stages, namely, (1) pre-treatment, (2) separation of macro and micro- nutrients, (3) extraction, (4) isolation-purification and finally (5) product formation or encapsulation (Galanakis 2015). Pre-treatment of the feed is an important step to

separate the large molecular weight compounds and is being carried out using either microfiltration (MF) or ultrafiltration (UF) membranes (Galanakis 2015; Kumar et al. 2012). Also, removal of microbes is an important step to be ensured during the processing of bioactives. However, majority of microbes are generally removed by 0.2 μm MF membranes and all of them are excluded by lower sized UF membranes. Currently, membrane based processes have become an integral unit operation for treatment of liquid streams of widely varying composition in chemical, food, biotechnology and pharmaceutical industries (Pabby et al. 2015). Membrane filtration finds diverse applications in separation and fractionation of bioactives, concentration of fruit juices, removal of coagulating proteins, fibrous substances and microorganisms. Such specialized filtration is pertinent for the extraction of bioactive compounds from plant extract because (1) the membrane processing can be done under room temperature precluding denaturation at higher temperature; (2) no chemicals are needed during separation and (3) microorganism can be removed easily in single step (Gerke et al. 2017; Mondal and De 2018). Although, the membranes are capable of separating compounds via sieving mechanism based on their molecular size, their selectivity can be tuned by exploiting the operating conditions and various membrane modification techniques thereby expanding their applications in the food industry over the last few years.

Application of membranes filtration for processing plant extracts or fruit juices for selective separation of various nutrients or specific compounds having pharmaceutical applications has been investigated extensively. Several researchers have studied the performance of membrane based separation processes for filtration of various fruit juices, e.g., apple, pomegranate, grape, orange, watermelon, kiwi etc., (Aghdam et al. 2015; Cancino-Madariaga et al. 2012; Conidi et al. 2012; Giacobbo et al. 2017; Mondal et al. 2011; Rai et al. 2010; Vladisavljević et al. 2003). The application of membranes to extract specific bioactive compounds from various plant extracts has been also attempted. For example, ultrafiltration membranes were used to enrich the important phytochemicals, such as epigallochatechin gallate (EGCG) from aqueous extract of green tea leaves (Kumar et al. 2012; Mondal and De 2018) Mondal and De 2019; dos Santa Sousa et al. 2016). Extraction of Stevioside from the extract of Stevia leaves using membrane filtration has been extensively studied owing to its high antioxidant, anti-carcinogenic and anti-diabetic properties (Das et al. 2015; Mondal et al. 2012a, b, 2013; Reis et al. 2009; Roy and De 2014, 2015). Rai et al. have used microfiltration membranes to separate nutrients like lycopene from watermelon extract (Rai et al. 2010). Few researchers have attempted selective separation of bioactive peptides from protein hydrolysate using membrane filtration (Agyei and Danquah 2011; Firdaous et al. 2009; Poulin et al. 2006).

The major drawback of the membrane separation process is the decrease in permeate flux due to the membrane fouling (Ilame and Satyavir 2015; Mondal et al. 2013; Roy and De 2015). Fouling of the membrane cannot be avoided but they can be minimized. Various techniques are used to reduce the membrane fouling. These are: (1) modification of the membrane surface by making it more hydrophilic and smooth, incorporating antifouling additives, surfactant treatment, etc. (Kurada and De 2018; Mukherjee and De 2016; Song et al. 2000); (2) altering the

hydrodynamics in the flow channel by increasing the turbulence, creating Dean vortices, use of turbulent promoters, etc. (Guo et al. 2012; Jaffrin 2012; Ma et al. 2000); (3) use of external fields, like, electric and magnetic (Jian et al. 2006; Wandera et al. 2010). Therefore, modelling of membrane filtration to quantify the flux decline a-priori is of paramount importance to have an efficient design of the process and also to estimate the membrane life.

The models of the membrane flux decline can be categorized into the following groups, namely, (1) empirical models, like, resistance in series models; (2) semi-empirical models, like, blocking models; (3) transport phenomena based models using first principles to quantify the underlying physics of the system. The resistance-in-series models are entirely empirical in nature and various transport resistances are estimated from the experimental permeate flux data. Since, the correlations are developed over a range of operating conditions, such models are valid within that range only and they lose their predictability beyond those. Although the semi-empirical blocking models (different models are proposed for various fouling mechanisms) are based on the theoretical background of the filtration mechanisms, the flux decline is expressed in terms of the filtration coefficient that is estimated by optimizing the experimental flux decline profile. The fouling mechanism is identified by testing the closeness of fitting the experimental flux decline data to the calculated ones, indicated by correlation coefficient between the experimental and calculated datasets. In majority of the cases, the correlations coefficients are too close to attain a definite conclusion about the flux decline mechanism. Additionally, both resistance-in-series model and blocking model can quantify the permeate flux, not the bioactive concentration in the permeate. Therefore, these models cannot account for the recovery and selectivity of the bioactive compounds in the filtrate. On the other hand, the transport phenomena-based models are derived from the first principles and they can estimate both the permeate flux and permeate quality as a function of time. The aqueous solution of a plant extract being a complex fluid having a large number of solutes with varying concentration, the transport coefficients, such as solute diffusivity, membrane permeation coefficient, etc., are estimated using the experimental data, imparting a semi-empirical flavour to such models. However, once the parameters are estimated from a selected experimental data, such model can be used for other operating conditions, scaling up calculations in completely predictive mode for the same plant product and bioactive component. Thus, the third category of the models is versatile having wider applicability and broader predictive capability.

The present chapter focuses on the critical challenges involved in the modelling of the membrane-based processes for extraction of bioactive molecules. The details of various fouling models as described above, their solution and applications are discussed. Given a model, the optimization procedure to select the operating conditions is also presented. The modelling aspects of the permeate flux hysteresis observed during ultrafiltration of plant extract is also addressed. It is envisaged that this chapter would be of immense help to the design engineers to adopt an appropriate model and design the membrane-based filtration for bioactive compounds efficiently.

2 Modelling Aspects of Membrane-Based Separation

The major drawback of membrane separation processes is the decrease in permeate flux i.e., throughput of the process, as well as the quality of permeate due to membrane fouling (De et al. 1997). Fouling of membrane takes place due to the blocking of pores by the solute particles or by the deposition of the solute particles over the membrane surface resulting into increase in osmotic pressure across the membrane surface (Bungay et al. 1983). Fouling is mainly of two types, reversible and irreversible (Mondal et al. 2012b). When membrane permeability can be regained after appropriate washing, it is termed as reversible fouling. On the other hand, irreversible fouling cannot be eliminated completely and corresponds to partial gain in the membrane permeability (Mondal et al. 2012b). The main contributing factor of reversible fouling is the accumulation of solute particles on the membrane surface also known as concentration polarization (De et al. 1997). Permeate flux throughput and product quality are two important parameters to be predicted for efficient design and subsequent scaling up. Following sections discuss different approaches used for modelling of membrane-based process used for separation of bioactive compounds.

2.1 Empirical Models

The operating parameters play an important role on the performance and life of the membrane during separation of complex solutions (Padaki et al. 2015). In this regard, a simple model for quantification of permeate flux decline is very useful. Identification of phase space of operating parameters for optimal performance of the filtration process can be an effective tool for easy scale up and design. Few authors have attempted quantification of flux decline for real life, complicated streams (Mondal and De 2018; Mondal et al. 2011; Rai et al. 2010; Roy and De 2015). Roy and De have used resistance in series model to optimize the operating conditions for filtration of Stevial glycoside extracts using ultrafiltration (Roy and De 2015). Mondal et al., have formulated the resistance in series model to model the flux decline during microfiltration of fresh green tea extract (Mondal and De 2018). Tasselli et al., have analysed the permeate flux decline of ultrafiltration of kiwi fruit juice in terms of this model (Tasselli et al. 2007). Several other authors have quantified the flux decline during membrane filtration of fruit juices and bioactive compounds using this model (Skinner and Hunter 2013; Vladisavljević et al. 2003). Therefore, the advantage of this model is the easy design and scaling up as already discussed. However, the limitations of the model are, (1) the permeate flux can only be quantified as a function of time but not the permeate concentration; (2) the model is specific to the system considered due to the empiricism involved in the model; (3) the model parameters are valid within the studied range of operating parameters. Thus, the resistance-in-series models are neither to be considered as predictive tools

to quantify the flux decline, nor they are generalized enough to be applicable for different juices/ extract, thereby losing their versatility.

2.1.1 Resistance in Series Model

Usually the plant extract is a complex mixture containing a large number of solutes with varying molecular weight and concentration. Therefore, it is difficult to identify each of them with their respective concentration. Moreover, their transport properties, such as diffusivity, intrinsic membrane rejection, solution osmotic pressure, etc., are not accurately known. For this reason, the resistance in series model becomes quite easy and handy for the description of the permeate flux decline. In this model, various resistances against the permeate flux are considered to be acting in series (with the analogy of electric circuit) and the permeate flux is quantified as the driving force (transmembrane pressure drop in this case) divided by the total resistance. One or more of these resistances may be function of time. The resistances are estimated from the experimental permeate flux decline data and their functional variation with time is correlated with the operating conditions, like, transmembrane pressure drop (TMP) and cross flow rate (CFR). This provides the utility of this model to interpolate the flux decline with the unknown operating conditions.

Various resistances encountered by the permeate flux are: membrane hydraulic resistance (R_m), fouling layer resistance (R_F) and pore blocking resistance (R_p). The membrane hydraulic resistance (R_m) is calculated using (Gerke et al. 2017) as:

$$R_m = \frac{\Delta P}{\mu_w J_w} \tag{13.1}$$

where, ΔP is the transmembrane pressure drop (TMP), μ_w is the viscosity of water and J_w is the permeate flux using pure distilled water (having no osmotic pressure). For some solutes, pore blocking resistance is absent, if the solute size is much larger than the membrane pore size. In such cases, pore blocking resistance can be neglected and the fouling layer resistance, R_F can be represented in terms of the experimental permeate flux as (Mondal and De 2018):

$$R_F = \frac{\Delta P}{\mu J(t)} - R_m \tag{13.2}$$

In above equation, μ is the viscosity of the permeating solution and $J(t)$ is the permeate flux at any time point t when the plant extract/juice is used as the feed solution. It may be mentioned that the fouling resistance is mostly reversible in nature in absence of membrane pore blocking.

In case of the presence of significant pore blocking resistance (R_p), it is estimated in two ways. In the first case, the irreversible resistance of the membrane during N^{th}

experiment is estimated by measuring the pure water flux before and after the experiment. This resistance is a measure of irreversible membrane resistance even after membrane cleaning (Roy and De 2015).

$$R_P^N = \frac{\Delta P}{\mu_w J_w^{N-1}} - \frac{\Delta P}{\mu_w J_w^N} \tag{13.3}$$

In the above equation, R_P^N is the pore blocking resistance during N^{th} experiment, J_w^{N-1} is the pure water flux after $N\text{-}1^{th}$ (i.e., the water flux before starting the N^{th} experiment) and J_w^N is the pure water flux after N^{th} experiment using the cleaned membrane. Thus, R_P^N is an indicator of the resistance corresponding to irreversible membrane fouling during N^{th} experiment. In such cases, the fouling resistance cannot be determined a straightforward way like the case without pore blocking resistance. Here, the fouling resistance at any time of filtration is estimated from the experimental permeate flux data as:

$$R_F = \frac{\Delta P}{\mu J(t)} - R_m - R_P^{N-1} \tag{13.4a}$$

where, $J(t)$ is the permeate flux at any time point t. The modelling aspects of these two cases are discussed in detail as follows.

In the second case, the pore blocking resistance during the filtration is measured by observing the nature of the flux decline. If the initial (short term) flux decline is rapid, it envisaged that some of the membrane pores are getting blocked completely or partially leading to rapid flux decline. The flux decline becomes gradual thereafter (long term) due to deposition of solute particles over the fouling layer. The short-term flux decline due to pore blocking is quantified as:

$$R_P = \frac{\Delta P}{\mu J(t)} - R_M \tag{13.4b}$$

The above equation is valid for $0 < t < t_{PB}$, where, t_{PB} is the time up to which the pore blocking prevails (time point at the end of rapid flux decline or the end of short term flux decline; this time point is identified for the experimental permeate flux decline data).

Resistance in Series Model Without Pore Blocking

For an industry relevant cross flow system, the growth of the fouling layer attains a steady value due to the arresting of the growth of the fouling layer over the membrane surface by the forced convection imposed by the cross-flow rate. Thus, the rate of increase of fouling resistance at any time point is proportional to the

difference between the fouling resistance at steady state and fouling resistance at that instance (De et al. 1997; Mondal and De 2018), as follows:

$$\frac{dR_F}{dt} \propto \left(R_F^S - R_F\right) \tag{13.5}$$

where, superscript *s* stands for steady state. The above expression, integrated with the initial condition, at $t = 0$, $R_F = 0$ results into:

$$R_F = R_F^S\left[1 - \exp\left(-k_g t\right)\right] \tag{13.6}$$

In the above expression, k_g is the constant of proportionality representing the parameter responsible for the rapid or slow growth of the fouling layer. Larger value of k_g indicates faster growth rate of the fouling layer. A plot of $\ln\left[\frac{R_F^S}{R_F^S - R_F}\right]$ against 't' indicates a straight line passing through the origin and the slope of this line gives the value of k_g. The fouling resistance at the steady state ($R_F{}^S$) is estimated from Eq. (13.2), by replacing *J(t)* by $J^s(t)$, the steady state permeate flux. The steady state permeate flux is a strong function of the operating parameters, TMP and CFR. In general, the permeate flux increases with TMP stronger at its lower range and the increase is sluggish at higher TMP. The permeate flux is typically an increasing function of cross flow rate due to higher Reynolds number (*Re*). On the other hand, k_g is mostly a characteristic of the solution (fruit juice or plant extract) and varies weakly with the operating conditions. R_m is measured from the permeability of the membrane using Eq. (13.1) and remains constant for all experiments. Thus, the time variation of the permeate flux (*J*) can be estimated by using the calculated values of k_g and the estimated values of R_m and $R_F{}^S$ at the operating TMP using the following equation (Mondal and De 2018):

$$J\left(t\right) = \frac{\Delta P}{\mu\left[R_m + \left\{R_F^S\left(1 - \exp(-k_g t)\right)\right\}\right]} \tag{13.7}$$

As discussed above, the steady-state fouling resistance is a function of different operating conditions and can be expressed in terms of TMP and Reynolds number. This model was used by Mondal and De to quantify the flux decline during the microfiltration of green tea extract with an aim to enrich the bioactive compound EGCG (Mondal and De 2018). The experiments were conducted in hollow fiber configuration and the variation TMP in that study was in the range of 35 to 172 kPa and that of *Re* was from 94 to 282. The functional variation of the steady-state fouling resistance was described through a correlation using the experimental data as (Mondal and De 2018):

$$\frac{R_F^S}{R_M} = \left(0.34 - 2.72\times10^{-4}\,\mathrm{Re}\right)\exp\left(1.148\times10^{-4}\,\Delta P\right) \tag{13.8}$$

The values of k_g were estimated as described earlier and found to vary in a narrow range 0.001 and 0.0017 s^{-1} and an average value of 0.0015 s^{-1} was considered. Thus, the overall design equation of permeate flux at a given instant for any operating condition was presented as (Mondal and De 2018):

$$J(t) = \frac{3.6\times10^{6}\,\Delta P}{\mu R_m\left[\begin{array}{l}1+\left(0.34-2.72\times10^{-4}\,\mathrm{Re}\right)\exp\left(1.148\times10^{-5}\,\Delta P\right)\\ \times\left\{1-\exp\left(-0.0015t\right)\right\}\end{array}\right]} \tag{13.9}$$

The permeate flux at the steady state (J^s) can be obtained from Eq. (13.9) by substituting$t \to \infty$.The limiting permeate was therefore determined using Eq. (13.9) by equating $\frac{dJ^s}{d\varnothing P}$ to zero. The resultant equation provides a trajectory of $\Delta P$and Re so that the limiting steady state permeate flux (limiting flux is defined as the flux that does not increase beyond a particular ΔP, termed as ΔP_{lim}) can be achieved (Bacchin et al. 2006; Field and Pearce 2011; Mondal and De 2018). Thus, the interrelation of $\Delta P_{\mathrm{lim}}$and *Re* for such limiting flux condition was:

$$\left[1.148\times10^{-5}\,\Delta P_{\mathrm{lim}} - 1\right]\exp\left(1.148\times10^{-5}\,\Delta P_{\mathrm{lim}}\right) = \frac{1}{0.34 - 2.72\times10^{-4}\,\mathrm{Re}} \tag{13.10}$$

The above relation provides a combination of TMP and *Re* that provides the limiting permeate flux. Using the above equation one can select a TMP at a particular *Re* number so that the maximum (limiting) permeate flux is obtained. At this point, the concept of threshold TMP may also be mentioned for better clarity. The steady state permeate flux increases with TMP at a particular *R*e and 'threshold TMP' is defined as the maximum TMP until the flux-TMP relation is linear (Bacchin et al. 2006; Field and Pearce 2011; Mondal and De 2018). Thus, the threshold TMP is always less than the limiting TMP. At a particular *Re*, permeate flux cannot be increases beyond limiting TMP. During microfiltration of tea extract, the variation of the steady state permeate flux with TMP at different *Re* is shown in Fig. 13.1(a) that shows excellent agreement of the calculated flux values with the experimental results. Also, the effect of TMP is more pronounced compared to *Re*. The limiting and threshold TMP calculated as discussed (Eq. 13.10) are plotted against *Re* in Fig. 13.1b. The limiting TMP increases slightly from 141 to 147 kPa with the increase in *Re* from 94 to 282 which indicates that the limiting TMP is delayed at higher *Re*. The threshold TMP also increases with *Re* at a faster rate and at higher *Re* approaches the limiting TMP.

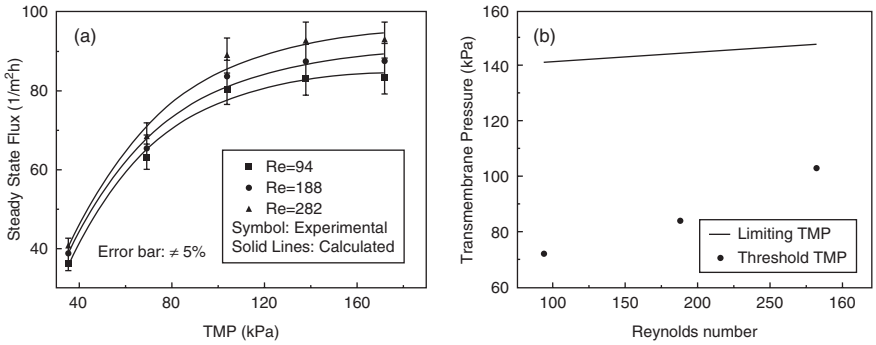

Fig. 13.1 Variation of (**a**) steady state flux with TMP at different *Re* and (**b**) limiting and threshold TMP with *Re*. (Reproduced from (Mondal and De 2018) with permission from Elsevier Science and Technology Copyright 2018)

Resistance in Series Model with Pore Blocking

Roy et al., have used the resistance in series model for quantifying the flux decline during ultrafiltration of Stevia extract using novel cellulose acetate pthalate-polyacrylonitrile blend membranes (Roy and De 2015). Their model considered additional resistance component (pore blocking, R_P) corresponding to the irreversible fouling, which was neglected in the model presented in the preceding section due to their small magnitude. The experimental permeate flux decline data provide a clue whether the pore blocking resistance, R_p needs to be considered or not. If there is a rapid decline of the permeate flux in initial few minutes of the experiments followed by a gradual decline that indicates that the membrane pore blocking by the solutes is prevalent during initial period of the filtration causing rapid flux decline in short term. Once pores are blocked, the solutes start depositing over the membrane surface growing with time slowly leading to the gradual flux decline in the long term. According to the study of Roy and De, such experimental flux decline trend was observed (Roy and De 2015). They observed that pore blocking was prevalent up to 125 s from the start of the experiments for various operating conditions. As discussed earlier, the pore blocking resistance during N^{th} experiment was estimated as follows:

$$R_P^N = \frac{\Delta P}{\mu J_w^N} - R_M^N \tag{13.11}$$

The above equation is valid for $0 < t < t_{PB}$, where t_{PB} is 125 s. Therefore, the overall flux decline during N^{th} is presented as:

$$J = \frac{\Delta P}{\mu\left(R_m^N + R_P^N(t)\right)} \quad \text{for} \quad 0 \le t \le t_{PB} \tag{13.12}$$

$$= \frac{\Delta P}{\mu\left(R_m^N + R_F^N\left(t - t_{PB}\right)\right)} \quad \text{for} \quad t_{PB} < t$$

The fouling resistance is expressed as (Roy and De 2015),

$$R_F^N(t) = R_F^{SN} - \left(R_F^{SN} - R_{PB}^N\left(t_{PB}\right)\right)\exp\left(-k_g\left(t - t_{PB}\right)\right) \tag{13.13}$$

It is interesting to note that the variation of membrane hydraulic resistance with number of experiments was correlated as:

$$R_m^N\left(m^{-1}\right) = 8.8\times10^{12}\,N^{0.42} \tag{13.14}$$

According to their study, the pore blocking resistance and the steady state fouling resistance had a trend with TMP and *Re* according to the following correlations (regressed over all the experiments),

$$\frac{R_{PB}^N}{R_m^N} = \left(2.4\times10^{-5} - 2.5\times10^{-7}\,\Delta P + 6.9\times10^{-10}\,\Delta P^2\right)\left(1.5\times10^5 - 0.6\,\mathrm{Re}\right) \tag{13.15}$$

$$\frac{R_F^{SN}}{R_m^N} = \left(40.4 - 0.26\Delta P + 4.9\times10^{-4}\,\Delta P^2\right)\exp\left(-1.2\times10^5\,\mathrm{Re}\right) \tag{13.16}$$

The steady state permeate flux for N^{th} experiment ($t \to \infty$) was expressed as follows:

$$J^{SN} = \frac{3.6\times10^9\,\Delta P}{\mu R_m^N\left[1 + \left(40.4 - 0.26\Delta P + 4.9\times10^{-4}\,\Delta P^2\right)\exp\left(-1.2\times10^5\,\mathrm{Re}\right)\right]} \tag{13.17}$$

where, the steady state flux is expressed as L/m^{2}h and $\Delta P$is in kPa, R_m^N is m^{-1} andμ is in Pa.s. The limiting conditions were obtained as explained earlier ($\frac{dJ^{SN}}{d\Delta P} = 0$) and the relationship was given below.

$$\Delta P_{\lim}\left(kPa\right) = 45.3\sqrt{40 + \exp\left(1.23\times10^{-5}\,\mathrm{Re}\right)} \tag{13.18}$$

It was observed that the fouling resistance is a strong function of TMP but a weak function of *Re* (Roy and De 2015). The experimental data (scattered points) and modelled values (continuous line) are plotted in Fig. 13.2. The variation of steady-state permeate flux with TMP at different *Re* shows excellent corroboration between experimental and calculated values. The results presented in Fig. 13.3 support the previous observation that increase in *Re* delays the onset of limiting flux. The

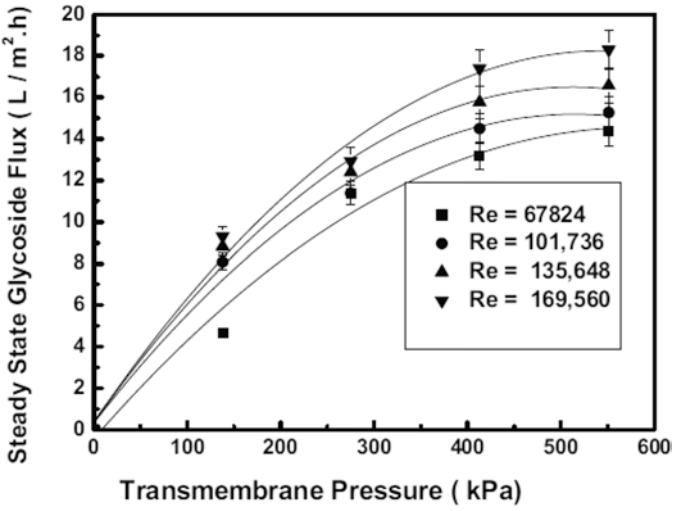

Fig. 13.2 Variation in steady state permeate flux with TMP and *Re*. (Reproduced from (Roy and De 2015) with permission from Elsevier Science and Technology Copyright 2015)

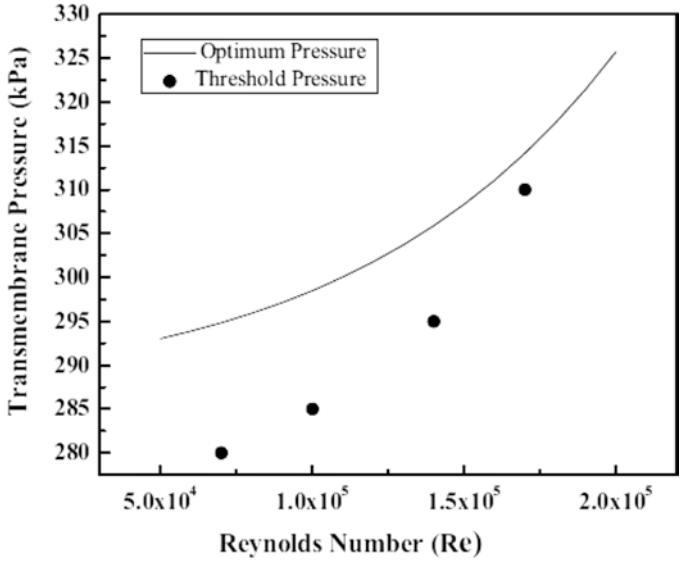

Fig. 13.3 Variation in limiting (Optimum) pressure and threshold. (Reproduced from (Roy and De 2015) with permission from Elsevier Science and Technology Copyright 2015)

threshold TMP is also showing similar trend with *Re*. The various parameters thus calculated can be an appropriate guide for selecting suitable operating conditions and design of scale up for specific applications.

2.2 Semi-empirical Models

Identification of the fouling mechanism is the first step in the process of developing any model from first principles. This can be done by carrying out filtration experiments at constant pressure either in a dead-end batch cell or a continuous cross flow cell. This section elaborates the different models available and their applications. The salient features of these models are they are semi-empirical in nature because they have a theoretical background for formulation. Some model parameters are estimated from the experimental data, imparting semi-empirical characteristics. However, the models are for quantification of the permeate flux decline behaviour, not for the estimation of the permeate concentration as a function of time.

2.2.1 Constant Pressure Dead End Filtration Cell (Batch Process): Hermia's Model

The prevalent flux decline mechanism can be identified by analyzing the characteristic curves of dead end batch cell using the equation (Hermia 1982; Ho and Zydney 2000)

$$\frac{dt^2}{dV^2} = k\left(\frac{dt}{dV}\right)^n \tag{13.19}$$

where, t and V are cumulative time and volume of the filtrate and k and n are model specific parameters. The parameter n assumes different values for various modes of filtration. It is 0 for the cake filtration, 1 for the intermediate pore blocking, 1.5 for the standard pore blocking and 2.0 for the complete pore blocking (Mondal et al. 2013). A schematic of different types of pore blocking mechanisms is presented in Fig. 13.4.

Complete Pore Blocking This is more common with solutes having molecular weight higher than the molecular weight cut-off (MWCO) of the membrane and the solute particles completely block the pores of the membrane (Fig. 13.4a). The permeate flux profile is given by (Bowen et al. 1995; Mondal et al. 2013)

$$J = J_0 \exp\left(-k_1 t\right) \tag{13.20}$$

where, J_0 and J are the initial and the permeate flux at any time t. k_1 is a constant related to the solute property.

Intermediate Pore Blocking In this mechanism, the particles do not have complete access to the pore and hence, deposit partly over already deposited solute particle (Fig. 13.4b). The permeate flux can be represented by (Bowen et al. 1995; Mondal et al. 2013)

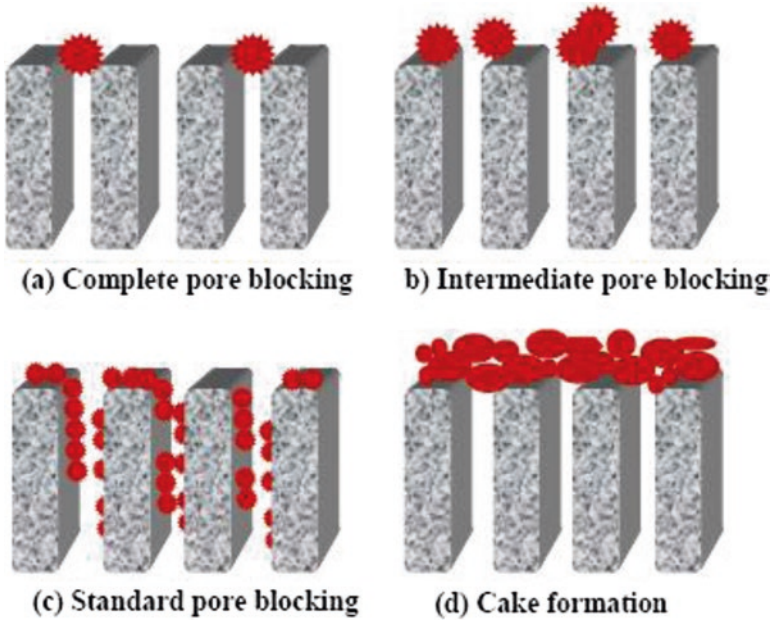

Fig. 13.4 Schematic of different pore blocking mechanisms. (**a**) Complete pore blocking. (**b**) Intermediate pore blocking. (**c**) Standard pore blocking. (**d**) Cake formation (Aghdam et al. 2015)

$$J = \frac{J_0}{\left(1 + k_2 t\right)} \tag{13.21}$$

k_2 is the model constant.

Standard Pore Blocking In this mechanism, solute particles deposit on the walls of the pores and therefore reduce the pore volume (Fig. 13.4c). The permeate flux decline can be represented as (Bowen et al. 1995; Mondal et al. 2013)

$$J = \frac{J_0}{\left(1 + \phi t\right)^2} \tag{13.22}$$

where, ϕ is the model constant.

Cake Filtration After initial filtration, the solute particles deposit over the blocked pores and form multiple layers of the solutes forming a cake layer over the membrane surface (Fig. 13.4d). Subsequently, this layer acts as the separation media and the porosity of this layer determines the permeate flux and quality. This mechanism is apparent at slightly later stage of filtration. The permeate flux during cake filtration is given as (Bowen et al. 1995; Mondal et al. 2013)

$$\frac{1}{J^2} = \frac{1}{J_0^2} + k_c t \tag{13.23}$$

Hermia's model has been extensively used by several researchers during separation of bioactive compounds from fruit juices using batch mode membrane separation processes. Mondal et al., have used the model to study the fouling mechanism during filtration of Stevia extract suing ultrafiltration membranes (Mondal et al. 2013). They reported both intermediate pore blocking and cake filtration equally important for 100 kDa membrane. However, cake filtration mechanism was observed to be the dominant mechanism for lower MWCO ultrafiltration membranes, whereas pore blocking was more prevalent with the increase in MWCO of the membrane. They established that with the increase in membrane pore size, the probability of the pore blocking was increased. This is also supported by the findings of Reis et al., that indicates pore blocking as the dominant fouling mechanism for membranes with higher MWCO during the filtration of Stevia extract using ceramic microfiltration membranes (Reis et al. 2009). Mondal et al. have reported marginal variation in the ratio of cake resistance (R_c) to membrane hydraulic resistance (R_m) with transmembrane pressure (less than ±10%) indicating formation of an incompressible cake layer (Mondal et al. 2013). In case of compressible cake, R_c is a function of TMP, which is demonstrated in subsequent sections of this chapter. A response surface model was developed to estimate $\frac{R_c}{R_m}$ as a function of filtration time and MWCO of the membrane (Mondal et al. 2013). The model was observed to be in excellent agreement with the experimental data and shows an increase in $\frac{R_c}{R_m}$ with time due to the increase in cake layer thickness. This model can be used to predict the life of the membrane using pilot run data.

Aghdam et al. studied the filtration of pomegranate juice using membrane separation and identified cake filtration as the prevalent fouling mechanism (Aghdam et al. 2015). They reported the value of k_c with and without the application of ultrasound waves and established that even with the application of ultrasound waves, the fouling mechanism remained as cake formation. However, the intensity of cake formation was much lower in case of ultrasound waves. Gerke et al. attempted clarification of Yerba mate extract, a plant native to South America used as a digestive drink and reported that the cake filtration was the dominant mode of flux decline (Gerke et al. 2017). Other than internal pore blocking model, all other models were reported to be very close and as already discussed, in many cases they were very close to select the best fit. They also measured the relative magnitudes of different components of resistance using resistance in series model as explained in Sect. 2.1. The hydraulic resistance of the membrane remained unaltered with the operating conditions, whereas the resistance due to fouling varied with the operating pressure and flow rate. The variation of these parameters can be studied and used for design of scaled up version of the filtration system and also to determine the suitable operating conditions.

Rai et al. have studied the mechanism of permeate flux decline during microfiltration of watermelon juice in an unstirred batch cell using Hermia's model (Rai

et al. 2010). The experimental data was fit to the four models represented by Eqs. (13.20) to (13.23) in their linear form and the goodness of fit was compared using correlation coefficient as shown in Fig. 13.5. It was evident from the graph that cake filtration is the dominant mechanism caused by the build up of suspended solids and

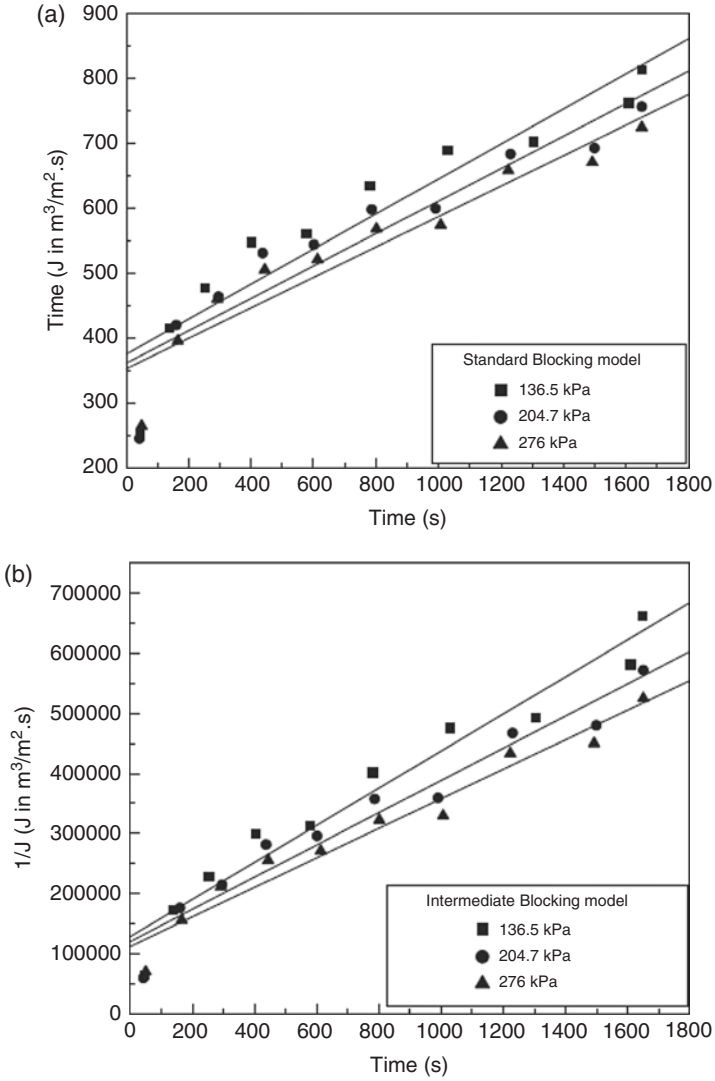

Fig. 13.5 Variation of (**a**) $n = 1.5$; $R^2 = 0.49$ to 0.52 $\frac{1}{\sqrt{J}}$ (**b**) $n = 1$; $R^2 = 0.57$ to 0.60 $\frac{1}{J}$ (**c**) $n = 2$; $R^2 = 0.37$ to 0.44 $\ln\left(\frac{1}{J}\right)$ and (**d**) $n = 0$; $R^2 = 0.96$ to 0.98 $\frac{1}{J^2}$ with time during microfiltration of watermelon juice in an unstirred batch cell. (Reproduced from (Rai et al. 2010) with permission from Springer Nature BV Copyright 2010)

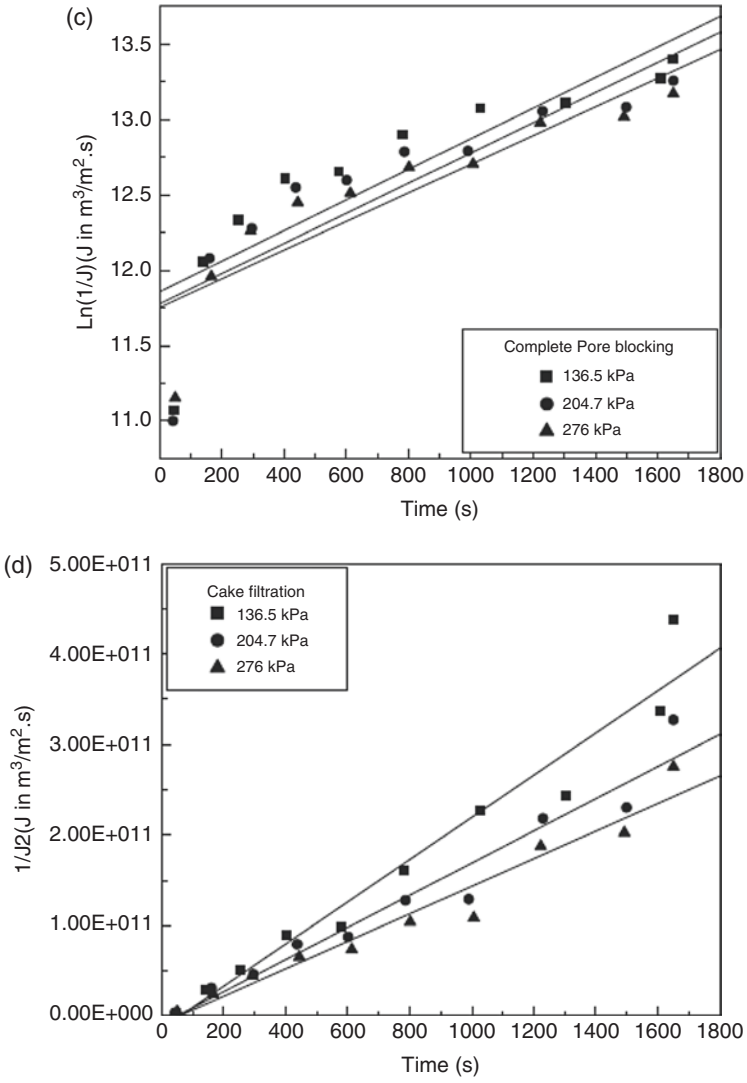

Fig. 13.5 (continued)

cell debris on the membrane surface. It may be mentioned that although the batch filtration is not industrially relevant, these models can be used to identify the mechanisms. However, they are useful for production of some high purity bioactive compounds that are expensive, and a low throughput is sufficient. Moreover, as mentioned previously, the modelling of batch filtration data for various models proposed by Hermia are sometimes too close to be differentiated statistically. In those cases, other physico-chemicals characterizations, like, scanning electron

microscopy of the cross section and top surface of the membrane before and after filtration with and without cleaning, as well as fourier transform infra red spectroscopy of the fresh and fouled membrane surface. These analyses would result into definite leads to understanding the prevailing mechanism of the membrane fouling (Jain et al. 2018).

2.2.2 Constant Pressure Cross Flow Filtration (Continuous Cross Flow Process): Field's Model

The flux decline models by Hermia for constant pressure dead end filtration is not applicable for cross flow filtration due to the presence of steady state flux (Mondal and De 2010). These models were modified by Field et al. for cross flow filtration (Field et al. 1995). Field's model was further used by several researchers for analyzing the filtration of bioactives using membrane separation (De Barros et al. 2003; Rai et al. 2006). According to this model, various mechanisms can be expressed by the generalized equation (Field et al. 1995)

$$\frac{dJ}{dt} = -k'\left(J - J^s\right)J^{2-m} \tag{13.24}$$

Similar to Eq. (13.19), the value and unit of k' and m depend on the mechanism of flux decline. For complete pore blocking ($m = 2$) and the flux decline is given by (Field et al. 1995; Rai et al. 2006):

$$J = J^s + \left(J_0 - J^s\right)e^{-k't} \tag{13.25}$$

For partial pore blocking ($m = 1$), the flux decline is expressed as:

$$k't = -\ln\frac{\left(J - J^s\right)J_0}{\left(J_0 - J^s\right)J} \tag{13.26}$$

For cake filtration ($m = 0$), the expression for flux decline is:

$$k't = \frac{1}{J^{s2}}\left[\ln\left(\frac{J}{J_0}\frac{\left(J_0 - J^s\right)}{\left(J - J^s\right)}\right) - J^s\left(\frac{1}{J} - \frac{1}{J_0}\right)\right] \tag{13.27}$$

Rai et al. used this model to analyse the cross flow ultrafiltration of depectinized mosambi juice (Rai et al. 2006). They observed that partial or complete pore blocking in the first few minutes of filtration followed the cake filtration model. However, they analysed considering only one mechanism for the entire duration and reported

the cake filtration as the dominant mechanism. Barros et al., studied the fouling behaviour of cross flow ultrafiltration of depectinized pineapple juice using the modified Field's model (De Barros et al. 2003). Similar analysis was carried out by Cassano et al. during the filtration of blood orange juice and reported standard pore blocking at lower *Re* and complete pore blocking at higher *Re* (Cassano et al. 2007).

All these studies reported the presence of two fouling mechanisms but analyzed using a single model throughout the entire duration of the filtration. In an actual filtration, it is likely that more than one mechanism act sequentially with a smooth transition at a particular time. In this regard, Mondal et al. have contributed significantly by proposing integrated models for characterization of the sequential fouling mechanisms (Mondal and De 2009, 2010). In the first work, they proposed the sequential occurrence of complete pore blocking followed by the cake filtration (Mondal and De 2009). With a rigorous mathematical treatment, they have developed a phase space defining three non-dimensional parameters that involved the combinations of the operating conditions as well as the model constants for the fouling mechanisms (Fig. 13.6a). The phase space clearly identified the three regions, the dominant complete pore blocking, comparable complete pore blocking and cake filtration and dominant cake filtration. Thus, one simply needs to evaluate these parameters from the operating conditions and the model parameters and confirm the prevalent membrane fouling mechanism. They gave a demonstration of the experimental data of pineapple juice filtration by Barros et al., and showed that the filtration was cake formation controlling at lower TMP and at higher TMP both cake filtration and complete pore blocking were important for the ceramic membrane used for the filtration (De Barros et al. 2003). Similar analysis was carried out for a sequential fouling by intermediate pore blocking and cake filtration (Mondal and De 2010). In this work, they also identified three non-dimensional parameters in terms of the operating conditions and the model parameters and generated a phase space plot (Fig. 13.6b) identifying the intermediate pore blocking controlling, both equally important and cake filtration controlling regions. They demonstrated this model for the filtration of the oily wastewater solution. They concluded that the increase in TMP led to dominant pore blocking, whereas increase in cross flow rate favoured cake controlling region, although the region of pore blocking controlling and both mechanisms controlling were really narrow. Therefore, by the generated phase space plot of sequential fouling mechanisms, one can identify the operating conditions so that the filtration can be belonging to the desirable controlling regime so that the permeate flux decline can be minimized.

A generalized formulation considering the simultaneous occurrence of complete pore blocking and intermediate pore blocking followed by cake filtration is useful in understanding the pore blocking mechanism. It is reasonable to consider that pore blocking proceeds from the beginning of the experiment up to a certain time of operation (t_{PB}) beyond which cake formation starts. Once the cake formation starts, solute particles start depositing over the membrane surface and there is hardly any scope of pore blocking to take place. As described earlier (Eq. 13.19), in the case of complete and intermediate pore blocking (till $t < t_{\mathrm{PB}}$), the flux decline is described by Eqs. (13.20) and (13.21).

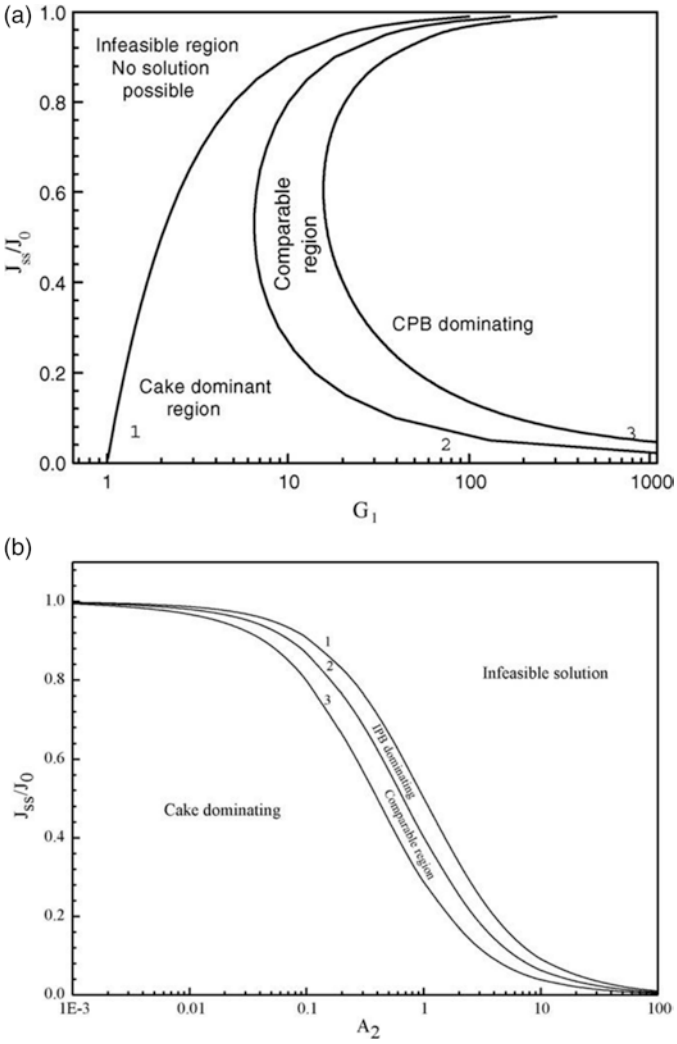

Fig. 13.6 Dominant filtration regimes in case of (**a**) complete pore blocking followed by cake formation (Reproduced from (Mondal and De 2009) with permission from Elsevier Science and Technology Copyright 2009) and (**b**) intermediate pore blocking followed by cake formation. (Reproduced from (Mondal and De 2010) with permission from Elsevier Science and Technology Copyright 2010)

In terms of resistance, the pore blocking resistances were defined as,

$$R^*_{CPB} = \frac{R_{CPB}}{R_m} = \exp\left(k_1 t\right) - 1 \tag{13.28}$$

$$R^*_{IPB} = \frac{R_{IPB}}{R_m} = J_0 k_2 t \tag{13.29}$$

The growth of cake resistance (for $t < t_{PB}$) is restricted due to external cross flow of the feed. In this case, the flux decline equation is obtained from Eq. (13.24) (Field et al. 1995). In terms of resistance, the expression of the flux becomes at $t > t_{PB}$,

$$J = \frac{\Delta P}{\mu\left[R_m + R_{CPB}\left(t_{PB}\right) + R_{IPB}\left(t_{PB}\right) + R_c\left(t - t_{PB}\right)\right]} \tag{13.30}$$

The above equation can be expressed in terms of non-dimensional resistances as:

$$J = \frac{J_0}{\left[1 + R^*_{CPB} + R^*_{IPB} + R^*_c\right]} \tag{13.31}$$

Permeate flux at time $t = t_{PB}$ is obtained as:

$$J_{t_{PB}} = \frac{J_0}{\left[1 + R^*_{CPB}\left(t_{PB}\right) + R^*_{IPB}\left(t_{PB}\right)\right]} \tag{13.32}$$

Combining the above two equations, the following expression is obtained,

$$J = \frac{J_{t_{PB}}}{1 + R^{**}_c} \tag{13.33}$$

where, R^{**}_c is defined as:

$$R^{**}_c = \frac{R^*_c}{\left[1 + R^*_{CPB}\left(t_{PB}\right) + R^*_{IPB}\left(t_{PB}\right)\right]} \tag{13.34}$$

Taking the derivative of equation Eq. (13.34) with respect to t, the rate of flux change is obtained as:

$$\frac{dJ}{dt} = -\frac{J_{t_{PB}}}{\left(1 + R^{**}_c\right)^2}\frac{dR^{**}_c}{dt} \tag{13.35}$$

Using Eqs. (13.31) and (13.34), the governing equation of cake resistance is obtained,

$$\frac{dR_c^{**}}{dt} = \frac{J_{t_{PB}} k_c}{\left(1+R_c^{**}\right)}\left[J_{t_{PB}} - J_{ss}\left(1+R_c^{**}\right)\right] \tag{13.36}$$

At steady state, $\frac{dR_c^{**}}{dt} = 0$ and therefore, from Eq. (13.36), the following criterion at the steady state is obtained,

$$J_{t_{PB}} = J_{ss}\left(1+R_{cs}^{**}\right) \tag{13.37}$$

Considering Eqs. (13.31), (13.32), (13.33), (13.34), Eq. (13.37) can be transformed as follows:

$$R_c^{*} = \frac{J_0}{J_{ss}} - \left(1+R_{CPB}^{*}+R_{IPB}^{*}\right) \tag{13.38}$$

From the continuity equations at $t = t_{PB}$, the flux obtained through both the mechanisms would be equal, which implies,

$$\left.\frac{dJ}{dt}\right|_{t=t_{PB}-\Delta t} = \left.\frac{dJ}{dt}\right|_{t=t_{PB}+\Delta t} \tag{13.39}$$

Using Eqs. (13.20), (13.21) and (13.23) in Eq. (13.39), we obtain,

$$k_1 \exp\left(k_1 t_{PB}\right) + J_0 k_2 = J_0 k_c \left(J_{t_{PB}} - J_{ss}\right) \tag{13.40}$$

Selecting non-dimensional parameters as $k_1 t_{PB} = \tau, \frac{k_c J_0^2}{k_1} = G_1$ and $\frac{J_0 k_2}{k_1} = G_2$, Eq. (13.40) can be written as:

$$\exp\left(\tau\right) + G_2 = G_1\left(\frac{1}{\exp\left(\tau\right)+G_2\tau} - \frac{J_{ss}}{J_0}\right) \tag{13.41}$$

Comparison of Resistances Since, from Eqs. (13.28) and (13.29), complete and intermediate pore blocking resistances are quantified. Therefore,

$$\frac{R_c^{*}}{R_{IPB}^{*}} = \frac{1}{J_0 k_2 t_{PB}}\left[\frac{J_0}{J_{ss}} - \exp\left(k_1 t_{PB}\right)\right] - 1 \tag{13.42}$$

In terms of non-dimensional terms (using Eq. 13.41) Eq. (13.42) can be transformed to

$$\frac{R_c}{R_{IPB}} = \frac{\left(e^{\tau} + G_2\right)\left(e^{\tau} + G_2\tau\right)^2}{G_2\tau\left[G_1 - \left(e^{\tau} + G_2\right)\left(e^{\tau} + G_2\tau\right)\right]} \tag{13.43}$$

Similarly, $\frac{R_c}{R_{IPB}}$, $\frac{R_c}{R_{CPB} + R_{IPB}}$ and $\frac{R_{CPB}}{R_{IPB}}$ can be obtained as:

$$\frac{R_c}{R_{CPB}} = \frac{1}{\left(e^{\tau} - 1\right)}\left[\frac{G_1 G_2\tau + \left(e^{\tau} + G_2\right)\left(e^{\tau} + G_2\tau\right)}{G_1 - \left(e^{\tau} + G_2\right)\left(e^{\tau} + G_2\tau\right)}\right] \tag{13.44}$$

$$\frac{R_c}{R_{CPB} + R_{IPB}} = \frac{1}{\left(e^{\tau} + G_2\tau - 1\right)}\left[\frac{\left(e^{\tau} + G_2\right)\left(e^{\tau} + G_2\tau\right)^2}{G_1 - \left(e^{\tau} + G_2\right)\left(e^{\tau} + G_2\tau\right)}\right] \tag{13.45}$$

$$\frac{R_{CPB}}{R_{IPB}} = \frac{e^{\tau} - 1}{G_2\tau} \tag{13.46}$$

Relative dominance of the each of these resistances can be compared by setting the values of the ratios to be greater or less than unity.

Infeasible solution will result when $\frac{R_c}{R_{CPB}}$, $\frac{R_c}{R_{IPB}}$, $\frac{R_c}{R_{CPB} + R_{IPB}}$ and $\frac{R_{CPB}}{R_{IPB}} < 0$. Considering Eqs. (13.43), (13.44), (13.45), and (13.46), the necessary and sufficient condition for infeasibility is:

$$\frac{G_1}{e^{\tau} + G_2} < e^{\tau} + G_2\tau < 1 \tag{13.47}$$

for all positive real solutions of τ from Eq. (13.41).

Figure 13.7 shows the infeasibility boundary of τ in the parameter space by solving Eq. (13.41). The region above the curves shows the realistic solution of τ for different combinations of G_1 and G_2. So, for existence of the fouling mechanisms one has to select G_1, G_2 and J_{ss}/J_0 suitably. Solution of τ in the feasible domain is presented in Fig. 13.8. Using the values of τ and the parameters (G_1, G_2 and J_{ss}/J_0) relative dominance of the blocking mechanism during filtration can be identified, for the instances of only complete pore blocking followed by cake formation and only intermediate pore blocking followed by cake filtration (Mondal and De 2009, 2010). The regimes of dominant fouling mechanisms are already shown in Fig. 13.6. An operator can preset these values of the parameters within the feasible boundary of τ to operate the cross-flow filtration in a preferential fouling regime.

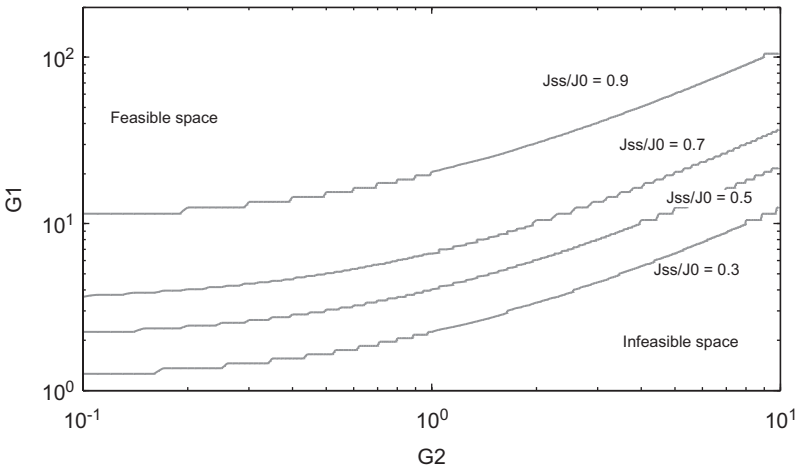

Fig. 13.7 Infeasibility regimes of solution of τ in the parameter space

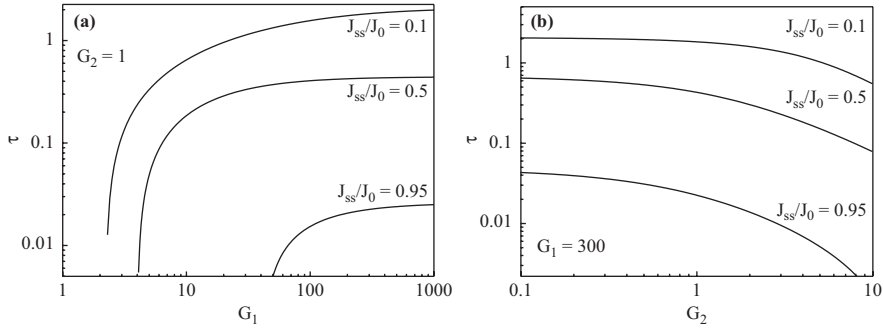

Fig. 13.8 Real solution of τ by solving Eq. (13.41) in the feasible domain of G_1, G_2 and J_{ss}/J_0 varying (**a**) G_1, keeping G_2 fixed and (**b**) G_2, keeping G_1 fixed

2.3 Transport Phenomena-Based Models

This section presents detailed discussion on modelling of ultrafiltration process derived from the first principles. They are broadly divided into two subsections, namely, (1) modelling of permeate flux and concentration and (2) modelling of permeability hysteresis.

2.3.1 Modelling of Permeate Flux and Concentration

The class of the models discussed earlier are incapable to predict the permeate flux and permeate concentration simultaneously. This can be achieved by the transport phenomena-based models. The main aim of ultrafiltration of fruit juices and

bioactive compounds is to remove different proteins, pectin, microbes and maximum permeation of nutrients and minerals. As discussed, the major challenge during this is the membrane fouling resulting in inconsistency in throughput as well as product quality. Mondal et al., have attempted to model the performance of the ultrafiltration of Stevia extract in cross flow (Mondal et al. 2013). The complexity arising in case of real-life effluents is the fact that in these cases, the feed stream comprises of a mixture of components and the transport properties viz., diffusivities and gel properties are not known. Mondal et al. have used the experimental results to estimate these parameters through optimization techniques and flux decline as well as concentration profile of the permeate stream are predicted using the model (Mondal et al. 2012a, 2013). This section is divided into three subsections viz., (1) modelling for the total recycle mode and (2) batch concentration mode.

Total Recycle Mode

Steady State Model

Mondal et al. assumed that the Stevia extract was a mixture of high molecular weight (HMW) components (proteins, polysaccharides etc.,) and low molecular weight (LMW) solutes (Steviosides etc.,) (Mondal et al. 2013). The HMW solutes were retained by the membrane forming a gel layer on the membrane surface. LMW solute like Stevioside (804.87 g/mol) was partially retained by the gel layer. The system under consideration along with the co-ordinate system is shown in Fig. 13.9, where, $y = 0$ and $y = \delta$ signify the two interfaces of the concentration boundary layer and L is the gel layer thickness. $y = 0$ indicates the bulk of the solution and $y = \delta$ shows the concentration boundary layer and gel layer interface.

All the experiments were conductedin rectangular cross flow set up and both permeate and retentate were recycled back to the feed tank. The HMW solute was the main constituent of the gel layer and hence, the steady state permeate flux (J) was expressed from the classical film theory as:

$$J = k_f \ln\left(\frac{C_{1g}}{C_{1b}}\right) \tag{13.48}$$

In the above expression, C_{1g} and C_{1b} are concentration of component 1 (HMW solutes) in gel layer and bulk, respectively. k_f is the mass transfer coefficient and can be estimated from the standard Sherwood number correlations, as follows:

$$Sh = \frac{k_f d_e}{D_1} = 1.85\left(\mathrm{Re}Sc\frac{d_e}{l}\right)^{\frac{1}{3}} \quad for\ \mathrm{Re} < 2100 \tag{13.49}$$

where, l is the characteristic length of the system, *Sh, Re*, and *Sc* are Sherwood, Reynolds, and Schmidt number corresponding to component 1. In an ideal gel controlling filtration model, the mass transfer coefficient is independent of TMP (Trettin and Doshi 1980). But several literatures reported that the mass transfer coefficient shows a weak dependence on TMP for membrane systems (Gekas and Hallström

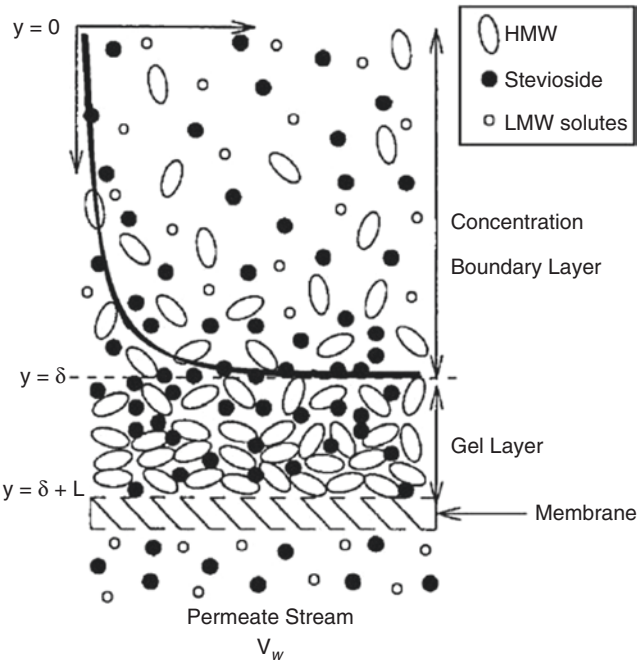

Fig. 13.9 Schematic of transport of mixed solutes through ultrafiltration membrane. (Reproduced from (Mondal et al. 2012b) with permission from Elsevier Science and Technology Copyright 2012)

1987; Johnston and Deen 2002; Mondal et al. 2011). Thus, the following expression of permeate flux was proposed.

$$J = k_{f1} \ln\left(\frac{C_{1g}}{C_{1b}}\right) \tag{13.50}$$

where, $k_{f1} = k_f(a + b\Delta P)$. The four parameters, namely, a, b, C_{1g} and D_1 (diffusivity of component 1) were estimated through optimization routine by minimizing the sum of square of errors (S_0) of permeate flux defined as:

$$S_0 = \sum_{i=1}^{N_{\exp}} \left[\frac{J^i_{\exp} - J^i_{cal}}{J^i_{\exp}}\right]^2 \tag{13.51}$$

In the above equation, $J_i^{\exp}$ and J_i^{cal} were the experimental and calculated flux of the ith experiment. The estimated parameters were $D_1 = 3.7 \times 10^{-11}$ m^2/s, $C_g = 51.5$ kg/m^3, $a = 0.35$ and $b = 1.22\text{x}10^{-6}$ Pa^{-1}. A comparative analysis of the model predicted permeate flux with experimental results is presented in Fig. 13.10 that shows reasonable agreement between the two (± < 15%).

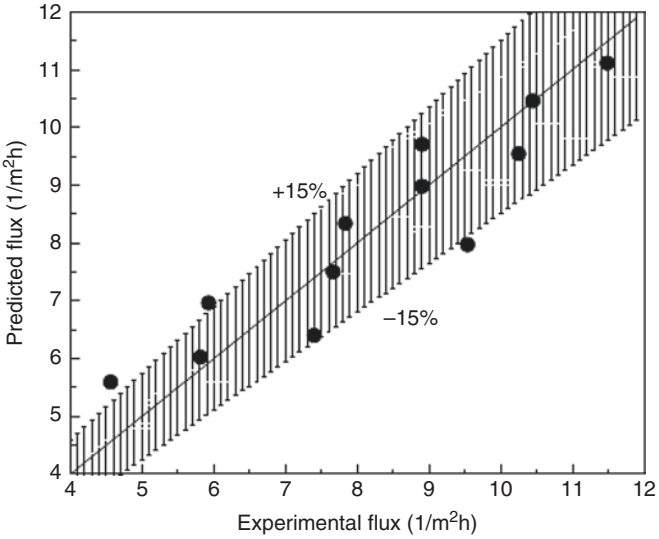

Fig. 13.10 Comparison of model predicted flux with experimental results for steady state ultrafiltration in total recycle mode. (Reproduced from (Mondal et al. 2012b) with permission from Elsevier Science and Technology Copyright 2012)

Transient Model

The mass balance of HMW solutes in the mass transfer boundary layer ($0 < y < \delta$) as shown in Fig. 13.6 results in the following equation de (De and Bhattacharya 1997)

$$\rho_g\left(1-\varepsilon_g\right)\frac{dL}{dt} = J_w C_1 - D_1\frac{dC_1}{dy} \tag{13.52}$$

where, $\varepsilon_g$and ρ_g are porosity and density of the gel layer. Integrating the above equation, within the limits, $y = 0$, $C_1 = C_{1b}$ and $y = \delta$, $C_1 = C_{1g}$ results in

$$\rho_g\left(1-\varepsilon_g\right)\frac{dL}{dt} = J_w\frac{C_{1g} - C_{1b}\exp\left(\dfrac{J_w}{k_{f1}}\right)}{1-\exp\left(\dfrac{J_w}{k_{f1}}\right)} \tag{13.53}$$

Similarly, mass balance of LMW solute (i.e., Stevioside) was carried out in the mass transfer boundary layer as well as gel layer, and following the derivation of De and Bhattacharyya, the concentration of Stevioside on the membrane surface can be expressed as (De and Bhattacharya 1997):

$$C_{2m} = \frac{C_{2b}\exp\left[J_w\left(\left(\dfrac{1}{k_{f2}}\right)+\left(\dfrac{L}{\varepsilon_g D_2}\right)\right)\right]}{\gamma_g R_{r2} + \left(1-R_{r2}\right)\left(\gamma_g - 1\right)\exp\left(\dfrac{J_w L}{\varepsilon_g D_2}\right) + \left(1-R_{r2}\right)\exp\left[J_w\left(\left(\dfrac{1}{k_{f2}}\right)+\left(\dfrac{L}{\varepsilon_g D_2}\right)\right)\right]} \tag{13.54}$$

In the above expression, $R_{r2}\left(=1-\frac{C_{2p}}{C_{2m}}\right)$ is the real retention of Stevioside and γ_g is the partition coefficient defined as $C_2(\delta^-)=\gamma_g C_2(\delta^+)$. The variation in concentration of Stevioside across the membrane results into osmotic pressure difference given as $\Delta\pi = \pi_m - \pi_p$. The osmotic pressure ($\pi$) can be expressed in terms of concentration from van't Hoff's relation $\pi=\frac{RT}{M_w}C$ that can be written as:

$$\Delta\pi=\frac{RT}{M_{2b}}C_{2m}R_{r2} \tag{13.55}$$

In the above equation, R is the universal gas constant, M_w is the molecular weight of the solute and T is the temperature in Kelvin scale. Hence, the permeate flux at any time instant can be written as

$$J_w(t)=\frac{\Delta P-\Delta\pi}{\mu\left(R_m+R_g\right)} \tag{13.56}$$

where, R_m and R_g are resistance offered by the membrane and the gel layer, respectively. According to the classical cake filtration model,

$$R_g=\beta L \tag{13.57}$$

and $\beta=\alpha(1-\varepsilon_g)\rho_g$ is a constant and the characteristic of the gel layer. α is the specific gel resistance. There are five parameters (D_2, ρ_g, β, γ_g and ε_g) to be estimated using the five algebraic equations represented by Eqs. (13.53), (13.54), (13.55), (13.56), and (13.57). R_{r2} was determined using dead end batch cell under high stirring and it was found to be 0.1. The remaining parameters were estimated by minimizing the sum of square of errors between the experimental and calculated values for permeate flux and Stevioside concentration represented as:

$$S_1=\sum_{j}^{N_2}\sum_{i}^{N_j}\left[\frac{J_{w,cal}^{ij}-J_{w,\exp}^{ij}}{J_{w,\exp}^{ij}}\right]^2+\sum_{k=1}^{N_p}\left[\frac{\overline{C}_{2p,cal}^{k}-\overline{C}_{2p,\exp}^{k}}{\overline{C}_{2p,\exp}^{k}}\right]^2 \tag{13.58}$$

In above equation, i and j represent the number of experimental data points and number of experiments, respectively. N_j represents the number of data at various time instants in *jth* experiment and N_p is the number of experiments at a particular TMP. Stevioside concentration of the cumulative permeate was measured at the end of each experiment and hence, the average Stevioside concentration in the permeate can be calculated from

$$\overline{C_{2p}}=\overline{C_{2m}}\left(1-R_{r2}\right) \tag{13.59}$$

$$\bar{C}_{2p}=\frac{1}{t}\left(1-R_{r2}\right)\int_0^t C_{2m}dt \tag{13.60}$$

where, $\overline{C_{2p}}$ and $\overline{C_{2m}}$ are time averaged concentration of Stevioside in permeate and on the membrane surface, respectively. The estimated five parameters were: $D_1 = 2 \times 10^{-11}$ m^2/s, $\varepsilon_g = 0.56$, $\rho_g = 1550$ kg/m^3, $\gamma_g = 3.15$ (averaged) and $\beta = 4.55 \times 10^{19}$ m^{-2} (Mondal et al. 2012b). The study of Mondal et al., for filtration of Stevia extract showed that the parameters, β and ε_g were invariant with pressure whereas, γ_g was observed to be varying with pressure in the range of 2.25 to 6.13 (Mondal et al. 2012b). According to their study, at higher TMP, gel layer retains more Stevioside. With the optimized parameters, the profiles of the permeate flux, Stevioside concentration, gel layer thickness and gel layer resistance were calculated. Effect of TMP and CFR on the gel layer thickness is presented in Fig. 13.11. As evident from the figure, with the progress of filtration, the gel layer thickness increases and permeate flux decreases. Finally, the gel layer growth is arrested due to the forced convection imposed by the crossflow velocity. Similarly, increase in CFR results into decrease in the growth of gel layer. Increase in gel layer thickness with TMP can be explained by the enhanced convection of gel forming solutes towards membrane surface at higher pressure.

Figure 13.12 shows the calculated and the experimental permeate flux profiles for a typical set of operating conditions. It is observed that the model adequately describes the permeate flux decline.

The predicted and experimental Stevioside concentration in the permeate for different operating conditions are presented in Table 13.1.

Mondal and De have prepared novel ultrafiltration hollow fiber membranes by blending polyvinylidene fluoride with polysulfone (PSf) for purification of polyphenols and EGCG from green tea extract (Mondal and De 2019). In their work, they also utilized the same model with satisfactory prediction of the permeate flux decline, as well as the polyphenol concentration in the permeate.

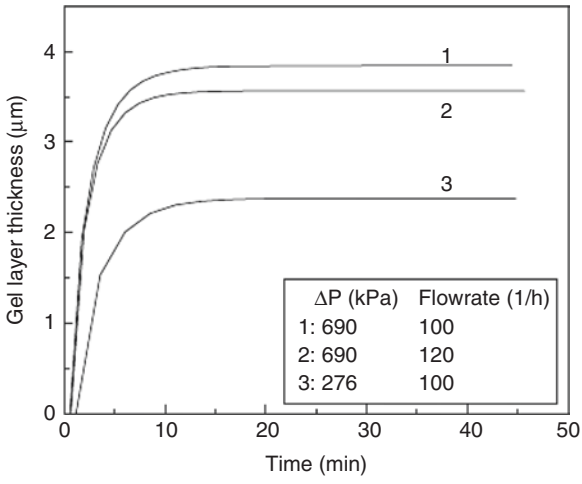

Fig. 13.11 Model predicted profile of gel layer thickness. (Reproduced from (Mondal et al. 2012b) with permission from Elsevier Science and Technology Copyright 2012)

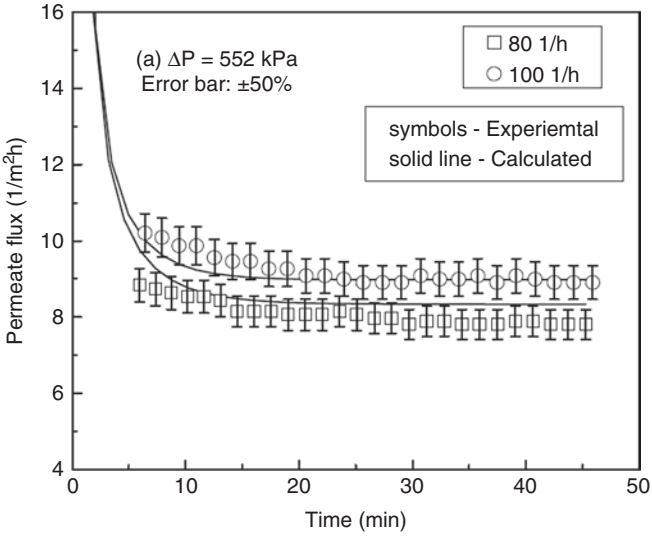

Fig. 13.12 Transient permeate flux profiles (both experimental and calculated). (Reproduced from (Mondal et al. 2012b) with permission from Elsevier Science and Technology Copyright 2012)

Table 13.1 Comparison of the experimental and predicted Stevioside concentration in the permeate for various operating conditions (Mondal et al. 2012b)

	80 LPH		100 LPH		120 LPH	
TMP (kPa)	Predicted	Experiment	Predicted	Experiment	Predicted	Experiment
276	51.6	58.0	51.4	49.0	51.3	49.0
414	43.0	45.0	42.7	43.3	42.5	40.4
552	39.3	40.5	39.0	39.7	38.9	37.3
690	29.5	29.7	29.3	31.1	29.1	27.5

Batch Concentration Mode

In this mode of operation, permeate is not recycled back but is withdrawn continuously leading to the continuous increase in concentration of the feed stream. This in turn leads to increase in gel layer thickness, which is a direct function of feed concentration. Therefore, in this mode, there is a significant flux decline as compared to total recycle mode. The total resistance to the filtration can be expressed as a sum of membrane hydraulic resistance (R_m), the resistance due to boundary layer (R_{bl}) and the gel layer resistance (R_g) (Mondal et al. 2012b).

$$R_T = R_m + R_g + R_{bl} \tag{13.61}$$

The average value of permeate flux is higher in total recycle mode than the batch mode under identical operating conditions and mass transfer coefficient is inversely

proportional to the boundary layer resistance. Therefore, mathematically, it may be expressed as $R_T^r < R_T^b$ and $k_{f1}^b < k_{f1}^r$, where, the subscripts *b* and *r* represent batch and total recycle mode, respectively. Simultaneously, due to deposition of gel layer over membrane surface the effective channel height (2*h*) decreases resulting into increased cross flow velocity (*u*). Mass transfer coefficient in batch mode can be rearranged as

$$k_f^b = \left(\frac{uD_1^2}{d_e L} \right) \tag{13.62}$$

Increase of *u* in the batch mode results into the inequality, $k_f^b > k_f^r$. The effect of TMP on the mass transfer coefficient can be written as

$$k_{f1}^b = k_f^b \left(a_b + b_b \Delta P \right) \tag{13.63}$$

Considering the overall material balance, the following equation is obtained

$$\frac{d}{dt}\left(\rho_f V \right) = -J_w A_m \rho_p \tag{13.64}$$

where, *V* is the volume of the feed, ρ_f and ρ_p are feed an permeate densities and A_m is the effective area of the membrane. Considering the species balance of gel forming material we get,

$$\frac{d}{dt}\left(C_{1b} V \right) = -J_w A_m C_{p1} \tag{13.65}$$

Considering that the permeate is devoid of any gel forming material, $C_{p1} = 0$ and using the boundary condition, at $t = 0$, $C = C_{01}$ and $V = V_0$ we get

$$C_{1b} = \frac{C_{01} V_0}{V} \tag{13.66}$$

The species balance of Stevioside results into

$$C_{2b} \frac{dV}{dt} + V \frac{dC_{2b}}{dt} = -J_w A_m C_{p2} \tag{13.67}$$

with the initial condition, at $t = t_0$, $C = C_{02}$ and $V = V_0$. The deposition of gel layer increases with time accompanied by the decrease in effective channel height, that can be quantified using the gel layer thickness, *L*, as

$$d_e^t = d_e - 2L\left(t \right) \tag{13.68}$$

Corresponding cross flow velocity can be mathematically represented as:

$$u^t = \frac{Q}{w \times \left(d_e^t / 2 \right)} \tag{13.69}$$

where, w is the width of the filtration cell. The cross-flow velocity thus evaluated has been utilized to estimate the mass transfer coefficient (k_f^b). Using Eqs. (13.53), (13.54), (13.55), (13.56), and (13.57) and combining Eqs. (13.63), (13.64), (13.66) to (13.69), a system of differential-algebraic equations was set up. Solving the optimization function in Eq. (13.58), five state variables (L, C_{1b}, C_{2b}, C_{2m} and V) were calculated as function of time. The parameters, a_b and b_b were found to be 0.22 and 2.22×10^{-7} Pa^{-1} (Mondal et al. 2012b).

In this mode of operation, the volume of the feed decreased continuously due to extraction of permeate resulting to the increase in the volume concentration factor (VCF=$V_0/V(t)$). Figure 13.13 shows the variation of VCF with different operating conditions indicating a good match between the experimental data and the calculated ones.

The profiles of flux and the Stevioside concentration in the permeate are shown in Fig. 13.14.

The permeate flux exhibits steep decline in the first 100 min. of the filtration time and the profile predicted by the model is in excellent agreement with the experimental data. In this mode, since the volume of the feed decreases and at higher TMP more filtrate is taken out. This is being accounted by considering a volume correction factor, which attains value of 1.4 after 10 h of operation. Recovery of Stevioside in the permeate was estimated at various operating parameters and found to be in close agreement with the experimental results. In batch mode, as more solvent is withdrawn, the gel layer thickness increases retaining more Steviosides, thereby decreasing its concentration with the filtration time. Thus, it may be concluded that the proposed model, can be efficiently used to scale up filtration of Stevia extract and recovery of Stevioside both in total recycle and batch concentration mode.

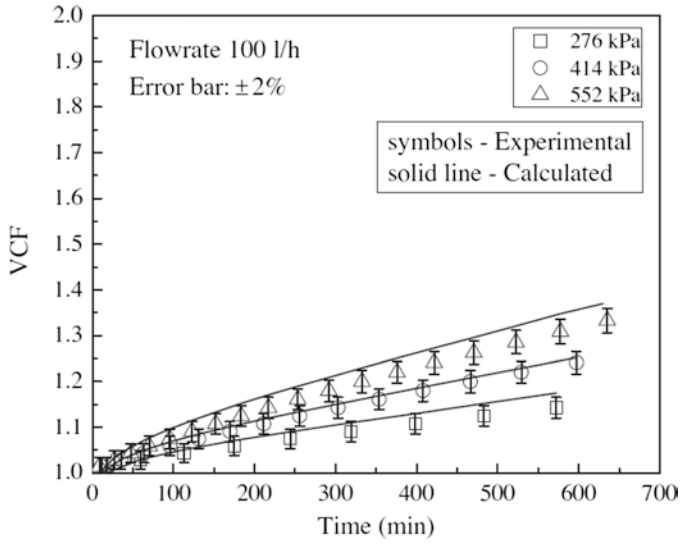

Fig. 13.13 Profiles of the VCF at different operating conditions. (Reproduced from (Mondal et al. 2012b) with permission from Elsevier Science and Technology Copyright 2012)

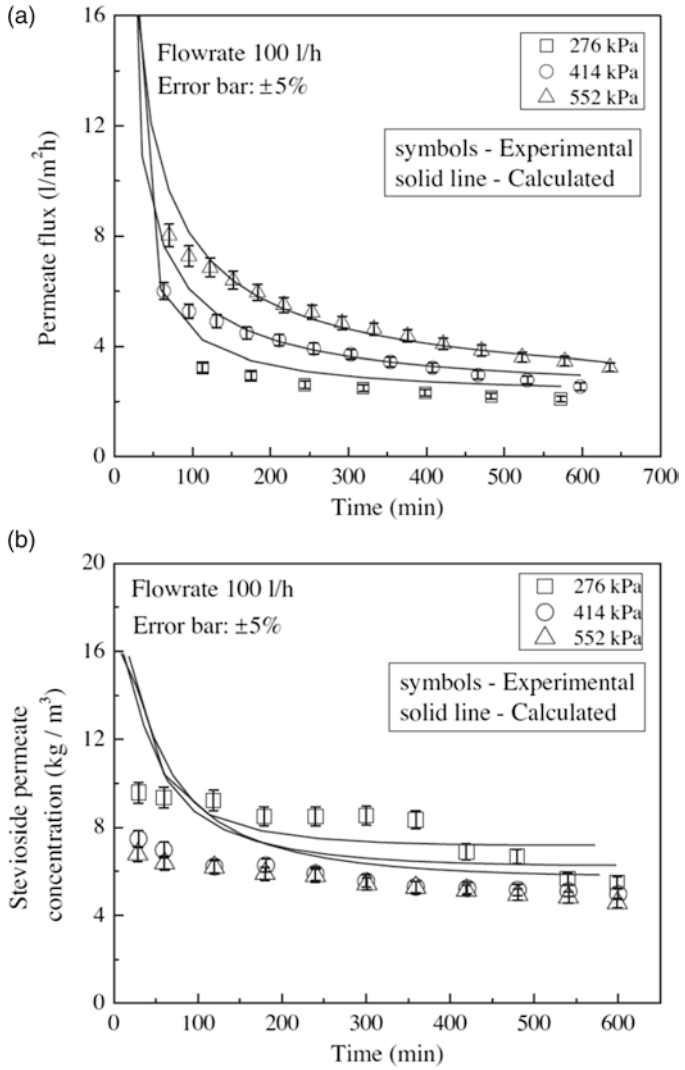

Fig. 13.14 Variation of profiles of flux and Stevioside in the permeate for different operating conditions. (Reproduced from (Mondal et al. 2012b) with permission from Elsevier Science and Technology Copyright 2012)

2.3.2 Permeate Flux Hysteresis

Real life solutions exist as a mixture of soluble and suspended substances consisting of LMW solutes such as vitamins, sugars, organic acids, as well as HMW solutes (such as proteins, pectins, cellulosic materials etc.) (Mondal et al. 2020). During filtration, some of the components may be rejected while some may permeate depending on the MWCO of the membrane. Typically, the HMW is retained on the membrane surface forming the gel layer. The permeate quality is dependent on the

size of the LMW components relative to the porosity of the gel layer and that of the membrane. The gel layer formed is compressible in nature and the thickness of the layer varies with the operating pressure. The linear flux-pressure relation deviates at higher pressure due to the consolidation of the gel layer. With increasing pressure cycle, the gel layer continuously grows, and the gel layer thickness is greater than the reducing pressure cycle. The pressure responsive variations in gel layer thickness result into hysteresis in the permeate flux during continuous operation of cross flow membrane system. Permeate flux hysteresis is a very significant aspect observed during the filtration of fruit juices for extraction of bioactive compounds. The quantification of permeate flux quantity and quality during the hysteresis is a key factor to be considered during scale up of the commercial units. However, the research in this area is scant and remains unexplored. In case of gel layer filtration operated below critical flux limit, Field et al. have reported the hysteresis in permeate flux (Field et al. 1995).

Mondal et al. have reported a detailed study on modelling of the transport of the HMW as well LMW solutes through the membrane for recovering phenolic compounds from clarified aqueous extracts of olive mill solid wastes (Mondal et al. 2020). The fundamental model used in their work was developed by De and Bhattacharya for ultrafiltration of a two component aqueous solution containing gel forming HMW and LMW solutes with known transport coefficients (De and Bhattacharya 1997). For actual fruit juices or plant extracts, independent determination of the system and model parameters is extremely difficult. Modelling approach adopted by Mondal et al. can predict the transport coefficient of permeating solutes in presence of gel forming solute for a continuous filtration of bioactives. The model also estimates the thickness of the gel layer, which is otherwise not possible to measure experimentally or analytically.

Membranes with High MWCO

In this model, component 1 is HMW and participates in the formation of gel layer. Component 2 is LMW and can permeate freely through the membrane, but their movement is hindered by the gel layer. The concentration profile of component 2 during filtration is shown in Fig. 13.15. Component 1 is retained on the membrane surface and forms the gel layer. At the steady state, the permeate flux (J_w) can be estimated from the film theory as (Blatt et al. 1970)

$$J_w = k_f \ln\left(\frac{C_{g1} - C_{p1}}{C_{01} - C_{p1}}\right) \tag{13.70}$$

where, k_f is the mass transfer coefficient and C_{g1}, C_{p1} and C_{01} are the concentration of component 1 in gel, permeate and bulk, respectively. k_f can be estimated from the theoretical Sherwood number (Sh) correlation, ignoring the effect of viscosity in the form,

$$Sh = \frac{k_f h}{D_1} = \xi\left(\mathrm{Re}\, Sc \frac{h}{l}\right)^{\frac{1}{3}}\left(\frac{C_{g1}}{C_{01}}\right)^{\frac{1}{3}} \tag{13.71}$$

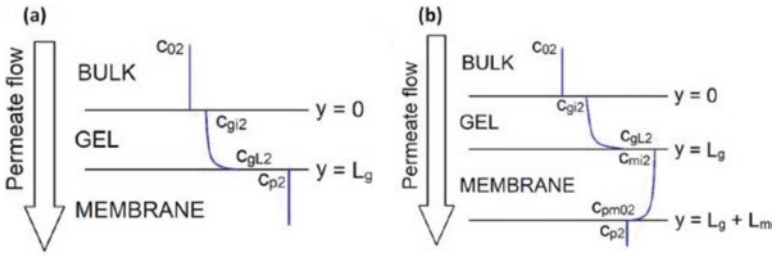

Fig. 13.15 Schematic of different membrane layers and concentration profile of 2nd component for membranes with (**a**) HMW and (**b**) LMW. (Reproduced from (Mondal et al. 2020) with permission from Elsevier Science and Technology Copyright 2020)

Table 13.2 Value of ξ for different geometries of the filtration module (Mondal et al. 2020)

Geometry	Classical Leveque solution (constant mass transfer boundary layer)	Considering developing mass transfer boundary layer
Rectangular	1.86	2.10
Tubular	1.62	1.816
Radial cross flow	1.47	1.65

where, *Re* and *Sc* are Reynolds and Schmidt number and *h* is the channel half-height. The value of the constant, ξ, depends on the geometry of the system and is presented in Table 13.2.

C_{p1} through the membrane can be obtained using the modified Kedem-Katchalsky equation (Katzir-Katchalsky and Curran 1965)

$$J_w C_{p1} = B_1 \left(C_{g1} - C_{p1} \right) + \left(1 - \sigma_1 \right) \bar{C}_1 v_w \tag{13.72}$$

where, $\bar{C}_1$ is the log mean average concentration of component 1 in the membrane represented as $\bar{C}_1 = \dfrac{C_{g1} - C_{p1}}{\ln\left(\dfrac{C_{g1}}{C_{p1}} \right)}$. σ_1 and B_1 are phenomenological membrane transport coefficients of reflection and permeation, respectively.

Transport of component 2 through the gel layer is

$$J_w C_{p2} = -\varepsilon_g D_2 \frac{dC_2}{dy} + J_w C_2 \tag{13.73}$$

where, C_{p2} and D_2 are the permeate concentration and diffusivity of component 2 and C_2 is the variable representing the concentration of component 2. ε_g is the gel

porosity and the compressibility effects are accounted using the functional form $\varepsilon_g = \varepsilon_0 \left(\Delta P\right)^{n_1}$. The above differential equation on integrating between the boundaries $y = [0, L]$ using the boundary condition, $C_2 = C_{gL2}$ *at* $y = L$leads to:

$$\frac{C_{gL2} - C_{p2}}{C_{gi2} - C_{P2}} = \exp\left(\frac{J_w L}{\varepsilon_g D_2}\right) \tag{13.74}$$

In the above equation, C_{gi2} and C_{gL2} are the concentration of component 2 at the gel-bulk and gel-membrane interface, respectively. Defining $v_1 = \frac{C_{gi2}}{C_{02}}$ and $v_2 = \frac{C_{gL2}}{C_{p2}}$, where, C_{02} as the feed concentration of component 2, Eq. (13.74) can be expressed as:

$$C_{p2} = \frac{v_1 C_{02} \exp\left(\frac{J_w L}{\varepsilon_g D_2}\right)}{v_2 - 1 + \exp\left(\frac{J_w L}{\varepsilon_g D_2}\right)} \tag{13.75}$$

The phenomenological equation to estimate the permeate flux is:

$$J_w = \frac{\Delta P}{\mu\left(R_m + R_g\right)} \tag{13.76}$$

In the above expression, μ is the solution viscosity, R_m is the membrane hydraulic resistance and R_g is resistance of the gel layer (Eq. 13.57). ρ_g is the gel layer density and the compressibility effect on specific cake resistance (α) is accounted as $\alpha = \alpha_0 \left(\Delta P\right)^{n_1}$. It may be noted the exponent (n_1) in the definition of α and ε is related to the effect of compressibility and considered to be the identical for both the parameters.

Thus, the problem reduces to the estimation of four variables J_w, C_{p1}, C_{p2} and L by solving the coupled Eqs. (13.70), (13.72), (13.75) and (13.75) simultaneously. The unknown parameters D_1, D_2 B_1, C_{g1}, ρ_g, σ_1, v_1, v_2, ε_0, α_0 and n_1 were determined by minimization of the sum of the residual function (S) represented by Eq. (13.77) using the experimental (superscript *exp*) and calculated (superscript *cal*) values. Optimization was carried out using twenty-seven experimental data points.

$$S = \sum\left(\frac{J_w^{cal} - J_w^{\exp}}{J_w^{\exp}}\right)^2 + \sum\left(\frac{C_{p1}^{cal} - C_{p1}^{\exp}}{C_{p1}^{\exp}}\right)^2 + \sum\left(\frac{C_{p2}^{cal} - C_{p2}^{\exp}}{C_{p2}^{\exp}}\right)^2 \tag{13.77}$$

Membranes with Low MWCO

In this model, component 2 cannot permeate freely through the membrane and its movement is hindered by both the membrane as well as the gel layer. Both component 1 and component 2 take part in the formation of gel layer. Therefore, the permeation of component 2 through the membrane also needs to be considered. Similar to the case of HMW solute, the expression for permeate flux and the permeation of component 1 through the membrane remains unaltered. In rearrangement of Eq. (13.74), v_2 is defined as $v_2 = \frac{C_{gL2}}{C_{mi2}}$, where C_{mi2} is the concentration of component 2 at the gel-membrane interface. Thus, Eq. (13.74) can be rearranged as

$$C_{p2} = \frac{v_2 C_{mi2} - v_1 C_{02} \exp\left(\frac{J_w L}{\varepsilon_g D_2}\right)}{1 - \exp\left(\frac{J_w L}{\varepsilon_g D_2}\right)} \tag{13.78}$$

The transport of component 2 through the membrane can be represented by modified Kedem-Katchalsky equation as:

$$J_w C_{P2} = B_2\left(C_{mi2} - C_{pm02}\right) + \left(1 - \sigma_2\right)\overline{C_2} v_w \tag{13.79}$$

where, B_2 and σ_2 are the phenomenological membrane transport coefficients of permeation and reflection, respectively. C_{pm02} is the concentration of component 2 at the membrane-permeate interface on the membrane side. $\overline{C_2}$ is the logarithmic average concentration of component 2 defined as $\overline{C_2} = \frac{C_{mi2} - C_{pm02}}{\ln\left(\frac{C_{mi2}}{C_{pm02}}\right)}$ Eq. (13.79) can be rearranged as:

$$J_w C_{p2} = B_2\left(C_{mi2} - v_3 C_{p2}\right) + \left(1 - \sigma_2\right)\overline{C_2} v_w \tag{13.80}$$

In the above equation, v_3 defined as $v_3 = \frac{C_{pm02}}{C_{p2}}$. Considering negligible mass transfer resistance between the membrane and the permeate side, $C_{pm02} \approx C_{p2}$ leading to the simplification $v_3 = 1$. Thus, the problem is reduced to determine the variables J_w, C_{p1}, C_{p2}, L and C_{mi2} by solving the coupled algebraic Eqs. (13.70), (13.72), (13.74), (13.78) and (13.80). Among the 13 unknown parameters (D_1, D_2, B_1, B_2, σ_1, σ_2, C_{g1}, ρ_g, v_1, v_2, v_3, α_0, ε_0 and n_1), the values of D_1, D_2, $\frac{C_{g1}}{C_{01}}$, $\frac{\rho_g}{\rho}$, v_1, ε_0, $\frac{\alpha_0}{R_m}$ and n_1 are intrinsic properties of the system and will remain identical as in case of the HMW case. This reduces the unknown parameters to be estimated as six, namely, B_1, B_2, σ_1, σ_2, v_2 and v_3. The solution methodology is similar to the HMW by minimizing the sum of residuals represented by Eq. (13.77).

The model as described above has been validated using experimental datasets with five different membranes, as presented in Table 13.3. Total dissolved solids

(TDS) is considered as component 1 and total polyphenols as component 2. Various parameters estimated using the model are presented in Table 13.3 for both high and low cut-off regimes. The non-zero value of *n* indicates compressible nature of the gel layer. The estimated values of gel layer thickness and permeate flux for high cut-off membranes are presented in Fig. 13.16, which indicates that the model predictions are within ±10% of the experimental results. The increase in gel layer thickness suggests continuous growth with TMP, which is higher in magnitude for GH membrane. Corresponding to this, the permeate flux also increases in the forward cycle due to increase in driving force but the effect of increased gel layer thickness is reflected as the diminishing slope. However, in reverse cycle, the permeate flux does not trace back the original path but exhibits lower values. This is due to the fact that the gel layer is not washed, and it keeps on accumulating offering increased resistance.

Similarly, the model predictions are also validated using experimental observations for low cut-off range and were observed to be within a relative error of ±10%. Theoretical results obtained have shown remarkable agreement of the gel layer thickness reported in literature. The additional variable in this case (C_{mi2}) was also estimated from the model and was found to be higher than the permeate concentration as expected. The variation in gel layer thickness was observed to be significantly less in reverse cycle as compared to the forward cycle for NFA and DK membranes. For the GE membrane, gel thickness increases with TMP up to 15 bar, beyond which it remains constant because of the counteracting flux of solute convection toward the membrane as well as solute permeation through the membrane. Thus, the permeate hysteresis is not observed

Table 13.3 Characteristics of membranes used in the experiments (Mondal et al. 2020)

Membrane type	GK	GH	GE	NFA-12A	DK
Membrane material	Polyamide-TFC				
Permeability (L/m^2.h.bar)	8.85	4.66	4.21	9.97	5.44
MWCO (Da)	3500	2500	1000	500	150–300
Operating pH range	2–10	2–10	2–10	3–11	3–9

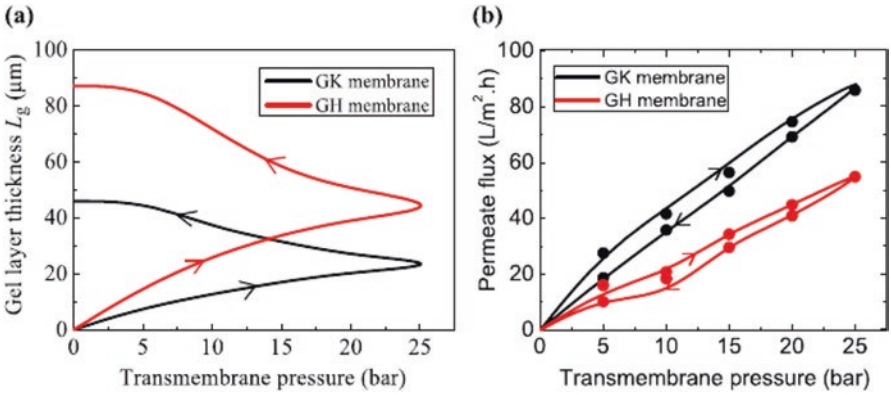

Fig. 13.16 For high MWCO membranes (a) variation in gel layer with TMP and (b) permeate flux as a function of TMP (symbols represent the experimental data points). (Reproduced from (Mondal et al. 2020) with permission from Elsevier Science and Technology Copyright 2020)

beyond 15 bar. At lower TMP, convective flux is less, and the gel thickness increases due to the deposition of solutes. It has been observed that the gel layer thickness is the maximum in case of GK membrane (87 μm) whereas for DK and NFA membranes, it is the lowest (5 μm). Thus, it may be concluded that membranes having higher MWCO exhibit thicker gel lay compared to low MWCO membranes. At all TMPs, the extraction of total phenols was observed to be the maximum for GK membrane.

3 Conclusions

The existing models for quantifying the performance of the membrane-based systems for processing of bioactive compounds were discussed in this chapter. The models were put under three broad classes as, empirical, semi-empirical and first principle-based models. The performance of the systems includes the prediction of permeate flux and permeate concentration. That indicates technical and economic feasibility, as well as the life of the membranes. The empirical models are basically black box type models assuming the permeate flux is represented by the driving force (TMP in this case) divided by several transport resistances in series (e.g., membrane resistance, fouling resistance, pore blocking resistance, etc.). The resistances were calculated from the experimental permeate flux data. One or more resistances were interrelated the dynamic permeate flux variations and the operating conditions (TMP and CFR). This resulted to the generation of the resistance in series models to predict the system performance at different operating conditions. Based on the consideration of membrane pore blocking during the filtration, two different variants of this model were discussed. The major advantages of empirical models are summarized as: (1) they provide easy and amenable method to model the system; (2) no in depth knowledge of the physico-chemical and transport properties of the solution and solvent are not needed; (3) no deeper knowledge of the mathematical or computational skill sets are required to use them; (4) the process operating parameters can be optimized easily and information about the limiting flux and corresponding operating conditions can be definitely determined. However, the limitations are: (1) these models can predict the permeate flux decline only, not the permeate concentration; (2) they are valid only within the studied range of the operating conditions and lose their predictive capability outside this range; (3) they lack the physical understanding of the involved transport process; (4) the results are system specific.

The semi-empirical models are one step ahead of the empirical models. In this case, the governing flux decline equations are based on the prevailing mechanisms and they are derived from the theoretical background. The original equations were obtained by Hermia and these models were modified by the continuous cross flow rate at steady-state (Field et al. 1995; Hermia 1982). The use of these models and their modified versions for sequential fouling mechanisms (like complete pore blocking followed by cake filtration) were demonstrated for quantification of flux decline of the solution containing bioactive compounds. The major advantage of

these models is that the underlying physical understanding behind the model equations is clear. The limitations of these models are: (1) they can predict only the permeate flux decline but cannot predict the history of permeate concentration; (2) the models fail when more than one mechanisms are in operation at a time; (3) since the model constants are evaluated for a particular solution and system, they are system specific and valid within the operating conditions studied.

The transport phenomena-based models are more versatile in nature. The underlying transport mechanisms provide strong foundation to formulate these models. In this case, the components of a complex plant extract / juice are clubbed in two groups, namely, larger sized components are grouped in higher molecular weight solutes that are mainly retained by the membrane forming a gel layer over the membrane surface. The lower molecular solutes are basically the desirable components (mostly the bioactive compounds) and the second component that is transported through the gel layer and the membrane reaching the permeate. Thus, the transport equations are written for various components in external mass transfer boundary layer, gel layer and membrane matrix. The equations are solved to get the system performance. The disadvantage of this model is that some of the transport coefficients of various components are unknown and they are obtained by using the experimental data. However, the advantages are many. These are (1) models are capable to predict the time history of permeate flux and permeate concentration; (2) the underlying physical principles are clear; (3) the model can be safely used for scaling up; (4) most importantly, they have the capability to predict the system performance at any operating conditions. Different variants of these models, for steady-state, transient under total recycle model, as well as the batch concentration mode, were presented in this chapter.

During a plant operation, it may not be possible to run the plant at constant TMP. Sometimes, TMP is increased to compensate the flux decline. Therefore, real time variation of steady state permeate flu with TMP is an important issue and it is termed as flux hysteresis. The modelling of hysteresis is therefore an important operating feature in actual plant operation and an a-priori knowledge would help the selection of the operating conditions and behavior of the flux history. The corresponding modelling of this complex phenomenon is also presented in this chapter. Demonstration of various modelling approaches in quantifying the performance of the membrane-based separation processes in case of filtration of bioactive compounds would be helpful to identify the flux decline mechanism, optimum operating conditions, system performance and definitely in designing and scaling up.

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