Chapter 28
Fruit and Vegetables and Health: An Overview

Yves Desjardins

Abstract A growing body of evidences suggests that the regular consumption of a diet rich in fruit and vegetables (FAV) reduces the risk of chronic human illnesses and increase lifespan and quality of life. FAV are considered energy poor, are rich sources of minerals, fibers, vitamins and most of all of many phytochemicals belonging to four main classes: polyphenols, terpenoids, sulphur compounds and alkaloids. Polyphenols, and to a certain extent carotenoids and sulphur containing compounds have been shown through epidemiological cohort studies or through mechanistic *in vitro* or animal studies, to prevent coronary heart diseases, chronic inflammatory diseases, obesity, diabetes, neurodegenerative diseases, cancer, macular degeneration, and many others. Owing to their particular chemical structure, theses phytochemicals display strong antioxidant capacity in vitro. Yet due to their poor bioavailability and their short residence time in the organism, it is more and more admitted that these molecules trigger detoxification mechanisms in the body and induce genes associated with energy metabolism, anti-inflammation and endogenous-antioxidant network at the cellular level.

This chapter describes the different phytochemicals found in FAV with emphasis on polyphenols, the most important class of compounds in relation to health benefits and amounts ingested on a daily basis in our diet. The contribution of these chemicals to the prevention of chronic diseases is covered and new insights on their possible mode of action are discussed. The scope of this chapter is broad and intends to brush an overview of this very complex and dynamic field of research, at the interface between plant and human physiology. The reader is guided and often referred to bibliographic reviews on topics as diverse and eclectic as phytochemicals biosynthesis, bioavailability, inflammatory responses, cancer etiology, appetite control, insulin resistance, and cognition.

Keywords Fruits · Vegetables · Health · Polyphenols · Carotenoids · Sulphur compounds · Cancer · Coronary heart disease · Obesity · Diabetes · Neurodegenerative disease · Bioavailability

Y. Desjardins (✉)
Institute of Nutrition and Functional Foods/Horticulture Research Center,
Laval University, Québec City, QC G1V 0A6, Canada
e-mail: yves.desjardins@fsaa.ulaval.ca

G. R. Dixon, D. E. Aldous (eds.), *Horticulture: Plants for People and Places, Volume 3*,
DOI 10.1007/978-94-017-8560-0_28,

Introduction

It is implicitly accepted that fruit and vegetables (FAV) are good for you. Actually, many nutritionists and clinicians now consider fruit and vegetables consumption as a solution to many "diseases of civilization". These horticultural products bring diversity and stimulate our senses by having organoleptic properties like color, flavor, and texture and contribute to our appetite. FAVs have long been recognized for their nutritive value. They are excellent sources of minerals, essential fatty acids and fibers, but are also unique sources of vitamins (C, E, B, and folic acid). Most of all, they are rich sources of bioactive phytochemicals. They are considered energy poor and contribute, through their high content in non-digestible fibers, to the feeling of satiety. For these reasons, the consumption of FAV and plants in general are at the base of most for food pyramid (Anon 2011). For some, FAV are the most important component of the diet and contribute to a healthy living (Hung et al. 2004). For example, the Mediterranean diet, which is reputed for its quality and is largely composed of fish, alpha-linoleic acid and FAV has been associated with the low incidence of cardiovascular disease of population living in the Mediterranean bassin (de Lorgeril et al. 1994). Other diets, like the Portfolio diet, a reconstitution of the diet of our simian ancestors, is relying on the consumption of high levels of fibers, phytosterols, vegetables and nuts and has been show repetitively to confer significant cholesterol-lowering capacity and reduce the incidence of atherosclerosis (Kendall and Jenkins 2004). Indeed, a growing body of evidence suggests that the regular consumption of a phytochemical-rich diet reduces the risk of many chronic human illnesses and increases life span and quality in humans (Anon 2007; He et al. 2006).

New evidences support the fact that FAV are important in the prevention of cardiovascular (Van't Veer et al. 2000), vision (Snodderly 1995), bone (Baile et al. 2011), and pulmonary health (Trichopoulou et al. 2003). The World Health Organization has recognized this fact and is actively promoting the consumption of FAV to reduce the incidence of chronic disease (Anon 2007) and public health and growers organization in different countries, regrouped under the umbrella of IFAVA (Anon 2006) are actively promoting the consumption of FAV through the different 5 to 10 a day programs worldwide. There are many epidemiological studies linking the consumption of FAV and/or their constituents to beneficial health effects. For instance, many cohort and case-control epidemiological studies and even intervention studies show the beneficial effects of FAV. In general, an inverse association is found between FAV consumption and cardiovascular disease (SUVIMAX cohort study) (Bazzano 2006; Hercberg et al. 2004), chronic inflammatory diseases (Hermsdorff et al. 2010), diabetes (Bazzano 2005; Hamer and Chida 2007), obesity (Carlton Tohill 2005), neurodegenerative diseases (Cherniack 2012), and many more. However, the evidence for this effect is not as solid for cancer (World Cancer Research Fund 2007) and recently some doubts have been expressed on the link between FAV and coronary hearth disease prevention (Dauchet et al. 2009) since FAV consumption is often confounded with other general healthier life habits like non-smoking, reduced alcohol consumption, just to list a few.

The majority of the studies published over the last 20 years have focused on the identification and demonstration of the activity of bioactive compounds of FAV *in vitro*. They are mostly observational and results are often conflicting. The validity of *in vitro* studies is contested because they provide an incomplete and often biased image of the benefits of FAV to health. Other parameters must thus be considered since the responses of humans to the food they consume are complex and influenced by many confounding factors. Too many studies have not taken into account the poor bioavailability, the interactions between the phytonutrients and have often used supra-optimal non-physiological doses of bioactive compounds to demonstrate their effect and have thus lead to incorrect conclusions on their potential effects. Moreover, these effects have proved to be difficult to reproduce in human clinical trials. Taking into account these caveats, new hypothesis on the mode of action of phytonutrients lean toward a general anti-inflammatory and cell-signaling action.

This chapter is thus intended to briefly review the most pertinent scientific literature on the topic of health effects of FAV and highlights which components are responsible for disease protection and the most probable mechanisms by which they confer these effects. Many excellent reviews on the topic are also available (Crozier et al. 2006, 2009).

FAV are Rich Sources of Nutrients

FAV are rich sources of minerals and vitamins in the diet. They provide large amount of phosphorus, potassium, calcium, magnesium, iron and zinc. They also contain unsaturated lipids and are a very rich source of vitamins and in particular vitamin-C (Table 28.1). Interestingly, they contain a high proportion of water, and have a high content in non-digestible fibers, which have been shown to reduce their energy density (Carlton Tohill 2005). Adding FAV to the diet reduces the overall energy density, increasing the amount of food that can be consumed for a given level of calories. Many comprehensive reviews have evaluated the effect of dietary fibre content on satiety, overall energy intake and body weight (Kim and Park 2011).

Phytochemicals Found in FAV

FAV accumulate several hundred of thousands of so-called "secondary metabolites" to protect themselves from biotic stress like bacteria, fungi and insects (Kliebenstien 2004) and abiotic stress (Dixon and Paiva 1995). These chemicals are essential components of the adaptive arsenal of the plant to the environment and are involved in biotic and abiotic stress protection, cell signaling, plant development, pollinator attraction, plant-microorganism interaction, plant defense, herbivore repulsion and seed dispersion. These phytochemicals are regrouped into four broad classes according to their chemical structure: polyphenols, terpenoids, sulphur compounds, and alkaloids (Fig. 28.1 and Table 28.2).

Table 28.1 Composition of typical fruit and vegetables. Values are per 100 g F.W. (Adapted from the USDA national nutrient database (Anon 2004, 2006)

	Water %	Energy (Kcal)	Protein (mg)	Lipid	Fibers	Sugar	Minerals (mg)							Vitamins				
Fruit							Ca	Fe	Mg	P	K	Na	Zn	C (mg)	B (mg)	E (mg)	A (µg)	Folate (µg)
Apples	85	52	0.3	0.2	2.4	13.8	6	0.1	5	11	107	1	0.05	4.6	0.2	0.2	3	3
Avocado	73	160	2	14.7	6.7	8.5	12	0.6	29	52	485	7	0.6	10	2.1	2	7	81
Banana	74	89	1	0.3	2.6	12.2	5	0.3	27	22	358	1	0.15	8.7	1	0.1	3	20
Blackberry	88	43	1.4	0.5	5.3	9.1	29	0.6	20	22	162	1	0.5	21	0.7	1.2	11	25
Blueberry	84	57	0.7	0.3	2.4	14.5	6	0.3	6	12	77	1	0.2	9.7	0.5	0.6	3	6
Cranberry	87	46	0.4	0.1	4.6	12.2	8	0.3	6	13	85	2	0.1	13	0.2	1.2	3	1
Figs	79	74	0.8	0.3	2.9	16.3	35	0.4	17	14	232	1	0.2	2	0.6	0.1	7	6
Grapefruit	88	42	0.8	0.1	1.6	10.6	22	0.1	9	18	135		0.1	31	0.3	0.1	58	13
Grapes	81	67	0.6	0.4	0.9	17.2	14	0.3	5	10	191	2	0.04	4	0.5	0.2	5	4
Melon	90	34	0.8	0.2	0.9	8.6	9	0.2	12	15	267	16	0.2	36	0.8	0.1	169	21
Oranges	86	47	0.9	0.1	2.4	11.7	40	0.1	10	14	181		0.1	53	0.5	0.2	11	30
Pears	84	57	0.4	0.1	3.1	9.8	9	0.2	7	12	116	1	0.1	4.3	0.2	0.1	1	7
Raspberry	85	52	1.2	0.7	6.5	11.9	25	0.7	22	29	151	1	0.4	26	0.7	0.9	2	21
Strawberry	91	32	0.7	0.3	2	7.7	15	0.4	13	24	153	1	0.1	59	0.5	0.3	1	24
Vegetables																		
Artichoke	85	47	3.3	0.2	5.4	1	44	1.3	60	90	370	94	0.5	12	1.2	0.2	14	68
Asparagus	93	20	2.9	0.2	2.8	2.5	32	2.9	19	70	271	3	0.7	7.5	1.7	1.5	51	70
Beans green	90	31	1.8	0.2	2.7	3.3	37	1.0	25	38	211	6	0.2	122	0.9	0.4	35	33
Beets	88	34	2.8	0.4	2.8	6.8	16	0.8	23	40	325	78	0.4	4.9	0.5	0.04	2	109
Broccoli	89	34	2.8	0.4	2.6	1.7	47	0.7	21	66	216	33	0.4	89	0.8	0.8	31	57
Brussels sp.	86	43	3.4	0.3	3.8	2.2	42	1.4	23	69	389	25	0.4	85	0.9	0.9	38	61
Cabbage	92	25	1.3	0.1	2.5	3.2	40	0.5	12	26	170	18	0.2	37	0.3	0.2	5	43
Carrot	88	41	0.9	0.2	2.8	4.7	33	0.3	12	35	320	69	0.2	6	1.1	0.7	835	19
Cauliflower	92	25	1.9	0.3	1.9	2.0	22	0.4	15	44	299	30	0.3	48	0.6	0.1	0	57
Celery	95	16	0.7	0.2	1.6	1.8	40	0.2	11	24	260	80	1.3	3.1	0.4	0.3	22	36
Garlic	59	149	6.4	0.5	2.1	1.0	181	1.7	25	153	401	17	1.2	31	1.0	0.1	0	3
Lettuce	95	17	1.2	0.3	2.1	1.2	33	1.0	14	30	247	8	0.2	4	0.4	0.1	436	136
Onion	89	40	1.1	0.1	1.7	4.2	23	0.2	10	29	146	4	0.2	7.4	0.2	0.02	0	19
Pepper	94	20	0.9	0.2	1.7	2.4	10	0.3	10	20	175	3	0.1	80	0.5	0.4	18	10
Spinach	91	23	2.9	0.4	2.2	0.4	99	2.7	79	49	558	79	0.5	28	1.0	2.0	469	194
Tomato	95	18	0.9	0.2	1.2	2.6	10	0.3	11	24	237	5	0.2	14	0.6	0.5	42	15

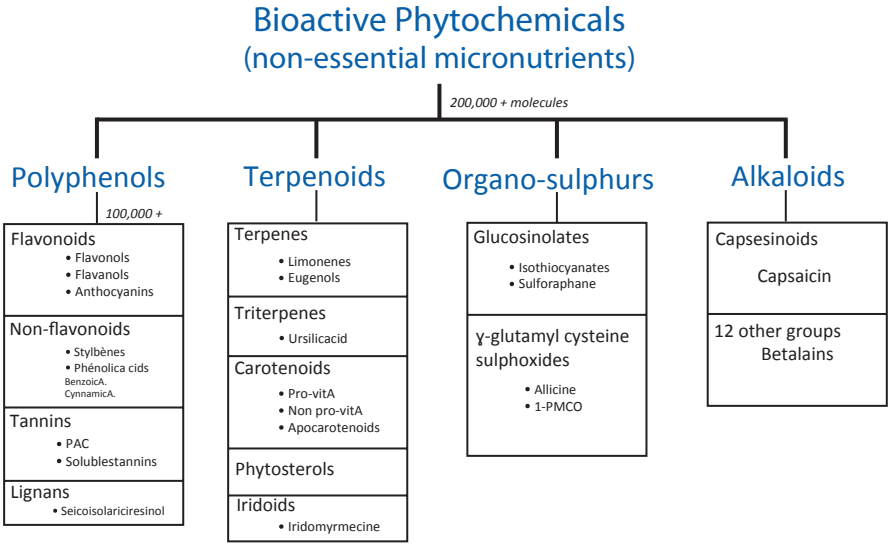


Fig. 28.1 Different classes of bioactive phytochemicals found in FAV

Table 28.2 Photochemicals found in fruit and vegetables

Bioactive compound family	Primary source in fruits and vegetables	Database/source
Terpenoids		
Carotenoids	Leafy vegetables, red and yellow fruits and vegetables	USDA nutrient database (Kimura and Rodriguez-Amaya 2003; Rodriguez-Amaya et al. 2008)
Monoterpenes	Citrus, cherries, mint and herbs	
Saponins	Alliaceae, asparagus	(Güçlü-Üstünda and Mazza 2007)
Apocarotenoids	Fruits	(Bouvier et al. 2005)
Polyphenols		
Phenolic acids	Small fruits, apples, fruit and vegetables	(Rothwell et al. 2012)
Hydrolysable tannins	FAV, pomegrenate, raspberry	(Clifford and Scalbert 2000)
Stylbenes	Grapes, small fruits	(Waffo-Teguo et al. 2008)
Proanthocyanidins	FAV, cacao, small fruits, cranberry, blueberry	(Anon 2003)
Monophenolic alcohols tyrosol	Olive oil, wine	(Romero et al. 2002)
Organo sulphur compounds		
Glucosinolates	Brassicaceae	(McNaughton and Marks 2003)
γ-Glutamyl cysteine sulphoxides	Alliaceae	(Griffiths et al. 2002)
Alkaloids		
Capsaicin	Chili Pepper	(Surh and Sup Lee 1995)
Betalain	Red Beet, Prickly pear, Pittaya	(Stintzing and Carle 2007)

Polyphenols

The evolution of terrestrial plants has coincided and probably been rendered possible through the acquisition of the capacity for phenol biosynthesis from phenylalanine. Central to plant biology is the fact that these phenols polymerized to form lignin which provided mechanical support to plants, and through combined action of cutin and suberin, provided protection against desiccation and consequently the conquest of dry environments (Parr and Bolwell 2000). These molecules designated as polyphenols constitute a very heterogeneous group of molecules with almost 100,000 individual chemical species. This large number of known structures owe to the glycoside complexity of flavonoids, the variable stereochemistry of the molecules and their capacity to form polymers (Harborne 1977).

Polyphenols are characterized by the presence of one or more benzene ring bearing one or many hydroxyl groups. They can be very simple ring molecules of 6C, but can be much more complex structures with many functional groups or polymers (Table 28.3). Within this complex class, flavonoids are the most relevant to biology and food technology. The flavonoids are made of 15 C and are regrouped into ten classes based on the structure of the central heterocycle (Fig. 28.2) and their degree of oxidation. The most oxidized form corresponds to the anthocyanins, which confer color to fruits, while the reduced form correspond to flavan-3-ols, known for their astringency and health properties. The vast majority of polyphenols is water-soluble and is sequestered in vacuoles in glycosylated form, while some are lipophilic (flavone, flavonol methyl esters) and will thus dissolve in waxes and be encountered in the epidermis of plants. The glycosylated flavonoids need to be stripped of their sugar moiety before absorption by the gut epithelium. Polyphenols are generally nucleophilic on the basis of their oxygen atom in the heterocyclic pyrane C ring, also the presence of many double bounds in the aromatic rings and the presence of hydroxyl groups in ortho- and para- position on the A and B ring. They are thus strong antioxidants. They will often complex with metal ions and contribute to the vivid blue color of some flowers. The presence of metal ions also multiplies the antioxidant capacity. Due to the presence of many hydroxyl groups, most flavonoids will interact strongly with proteins (Dangles and Dufour 2006) and with enzymes (McDougall and Stewart 2005). They will contribute to the sensation of astringency by binding proline and tyrosine found in saliva and mouth epithelial proteins (Haslam and Lilley 1988).

Food Sources of Polyphenols

FAV and beverage like wine are especially rich sources of polyphenols and in particular of flavonoids (Table 28.4). Their specific content depends on the species, the degree of maturity of the crop, the cultural management, the processing, the way they are cooked and stored. It is generally considered that the total flavonoid

Table 28.3 Main classes of phenolic compounds found in fruit and vegetables. (Macheix et al. 1990)

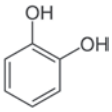
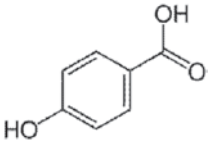
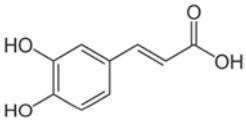
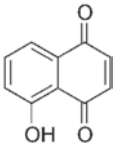
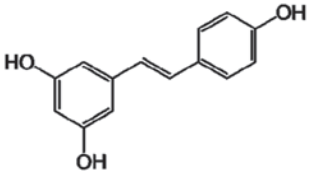
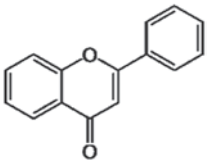
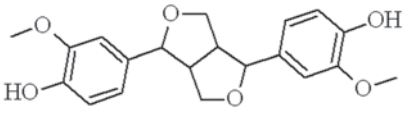
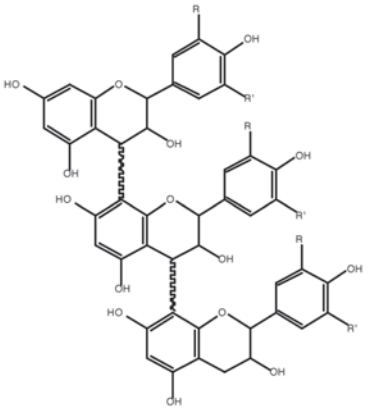
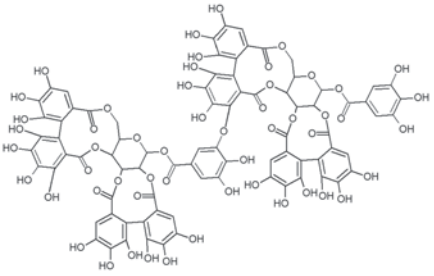
Carbon skeleton	Class	Type	Source
C6 	Simple phenol	Catechol	Many species, degradation products
C6-C1 	Hydroxybenzoic acid	P-benzoic acid, gallic acid, protocatecuic acid	Spices, strawberry, raspberry, blackberry
C6-C3 	Hydroxycinnamic acid, coumaric acid	Caffeic acid	Apples, citrus, potatoes, coffee (green), blueberry, spinach,
C6-C4 	Naphtoquinones	Juglone	Nuts
C6-C2-C6 	Stylbenes	Resveratrol, viniferine	Grapes, wine
C6-C3-C6 	Flavonoids	Quercetine, anthocyanin	Fruits, onion
$(C6\text{-}C3)_2$ 	Lignans	Pinoresinol, seicoisolariciresinol	Pine, kale, broccoli, apricot, strawberry

Table 28.3 (continued)

Carbon skeleton	Class	Type	Source
$(C6\text{-}C3)_n$	Lignin		Stone fruits
$(C6\text{-}C3\text{-}C6)_n$	Condensed tannins	Proanthocyanidins	Most fruits, cranberry, persimmon, nuts, chocolate
			
	Hydrosoluble tannins	Ellagitannins, Sanguiin H10	Strawberry, rubus, pomegranate, nuts

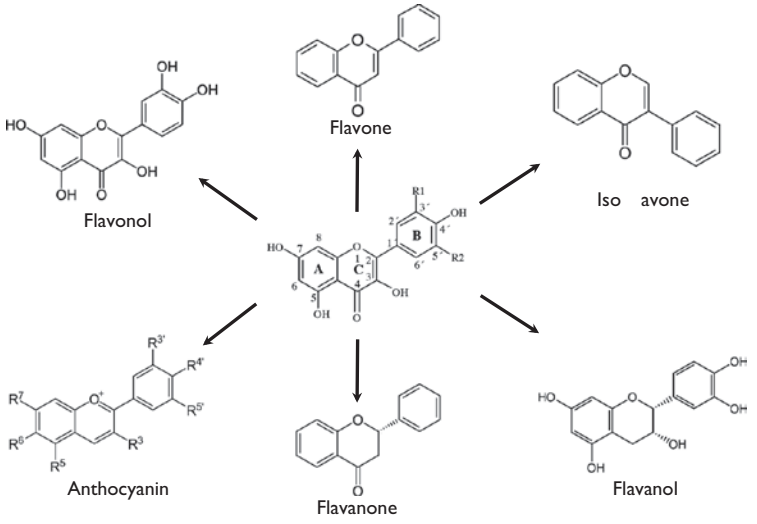


Fig. 28.2 Different classes of flavonoids found in FAV

Table 28.4 Sources of flavonoids in fruit and vegetables

Subclass	Compounds	Primary source
Flavonols	Quercetin, myricetin, kaempferol, rutin, isorhamnetin	Onion, apples, cranberry, broccoli, berries, olives, bananas, lettuce, plums, grapes, wine
Favanones	Hesperin, hesperidin, naringin, naringenin, eriodictol	Citrus
Flavan-3-ols	Catechin, epicatechin, galloylated derivatives	Tea, plums, apple, cranberries, berries, chocolate
Flavones	Luteolin, apigenin	Apples, Apiaceae, celery, sweet red pepper, parsley, oregano, lettuce, beet
Anthocyanins	Cyanidin, delphinidin, pelargonidin, malvidin, peonidin, petunidin (mostly as glycosides)	Berries, red fruits, red cabbage, eggplant

intake of occidentals is about 1 g/d (Kuhnau 1976; Scalbert and Williamson 2000). According to Brat et al. (2006), FAV consumption in France accounts for about 30% of the overall daily polyphenol intake, which reach about 287 mg GAE/d. Other sources of polyphenols in the diet come from beverages like tea, coffee and wine but also from cereals. Moreover, humans consume a significant proportion of their polyphenols in a polymeric form as proanthocyanidins (PAC), which are often neglected (Saura-Calixto 2012). It is believed that oligomeric and polymeric forms of PAC are not absorbed by the enterocyte (Deprez et al. 2001) and are thus broken down by the gut bacteria where they provide prebiotic benefits (Williamson and Clifford 2010). The PAC are found in large quantities in small fruits like blueberry, cranberry and strawberry and are also abundant in nuts and especially hazelnuts, pecan, pistachio and almonds where their concentration can reach 500, 494, 237 and 184 mg/100 g F.W. respectively (Anon 2003).

Sulphur Compounds

Glucosinolates

Glucosinolates are amino-derived secondary plant metabolites containing a β-thioglucosyl moiety linked to an α-carbon forming a sulphated ketoxime (Fig. 28.3). They are found in the family of *Brassicacea* and are involved in plant/insects-pathogens interactions, and in plant development. The glucosinolate molecule is not involved as such in the biotic interactions but requires an hydrolysis catalyzed by a β-thioglucosidase, also called myrosinase to release the toxic isothiocyanate molecules. More than 120 glucosinolates have been identified in different species (Rosa et al. 1997) (Table 28.5).

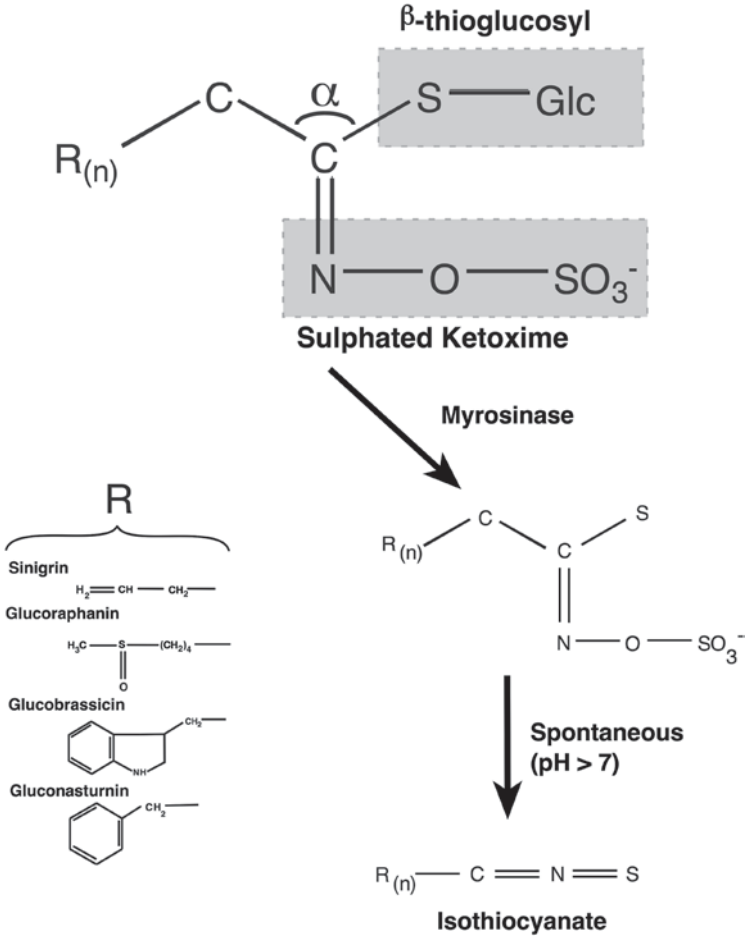


Fig. 28.3 Chemical structure of different common glucosinolates and ensuing thiocyanate

Glucosinolates levels in plants are largely determined by their genetic make up (Rosa et al. 1997) but they are also influenced by abiotic factors like nitrogen, sulphur, or potassium supply (Verkerk et al. 2009). However, genes involved in glucosinolate biosynthesis are also induced by herbivore and pathogen attacks (Agrawal and Kurashige 2003; Brader et al. 2001). Jasmonate and salicylate involved in wounding and herbivory signal transduction increases glucosinolate concentration (Doughty et al. 1995; Kiddle et al. 1994).

Plants have developed efficient defenses against herbivores and pathogens whereby glucosinolate are transformed into isothiocyanate when placed in presence of a thioglucosidase also known as myrosinase (Fig. 28.4). Under normal conditions, the precursor molecule and enzyme are compartmentalized in different tissues; glucosinolates are scattered in vacuoles of most organs while the glucosidase occur only in specific cells called myrosin cells, scattered throughout the plant

Table 28.5 Type of glucosinolate accumulated in different Brassica species, and their related thiocyanate. (Adapted from Verkerk et al. (2009)

Species	Glucosinolates	Average range (mg/100 g F.W.)
Cabbage	Sinigrin	21
Brassica oleracea var. capitata F. alba	Indole glucosinolate	30
	Glucoiberin	
Radish	Dihydroerucin	168
Raphanus sativus var. sativus	Gluraphenin	7
	Indole glucosinolate	6
Mustard	Sinigrin	330
Brassica juncea	Gluconapin	96
	Indole glucosinolate	44
Rocket (Arugula)	4-mercaptobutyl	51
Eruca sativa	Gluraphanin	3
	Glucoerucin	3
	Indole glucosinolate	0.5
Broccoli	Glucoraphanin	20
Brassica oleracea var italic	Indole glucosinolate	6
Cauliflower	Glucoraphanin	11
Brassica oleracea var botrytis	Sinigrin	8
	Glucoiberin	3
Turnip	Pro-goitrin	10
Brassica rapa ssp. Rapa	Indole glucosinolate	15
	Gluconasturnin	10
Red cabbage	Glucoraphanin	11
Brassica oleracea var. capitata F. alba	Sinigrin	10
	Glucoiberin	9
	Indole glucosinolate	22
Chinese broccoli	Gluconapin	76
Brassica rapa var. alboglabra	Glucoraphanin	39
	Pro-goitrin	19
	Indole glucosinolate	127
Brussels sprouts	Sinigrin	23
Brassica oleracea var gemmifera	Glucoiberin	9
	Indole glucosinolate	36
Chinese cabbage	Glucobrassiconapin	4
Brassica campestris spp. pekinensis	Progroitrin	3
	Indole glucosinolate	6
	Aromatic glucosinolate	5

along the vascular system. Following physical damages, crushing or biting, glucosinolates will be placed in physical contact with the hydrolyzing enzyme and will release the thiocyanate. The type of hydrolysis product generated depends on the chemical nature of the parent glucosinolate side-chain and is also modulated by the presence of proteins associated to the enzyme myrosinase (epithiospecifier protein) responsible for cleaving glucose from its bond to the sulphur atom of the molecule (Kliebenstein et al. 2005) (Table 28.6).

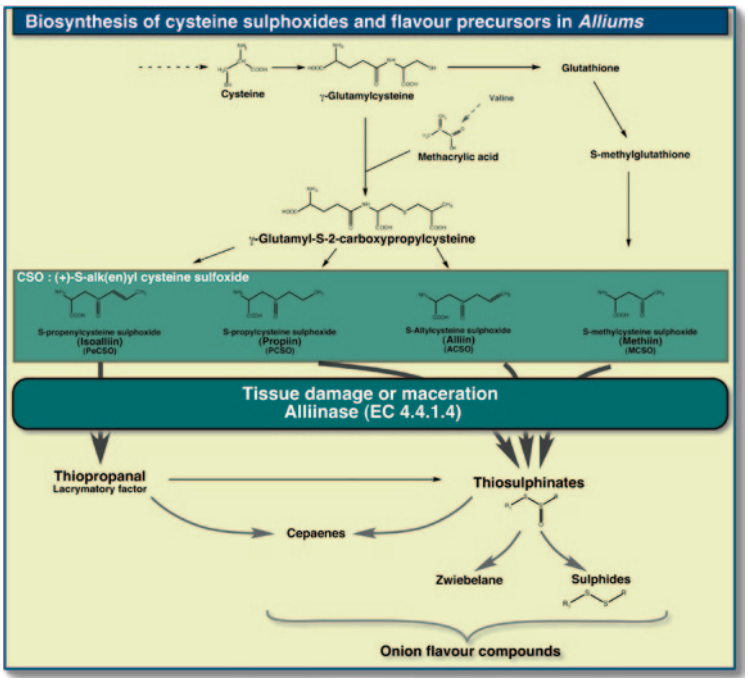


Fig. 28.4 Biosynthetic pathway of S-Alk(en)yll cysteine sulphoxides in Alliaceae

Glucosinolate *per se* have no beneficial biological activity once ingested. Yet, once the sugar moiety is cleaved by myrosinase or by digestive enzymes, the resulting unstable aglycone form iso-thiocyanate or thiocyanate, which display beneficial health properties. One of these, sulphoraphane, is the active hydrolysis compound of the glucosinolate glucoraphanin found especially in broccoli florets, stems and sprouts (Fahey et al. 1997). Keck and Finley (2004) have shown that sulphoraphane is a strong inducer of phase II enzymes and can thus conjugate xenobiotics and transform them is such a way that they can be excreted through urine of the digestive tract (Verkerk et al. 2009).

S-Alk(en)yl-Cysteine Suphoxides

Allium species are important agronomic crops worldwide. They possess characteristic flavor, conferred by specific sulphur compounds and by numerous volatiles and are largely utilized by different societies around the world as a staple food. The volatile sulphur compounds are generated through enzymatic reactions of non-volatile precursors (S-alk(en)yl L-cysteine sulphoxides). Different alliums will accumulate different amounts of these precursors; onion for instance will majorly accumulate 1-propenyl(vinyl-methyl), while garlic accumulate the allyl (methyl-vinyl 2-prope-

Table 28.6 Polyphenol content of typical fruit and vegetables. (Adapted from Phenol-Explorer 2 (Rothwell et al. 2012; Brat et al. 2006))

Fruit and vegetable types	Polyphenol content (mg/100 g F.W.)
Apple	328
Asparagus	23
Banana	52
Blueberry	630
Blackcurrent	621
Broccoli	98
Cabbage	
Cashew nuts	295
Carrots	16
Cauliflower	13
Cranberry	17
Cherry	94
Onion	76
French bean	10
Grapes	195
Guava	186
Leek	33
Papaya	27
Lettuce	
Pear	69
Pineapple	103
Mango	68
Melon	8
Oranges	31
Starfruit	66
Watermelon	12
Tomato	14

nyl) derivatives and chives accumulate 5-propyl cysteine sulphoxides (Fig. 28.5). Sulphur compounds are integral part of allium metabolism and cysteine sulphoxide in some alliums represent up to 1 % of their fresh weight (Kubec et al. 2000). According to Lancaster and Kelly (1983), non-protein cysteine and glutathione and its derivatives account for almost 5 % of the plant dry weight. As for glucosinolates in brassicas, sulphur compounds in alliums are believed to participate to defense protection against pathogens and herbivores (Brewster 1994). They present both antifungal and antibacterial properties. The enzyme is also stored in a different cellular compartment (vacuoles) than its substrate (cytoplasm) and will generate the highly reactive sulfenic acids upon disruption of the cellular integrity after either slicing, mashing or bruising the bulbs. Sulfenic acids will spontaneously condense and inter-react to form many different thiosulfinates, a class of highly volatile and strong smelling compounds characteristics to most allium species. More than 80 volatile compounds of this class have been identified in the head-space of fresh or cooked alliums (Brewster 1994). The kinetics of cysteine sulphoxide hydrolysis and the reactivity of the initial sulfenic acid generated influence the type of thiosulfinates formed, hence the difference in flavor of fresh, boiled or fried onions.

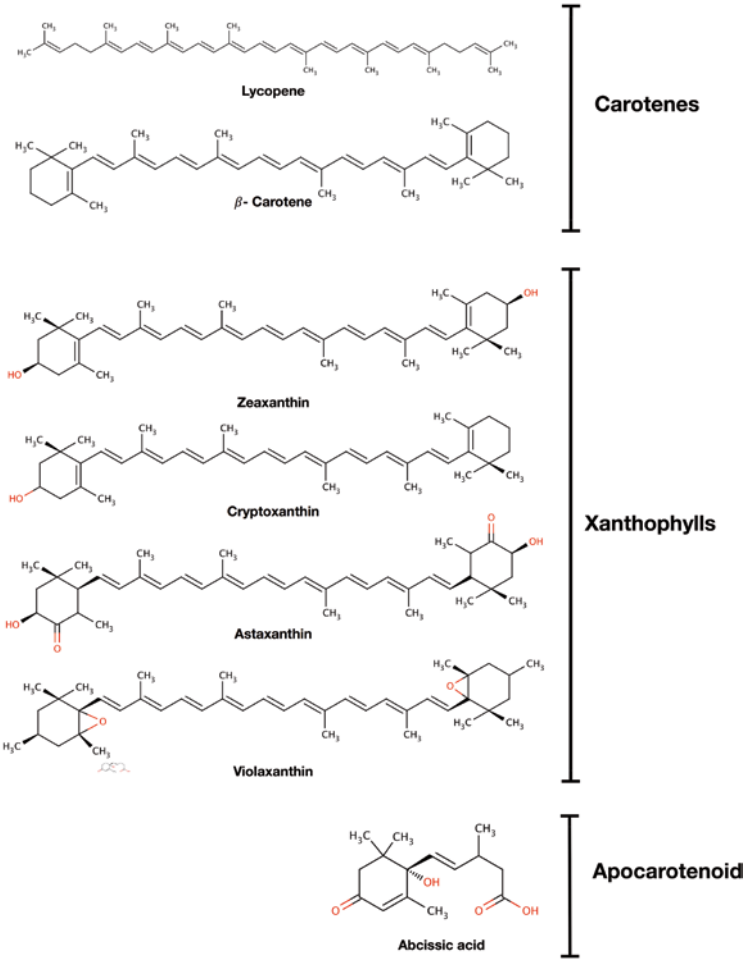


Fig. 28.5 Typical structure of carotenoids and apocarotenoids found in fruit and vegetables

Both volatile and non-volatile compounds from alliums are reported to be effective in the prevention of many diseases (Griffiths et al. 2002). Traditional wisdom, and scientific literature to date, which represent more the 3000 publications, have confirmed the health benefits of onion and garlic in particular (Corzo-MartÌnez et al. 2007). These benefits include reduction of risk factors for cardiovascular diseases (Ali et al. 2000; Milner 2001), reduction in cancer incidence (Fleischauer and Arab 2001), reduction of inflammatory response (Srivastava 1986), enhanced xenobiotic detoxification (Munday et al. 2003), antioxidant properties (Prasad et al. 1995), antibiotic and antifungal properties (Lancaster and Kelly 1983; Rose et al. 2005).

Table 28.7 Total carotenoid content of common FAV. (Adapted from van den berg et al. (2000) and Almeida-Melo et al. (2006)

	Total carotenoids (mg/100 g F.W.)	Type of carotenoids
Fruits		
Banana	1	β -carotenoid, lutein
Guava	4.3	Lycopene, β-carotene
Mango	0.3–7.6	β -carotene, β -cryptoxanthin
Melon		β -carotene, β -cryptoxanthin
Orange	2.8	β -cryptoxanthin, β -carotene, α-carotene
Papaya	2.4–7.3	Lycopene, β -carotene, β -cryptoxanthin,
Peach	0.5–2.1	β -carotene, β -cryptoxanthin
Watermelon	2.4–7.3	Lycopene, β -cryptoxanthin, β -carotene
Vegetables		
Broccoli	1–44	Lutein, β -carotene
Carrots	1–64	β -carotene, α -carotene
Green bean	3	β -carotene, lutein
Kale		
Lettuce	7.5	Lutein, β -carotene
Pepper red	5	β -carotene, β -cryptoxanthin, lutein
Spinach	2.8–44	β -carotene, lutein
Sweet potato	0.3–8	β -carotene, β -cryptoxanthin
Tomato	1–63	Lycopene, lutein, β -carotene

Terpenoids

Carotenoids

Carotenoids belong to a widespread group of plant pigments, represented by more than 600 structurally different molecules (Fraser and Bramley 2004). According to Bendich (1993), more than 60 sources of carotenoids are found in the human diet and they provide a number of beneficial effects on health. FAV constitute the major source of carotenoids in the human diet (Table 28.7). Carotenoids are isoprenoid polymers (C40) made up of a long symmetric aliphatic chain with many double bounds (Fig. 28.5). This molecule can undergo many conformational changes and is found mostly as *trans*- stereoisomers in FAV. Most non-oxygenated forms of carotenoids display pro-vitamin A activity (Fraser and Bramley 2004), act as strong antioxidants (Gramann and Gerald 2005; Palozza and Krinsky 1992), enhance immune function (Rao and Rao 2007), can protect the skin from UV radiation (Mathews-Roth 1993), and can prevent macular degeneration (Snodderly 1995). Moreover and more generally, carotenoids have been shown to reduce the incidence of certain types of cancer (Knekt et al. 1999; Limpens et al. 2006), reduce the incidence of cardiovascular diseases (Klipstein-Goldberg et al. 2000; Voutilainen et al. 2006), reduce diabetes (Ford et al. 1999), and strengthen the immune system (Hughes 1999;

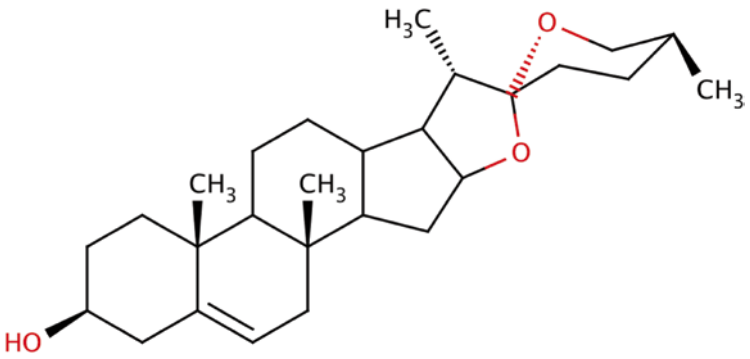


Fig. 28.6 Chemical structure of Diosgenin a common saponin found in FAV

Riso et al. 2006). These beneficial effects are believed to derive from the presence of the many conjugated double bonds (up to 13). This unique arrangement of double bonds on the aliphatic chain, imparts the characteristic yellow, orange and red colour of carotenoid pigments. It also explains the strong antioxidant capacity of these molecules in lipophilic environments, owing to their singlet oxygen quenching capacity and electron delocalisation. Yet carotenoids as most antioxidant molecules can become pro-oxidants in certain conditions. As a matter of fact, two studies, the Alpha-Tocopherol Beta-Carotene (ATBC) (Goodman et al. 2004) and the β-Carotene and Retinol Efficiency Trial (CARET) (Omenn et al. 1996) respectively showed that β-carotene increased the incidence of cardiovascular diseases and increased mortality in groups of smokers probably through a pro-oxidant activity.

Apocarotenoids

Greater attention is recently being placed on the health effects of carotenoids degradation products also known as apocarotenoids (Bouvier et al. 2005). Among this group of molecules, ABA and ABA metabolites are standing out for their bioactivity. Indeed, recent report from Guri's laboratory demonstrate that administration of pure ABA is involved in the etiology of diabetes (Bassaganya-Riera et al. 2010; Guri et al. 2010a), atherosclerosis (Guri et al. 2010b), and inflammatory bowel disease (Guri et al. 2007). Work by Bruzzone et al. (2008) show that picomolar concentration of ABA can influence insulin release from human pancreatic islets via cyclic adenosine signaling cascade. These authors claim that ABA is endogenously produced by human granulocytes and act as pro-inflammatory cytokines (Bruzzone et al. 2007). Since ABA was identified in mammalian brain (Lepage-Degivry et al. 1986), it is believed that it could also act as a neuromodulator (Bodrato et al. 2009). Berries are rich sources of ABA and ABA-glucose esters so are other seed sources (Jia et al. 2011; Zifkin et al. 2012).

Triterpene Saponins

Saponins are constituted of a triterpene backbone to which are attached different glycosides (Fig. 28.6). They are present in oats, allium species (leek, garlic), asparagus, tea, spinach, sugarbeet, and yam (Price et al. 1987). Saponins have been reported to possess a wide range of biological activities and in particular to have analgesic, anti-inflammatory, antimicrobial, antimutagenic and antiobesity) properties (Güçlü-Üstünda and Mazza 2007).

Alkaloids

Capsaicins

Capsaicins are amide derivatives of vanillylamine and branched fatty acids chain. Typically, chilli pepper (*Capsicum sp.*) accumulates capsaicinoids in their fruits. For example, this molecule class displays a very strong pungency due to its ability to interact with non-selective cation channel protein receptors and thus trigger a general sensation of pain and heat in mammalians (Jordt et al. 2003). Healthwise, Surh and Lee (1995) have shown that capsaisins have anticarcinogenic properties and can induce apoptosis and thus display antitumoral activity. Capsaicinoids are also potent antioxidants (Kogure et al. 2002) and have been associated with increased energy expenditure in human and a decreased in long-term excess energy intake (Doucet and Tremblay 1997) and may thus be used therapeutically to control weight (Reinbach et al. 2009).

Health Effects of FAV Phytochemicals

FAVs and the Burden of Chronic Diseases

A huge body of evidence indicates that our current lifestyle, which includes smoking, low physical activity and poor diet, has a major influence on our health. The WHO global report entitled ‘Preventing Chronic Diseases: A Vital Investment’ (Anon 2007), informs us that 60% of all death on the globe are due to chronic disease and that 80% of these deaths occur in low and low-middle income countries. Shockingly, a large proportion of these casualties could be avoided by simply adopting a healthier lifestyle. Indeed, a recent paper by Khaw et al. (2007) evaluated the impact of behavioral factors to health and clearly demonstrated that adopting a healthy lifestyle could improve life expectancy of a population by 14 years. It can also reduce the incidence of diabetes by 80% and cancers by 40% (Anon 2004). Nutrition is probably the single most important factor affecting the health status of

the population; diet has long been linked to the development of chronic diseases and dietary modifications are one of the cornerstones of chronic disease prevention.

There is a substantial and growing body of evidence linking increase in FAVs consumption to a reduction of the risk of chronic diseases, increases lifespan and quality of life, while decreasing medical costs (Tomas-Barberan and Gil 2008). However, the components of FAVs responsible for these beneficial health effects are not entirely identified and the manner by which they exert this effect is still open to debate. FAVs accumulate several thousands phytochemicals with shown biological activity against a number of illnesses *in vitro*. For example, glucosinolate and isothiocyanate found in Brassicas have been linked to cancer prevention (Talalay and Fahey 2001), polyphenols have been linked to cancer prevention, anti-inflammatory responses and prevention of coronary heart diseases (CHD) (Habauzit and Morand 2012), carotenoids found in leafy vegetables and carrots have been associated with a reduced incidence certain types of cancer (Gallicchio et al. 2008), prevention of cardiovascular diseases (Riccioni 2009), of macular degeneration (Sabour-Pickett et al. 2012) and with the strengthening of the immune system (Riso et al. 2006), while sulphur compounds found in onions have been related to CHD and cancer prevention (Corzo-Martínez et al. 2007).

Antioxidant Capacity

Much work has been conducted to determine the antioxidant capacity of FAV (Proteggente et al. 2002). Antioxidants are protective agents that inactivate reactive oxygen species and therefore significantly prevent oxidative damages. Most organisms living on earth have developed strong defenses against oxidation and rely in particular on superoxide dismutases, catalases, and glutathione peroxidases to attenuate the reactive oxygen species generated by the metabolism. In addition, antioxidants such as vitamin E, vitamin C, carotenoids and to a certain extent polyphenols are available from foods (Anon 2004, 2006). The role of dietary antioxidants in disease prevention has received much attention over the years. It is nowadays less prominent since recent evidences from research are shedding new light on the role of antioxidants in the etiology of diseases; the tenet that dietary antioxidants are responsible for the prevention of diseases is now much contested (Hollman et al. 2011a; Scalbert et al. 2005). As a matter of fact, very few studies have shown that antioxidants were active *in vivo* (Frankel and German 2006; Halliwell et al. 2005) and some report that antioxidants can even have harmful effects *in vivo* (Perera and Bardeesy 2011; Ristow et al. 2009). Halliwell et al. (2005) caution that reports of increase in plasma total antioxidant activity after flavonoid intake, must be interpreted with care since these may be caused by many confounding factors. For instance, the antioxidant effect of polyphenol on plasma has recently been challenged since any change in plasma antioxidant capacity after fruit consumption may be caused by fructose mediated increases in uric acid rather than fruit-derived antioxidants (Godycki-Cwirko et al. 2010; Lotito and Frei 2006). According Halliwell et al.

(2005), results obtained from *in vitro* experiments demonstrating positive response of antioxidants on disease end-points may simply be measurement artifacts and biases of experimentation (Long et al. 2000). Yet, it appears clear that many classes of phytochemicals found in FAV can stimulate the natural antioxidant capacity of the organism and prime the defense system against a number of diseases (Hollman et al. 2011b; Traka and Mithen 2009).

Bioavailability

For any phytochemicals to exert a systemic activity in the organism it has first to be bioavailable, in other words it has absorbed, enter the systemic circulation and reach the target tissues or organs at adequate levels and in an active form. Most bioactive phytochemicals derived from plants are recognized as xenobiotics and are thus poorly absorbed, or are aggressively conjugated in order to make them more water-soluble and ease their excretion. For instance, many researchers have reported that the bioavailability of plant polyphenols is very low (Del Rio et al. 2010; Kroon et al. 2004; Manach et al. 2005; McGhie et al. 2003; Milbury et al. 2010; Prior and Wu 2006; Scalbert and Williamson 2000; Spencer 2008). It is also accepted that the polyphenol glycoside moiety has to be removed before absorption. Yet, depending on the position of the glycoside attached to the flavonoid, the degree of polymerization or galloylation of flavan-3-ols, different quantity of the compound will be absorbed. Considering the complex and varying nature of the flavonoid glycosides found in FAV, one can understand that the bioavailability of the different polyphenols will fluctuate markedly in line with the different benefits stemming from their consumption. It is believed that interaction between different polyphenolic species can result in synergism or antagonisms (Scheepens et al. 2010). Knowing that specific polyphenols transporters are found at the surface of the intestine brush border, in particular the sodium-dependent glucose transporter (SGLT1), and that multidrug resistance proteins also participate in the elimination of xenobiotics and polyphenols, which are incidentally recognized as extraneous chemicals, it is assumed that different polyphenols can competitively interact at their site of absorption or elimination. In this context, the consumption of whole FAV, bringing a variety of polyphenols, is assume to confer more benefits than isolated molecules owing to the potential synergies that can develop between the many polyphenols and an improved bioavailability at the target sites of action.

On the contrary, carotenoids are more bioavailable and can be found in relatively higher concentration unchanged in the plasma and in certain tissues and organs (Verkerk et al. 2009). Being liposoluble, they will be absorbed by passive diffusion after being incorporated into micelles formed by dietary fats and bile acids. The micellar carotenoids are then incorporated into chylomicrons and eventually into lipoproteins to be released into the blood stream (van den Berg et al. 2000). The carotenoids are mostly included into plasma membrane or stored in adipose tissues. Interestingly, cooking and heat liberate the carotenoids from the food matrix and

augment their bioavailability. It has been well demonstrated that absorption of lycopene from processed tomato products for instance is higher than from raw tomatoes (Rao and Agarwal 1998). The half life of the carotenoids in the system is about 2 to 3 days (Stahl and Sies 2005). β-carotene have been shown to accumulate in fat tissues but lycopene accumulate in human adrenal glands, prostate, breasts, testes, and liver. Intake is about 4–25 mg/d in North America (Rao and Rao 2007).

A large proportion of the glucosinolates and metabolites reach the intestine where they undergo a massive attack and degradation by the colonic microflora. The remaining glucosinolates and thiocyanates are absorbed passively through the gut epithelium. Once in the enterocyte, they will be rapidly conjugated with glutathione and transported in the systemic circulation to be metabolized via the mercapturic acid pathway for their subsequent urinary excretion. As for polyphenols, glucosinolates and their bioactive products are recognized as xenobiotics and are rapidly eliminated from the body after extensive metabolism in the liver, and enterocytes. Yet, by the action of sulfotransferases, isothiocyanate conjugates can release the free isothiocyanate at specific target tissue to display their biological activity (Traka and Mithen 2009). These molecules strongly bind to proteins like albumin and other glycoproteins. Sulforaphane is considered a poorer substrate that other glucosinolate to phase I enzymes which explains its longer residency in the body and thus higher bioactivity. The metabolites are most likely the molecules responsible for the beneficial effects.

Cardiovascular Diseases

Nutritional epidemiology has provided convincing evidence for the cardio-protective effects of the frequent consumption of FAV prompting health authorities to promote their consumption (Ness and Powles 1997). For instance, in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), Rissanen et al. (2003) observed a clear association between FAV consumption and cardiovascular health. However, recent reassessment of the data reveals that FAV consumption is weakly associated with reduced risk of coronary heart disease in cohort studies; evidences for FAV consumption preventing cardiovascular disease remains scarce (Dauchet et al. 2009). Yet, flavonoid and carotenoid intake have been linked to decreased morbidity and mortality from coronary heart diseases (CHD) (Hertog et al. 1995; Riccioni 2009; Voutilainen et al. 2006). The reported beneficial effects of these molecules on CHD risk are more than likely the result of a reduction in inflammation (Loke et al. 2008b), and a reduced inhibition of LDL oxidation, which has been demonstrated both *in vitro* and *in vivo* (Fuhrman and Aviram 2001). The underlying mechanisms for these beneficial effects are believed to include improved endothelial function through improved nitric oxide balance (Schewe et al. 2008), decrease in cellular oxidative stress (Steffen et al. 2008), and inhibition of inflammation (Loke et al. 2008b).

Oxidative stress and inflammation play a pivotal role in the initiation and progression of atherosclerosis and CHD. Atherosclerosis is a condition affecting the

coronary arteries in which gradual uptake of oxidized lipoproteins by the endothelium and the resulting inflammatory response leads to deposition of plaques in the arterial walls and eventual restriction of blood flow which can aggravate or produce hypertension and eventually cause irreparable damage to the heart. The accumulation of oxidized LDLs in the intima and their uptake by macrophages are early events in atherosclerosis that could be lessened by the presence of polyphenols. Flavonoids contained in FAV may decrease the risk of developing atherosclerosis, due to their ability to inhibit low-density lipoprotein (LDL) oxidation (Arai et al. 2000; Basu et al. 2010), (Perez-Vizcaino et al. 2006), to up-regulate antioxidant enzyme expression (Wu et al. 2010), to reduce platelet aggregation and adhesion (Hubbard et al. 2006; Ostertag et al. 2010; Steffen et al. 2008), to reduce inflammatory response of the vascular tissues (Perez-Vizcaino et al. 2006; Xie et al. 2011; Youdim et al. 2000), while also inducing endothelium-dependent vasodilation (Andriambeloson et al. 1998; Kalea et al. 2009; Loke et al. 2008a) and reducing blood pressure (Edwards et al. 2007). Many researches show that polyphenols interact with the signaling pathways of immune and inflammatory cells (DeFuria et al. 2009; Rechner and Kroner 2005; Youdim et al. 2000). Such an action has been attributed to an improved vascular reactivity (Kalea et al. 2009) and in particular to an effect on iNOS activity and up-regulation of the endothelial nitric oxide synthase, both of which play a crucial role in maintaining cardiovascular homeostasis by favorably modulating blood pressure and reducing endothelial dysfunction, so as to maintain normal vascular function and blood pressure.

Obesity

Obesity, is fast becoming a worldwide health problem and has dramatically increased in every continents in the last decade. The recent survey from the USA National Health and Nutrition Examination Survey (NHANES) show that approximately 35 % of men and women are obese (Flegal et al. 2012). In Europe, the prevalence of obesity (body mass index $\geq$ 30 kg/m^2) has reached epidemic proportions, affecting more than 25 % of the population in countries like Spain, Poland, Czech Republic and Italy, in both men and women. A dramatic increase in overweight and obesity prevalence has also been observed in mainland China with 22.8 % and 7.1 %, respectively, which represent an increase of 41 % and 97 % of the respective incidence when compared to 1992 (Chen 2008). This disturbing reality is correlated with an the exponential rise in the prevalence of type 2 diabetes (T2D), which is estimated to reach the appalling rate of 439 million cases by 2030 (Shaw et al. 2010).

Obesity is a complex outcome influenced by a variety of interacting factors involving genetic, environmental, social and behavioral factors. It is ultimately the result of a disruption of the energy balance equation where energy intake surpasses its expenditure, resulting in the storage of excess energy into adipose tissue. Regulating energy intake is not as easy as it may sound, since eating is regulated by an intricate network of hormonal messages affecting the central nervous system at the level of the hypothalamus and regulating appetite (Woods and D'Alessio 2008).

Indeed, more than 20 peptides with hormone activity (insulin, GLP-1, CCK, PYY, ghrelins, leptin, adiponectin and others) are produced by peripheral tissues (adipose, muscular, pancreas, and the gut) linking adiposity levels and energy intake to the central nervous system (Kim and Park 2011).

A number of bioactive phytochemicals found in FAV have been shown to regulate energy balance and have an effect on weight gain and energy homeostasis (Kim and Park 2011). Specifically, many excellent literature reviews on the effect of polyphenols on energy metabolism and reduction type-2 diabetes (T2D) have recently been published (Basu and Lyons 2012; Cherniack 2011). T2D, a sequel of obesity and characterized by an hyperinsulinemia and insulin resistance belongs to a constellation of factors (hyperglycemia, hypertension, insulin resistance, glucose intolerance and dyslipidemia) leading to a diet sensitive condition called the metabolic syndrome (Bland 2011). Adipocyte dysfunction is at the origin of the syndrome and is associated with macrophage infiltration in adipose tissue leading to the release of pro-inflammatory cytokines and activation of inflammatory signalling pathways, which can interfere with insulin action in skeletal muscle, liver and adipose tissue thus the concept of insulin resistance.

Mechanistic studies using *in vitro* models have provided evidence of the beneficial effects of FAV polyphenols on hyperglycemia and hypertension, two significant CHD risk factors that coexist in metabolic syndrome (Hanhineva et al. 2010). For instance, polyphenols have been reported to exert beneficial effects on glucose homeostasis by (i) inhibiting sugar and lipid digestive enzyme (McDougall et al. 2008), (ii) inhibiting glucose absorption (Serrano et al. 2009) (iii) protecting from glucotoxicity through the reduction of advance glycation product formation (McIntyre et al. 2009) and from pancreas β-cells toxicity(Martineau et al. 2006) (iv) increasing insulin secretion (Adisakwattana et al. 2008), (v) improving glucose uptake in muscle and adipocytes (Grace et al. 2009), (vi) increasing hepatic glucokinase activity, (vii) suppressing gluconeogenesis (Burton-Freeman 2010) and (viii) controlling satiety (Molan et al. 2008). They can also protect against T2D through anti-inflammatory effect (González et al. 2011; Comalada et al. 2005). Indeed these authors showed that FAV polyphenols reduced a number of inflammatory biomarkers linked to insulin resistance and hyperglycemia such as TNF-a, IL-6, MCP-1, and iNOS (González et al. 2011). It is generally considered that polyphenols like quercetin (Dias et al. 2005), proanthocyanidins (Serrano et al. 2009), hydroxycinnamic acids (Barone et al. 2009), and stylbenes (Alberdi et al. 2011; Baile et al. 2011) prevent the occurrence of T2D by modify carbohydrate, lipid and energy metabolisms. Moreover, many polyphenols and in particular flavonols and stylbenes present in large quantities in onions and many other berries exert a myriad of anti-inflammatory, anti-obesity, anti-steatosis and hypoglycemic effects through an AMPK-SIRT1-PPARγ-dependent mechanisms (Alberdi et al. 2011; Baile et al. 2011), can lead to adipocyte differentiation (Moghe et al. 2012; Vuong et al. 2007) and increased the number of mitochondria and the energy expenditure (Pajuelo et al. 2011). In this context, resveratrol has been shown to mimic caloric restriction, increase lifespan and reduce inflammatory response leading to reduce T2D and energy metabolism dysfunction (Aires et al. 2012; Brasnyó et al. 2011; Szkudelska and Szkudelski 2010).

Cancer

It is well accepted that consumption of FAV is associated with decreased risk of developing cancer (Cooke et al. 2005; Potter 2005; World Cancer Research Fund 2007). Among all FAV, berries probably possess the best documented anti-tumoral properties (Duthie 2007; Neto 2007; Neto et al. 2008; Seeram 2008), but there are also strong epidemiological evidences showing that Alliaceae and Brassicaceae consumption are linked to reduced incidence of cancers (Griffiths et al. 2002; Verkerk et al. 2009). Cancer development is complex and is commonly recognized as a multi-factor process that requires the cumulative action of three main events: initiation, promotion and progression. At the base, the incipient causes leading to the initiation of cancers are DNA damages and the succeeding accumulation of mutations. Phytochemicals found in FAV have been shown to interfere at all stages of the etiology of cancer.

Polyphenols found in FAV have been shown to prevent the growth and progression of cancers in many *in vitro* and in animal models; (e.g. mice endothelial neoplasms (Gordillo et al. 2009), colorectal mucosal cells (Håkansson et al. 2012), prostate cancer cells (Matchett et al. 2006), colon cancer cells (Seeram et al. 2006; Suh et al. 2007), breast, cervix cancer cells (Wedge et al. 2001), HepG2 liver cancer cells (Kraft et al. 2006), HL-60 leukemia cells (Murphy et al. 2003), HCT-116 and HT-29 human colon cells (Murphy et al. 2003; Ono et al. 2002), mammary carcinoma 4T1 cell lines (Mantena et al. 2006), breast cancer cells (Adams et al. 2011; Adams et al. 2010) (Aiyer et al. 2012; Faria et al. 2010), prostate cancer cells (Matchett et al. 2006; Schmidt et al. 2006), meduloblastoma cell lines (Labbe et al. 2009), and lung cancer cell lines (Kausar et al. 2012)). Actually, Aiyers et al. (Aiyer et al. 2012) has thoroughly reviewed the effect of polyphenols found in Vacciniums on receptor signaling and induction of cell death pathway. Moreover, polyphenols can mitigate the initial formation of tumors by blocking the action of carcinogens responsible for mutations. For instance, a blueberry extract was shown to induce phase II detoxification xenobiotic enzymes (quinone reductase) (Bomser et al. 1996) and inhibit the initiation stage of chemically induced carcinogenesis in liver cancer cells (Smith et al. 2000).

In a similar manner, many prospective and epidemiological studies have also shown that the regular consumption of *Alliums* could have protective effects against cancer (Griffiths et al. 2002; Lampe 1999). For instance, there appears to be a strong link between the consumption of onions and the reduced incidence of stomach and intestine cancers (You et al. 2005). The Epic Prospective Study, conducted on more than half a million subjects, showed clear correlation between onion consumption and reduction in intestinal and stomach cancers (Gonzalez and Riboli 2006). A synthesis of case-control studies carried in Italy and Switzerland revealed that consumption of one to seven portions of onions per week reduce the risks of colon, ovary, larynx and mouth cancers (Galeone et al. 2006). Similar correlations are also observed for brain and stomach cancers in a case-control study in China (Hu et al. 1999) and breast cancer in France (Challier et al. 1998). Mortality due to prostate

cancer also appears to be reduced by a diet making a large place to onions (Grant 2004). Onion is probably the most important source of polyphenols in the diet (Hollman and Arts 2000) and it has been showed in many studies to have anticarcinogenic properties *in vitro* (Wilms et al. 2005).

There is also an inverse relationship between the consumption of dark green vegetables, and in particular of brassica vegetables and the risk of colorectal cancer (Voorrips et al. 2000). Glucosinolates and isothiocyanates found in Brassicas appear to explain this reduced risk. These molecules are triggering phase I and II enzymes involved in carcinogen metabolism and detoxification (Talalay and Fahey 2001). They are also priming the natural antioxidant defenses as evidence by the decreased in DNA damages and inhibition of aberrant crypt foci formation in animal studies. This protection appears to be mediated by antioxidant response elements in the promoter region of phase II detoxification enzymes and antioxidant enzymes and specifically through the activation of the Nfr2 transcription cascade (Jeong et al. 2006).

Neurodegenerative Diseases and Cognition

Normal aging is accompanied by a decline in motor and cognitive performance (Lau et al. 2005). The mechanisms responsible for behavioral and neuronal changes seen during aging are not fully understood, but it appears that dietary FAV supplementation can slow or even reverse various age-related neuronal declines (Gu et al. 2010). The molecular mechanisms involved in the beneficial action of FAV on the brain remain unclear but likely relate to the modulation of processes, such as neuronal plasticity affected during aging. Alzheimer's disease is multifactorial, with a complex combination of genetic and non-genetic components but share a common biochemical pathway, that is, the altered production of the amyloid β peptide, which leads to neuronal death and dementia.

In vitro mechanistic investigations have begun to elucidate the molecular mechanisms involved in the beneficial effect of dietary polyphenols found in FAV on cognition and neurodegenerative diseases. These studies suggest that flavonoids can i) reduce the pro-inflammatory state (Frisardi et al. 2010), characteristic of the metabolic syndrome; ii) modulate intracellular signaling pathways controlling neuronal cell apoptosis (Choi et al. 2012; Spencer 2008); iii) have a neuroprotective effect on neurons and glial cells (Galli et al. 2006; Vuong et al. 2010); decrease cerebral inflammation through a retardation of the systemic vascular inflammation (Williams and Spencer 2011); and improve cerebral blood flow leading to new hippocampal cells formation and enhanced memory (Ghosh and Scheepens 2009).

In particular, there are many recent reviews on the beneficial effects of berry on neurodegeneration and improvement of cognition (Giacalone et al. 2011; Ramassamy 2006; Shukitt-Hale et al. 2008; Williams and Spencer 2011). These reviews specifically show that polyphenols convey beneficial effects on memory and learning in both animals and humans. However, there are few epidemiological data correlating the consumption of berry per say to neurodegenerative diseases and cogni-

tive decline. One of these, the PAQUID study following a population over 10 years, showed that and average intake of about 14 mg/day of flavonoids was associated with a reduction in cognitive decline (Letenneur et al. 2007). There is also a paucity of human intervention study on berry polyphenols and cognition (Lamport et al. 2012). Among those published, Krikorian et al. (2010) were able to demonstrate, in a single blind clinical study trial with only 9 adults displaying mild cognitive impairment, that the consumption of a blueberry juice, providing 1.8 mg polyphenol/d for 12 weeks, had a significantly better verbal paired associate learning, but there was no difference in the California Visual Learning Test. In this study, there was a trend for the berry group to have a better mood while have a normalized glycemia and insulin level.

If there are only a few human studies on the effect of polyphenols on cognition, there are many animal studies showing that polyphenol supplementation and in particular blueberry polyphenols can prevent cognitive decline and memory (Cherniack 2011). For instance, Andres-Lacueva and Shukitt-Hale (2005) showed that blueberry anthocyanins could reach the cerebral cortex, the hippocampus, the striatus and the cerebellum and that they correlated with the performance of mice in a maze test. Similarly, Galli et al. (2006) showed that a blueberry diet fed for 10 weeks to aged rats improved had a better capacity to generate heat shock protein (HSP-70) a reflection of their ability to support neurodegenerative process in the brain. Blueberry supplementation also improved the ability of elderly rats to recognize objects through a preservation of neurogenesis in the hippocampus. This beneficial effect was not linked to a loss of amyloid plaque. Young rats fed with a blueberry polyphenol extract had a better performance in the water maze test (Joseph et al. 2008), while old rats fed with a blueberry diet maintained a better balance while walking across a wire and had a better performance in the water maze test (Joseph et al. 1998). Williams et al. (2008) were able to show that rats fed for 12 weeks with a 2 % blueberry diet had an improved special working memory and an improved cognitive performance. This effect was attributed to an improved phosphorylation of C-AMP Responsive Element-Binding Protein, involved in signal transduction and associated with long-term memory. Papandreou et al. (2009) also showed that mice fed with a blueberry extract had improved cognitive performance, had higher brain antioxidant capacity and had an improved acetylcholinesterase activity. Blueberry supplemented diet improved the hippocampal neurogenesis and improved special memory through an activation of the Insulin-Growth Factor-1, a key protein in the learning process and the modulation of neurogenesis (Casadesus et al. 2004). Vuong et al. (2010) showed that a fermented blueberry juice had a neuroprotective effect by activating cell survival pathways associated with p38 and JNK pathways. Recently, Rendeiro et al. (2012) showed that elderly rats feed with a 2 % blueberry diet had a better special memory, a faster rate of learning than the control group. This effect was linked to the activation of the ERK-CREB-BDNF pathway.

Conclusions

In conclusions, research conducted over the last 15 years demonstrates that FAV consumption definitely provides positive effects against a number of chronic diseases. The exact mode of action of the different bioactive compounds on health is slowly being unraveled. It is becoming clear that their preventative influence is not only mediated directly through their antioxidant capacity but chiefly through their effects on specific gene expression. In particular, signaling cascades associated with anti-inflammatory responses and control of energy metabolism are clearly affected. Polyphenols, but also carotenoids and sulphur compounds may act at different levels. Due to their low bioavailability, much emphasis is now placed on the activity of the circulating metabolites on target organs and cells.

We are definitely at a turning point with respect to the demonstration of health effects of FAV phytochemicals. A consensus is slowly emerging that the beneficial properties of its phytochemicals must be studied by conducting human clinical trials or animal studies. The demonstration of positive effects in human will undoubtedly stimulate FAV consumption all over the world.

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