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Supercritical methodologies applied to the production of biopesticides: a review

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Abstract Supercritical technologies are new, environmentally friendly, advanced separation techniques that have attracted the attention of both industry and academy in their aspirations of producing safer products with cleaner processes. In the field of biopesticides, supercritical fluids are being used in different stages, from the extraction of active ingredients from natural matrices to the encapsulation of blends during the formulation of the final commercial pesticide. This review summarizes different supercritical processes that arise in literature comprising supercritical fluid extraction, supercritical antisolvent fractionation or extraction, supercritical assisted atomization, particle from gas saturated solutions and supercritical solvent impregnation among others. The aim of this work is to give a general view of supercritical fluids in the field of biopesticides production, optimization and formulation, emphasizing in the extraction, fractionation and encapsulation and highlighting their importance when green, solvent free processes have to be designed.

Keywords Natural pesticides · Extraction · Formulation · Fractionation · Supercritical fluids

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Introduction

The interest for biopesticides has been growing rapidly since the awareness for sustainability, climate change and organic farming has risen dramatically. Biopesticides, according to the United States Environmental Protection Agency (USEPA) include naturally occurring substances and microorganisms that control pests and pesticidal substances produced by plants containing added genetic material (US Environmental Protection Agency 2012). Economically speaking, pesticides have a worldwide emerging market (1,600 million dollars in 2008 and 3,300 million dollars in 2014 according to previsions) (The 2010 Worldwide Biopesticides Market Summary 2011) due to two factors: organic agriculture and its regulations (Isman 2006) grow exponentially every

year and restrictions for the use of synthetic pesticides are increasing rapidly. Biopesticides are forced to comply with the legislation in different fields. Inside the European Union, in the Sixth Environment Action Programme in matter of organic farming (European Commission 2007) the following aspects are prioritized: crops rotation, locally organized renewable resources, adequate species selection and also adequate products for handling with pests. Among these products to handle pests, those preferred are: the derived from organic farming, low solubility fertilizers and natural products or derived. Synthetic organic pesticides, on the contrary, are known for causing ecological disasters in their industrial production such as the Bhopal accident in 1984 (Lapierre and Moro 2002), ecological problems in their massive use such as aquifer contaminations (Diaz-Cruz and Barcelo 2008) or bioaccumulation (Katagi 2010).

In this context, the production of biopesticides is included in the philosophy of Green Chemistry, a current within the Chemistry which seeks safer products with cleaner processes, whose twelve principles were enumerated by Anastas and Warner (2000). Some of them can be found in the production of biopesticides such as: the energy and raw materials saving, the promotion of safer industries, the non toxicity of the products or the use of renewable raw materials (those considered inexhaustible in a human life cycle). Among these principles, supercritical fluids, especially supercritical CO_2 ($scCO_2$), are a paradigm as alternative solvents, minimizing the quantities of organic solvents used and complying with sustainability.

A supercritical fluid is by definition an element or compound above its critical pressure and temperature. In a simpler form, behind this definition a fluid with extraordinary properties can be seen. It combines physicochemical properties of a gas and of a liquid; it has the viscosity and diffusivity of the former and the solving power of the latter. Furthermore, its density, that is to say, its solvating capacity, can be tuned by varying slightly the pressure and temperature conditions (Taylor 1996). Moreover, if the supercritical fluid is depressurized enough, it passes to gas, separating itself from the solute, which precipitates solvent-free. These characteristics can make a supercritical fluid an ideal alternative solvent in Green Chemistry.

The first reported observation of the occurrence of a supercritical phase was made by Baron Cagniard in 1822 (Cagniard de la Tour 1822), however the development of supercritical techniques did not start until the 1970s, when Supercritical Fluid Extraction (SFE) was found to be efficient in the removal of lower boiling products from the residue of crude oil distillation (Gearhart and Garwin 1976) or in the decaffeination of coffee beans (Zosel 1981). Since then, several techniques have been applied in different fields including chemical reactions (Aresta et al. 2003; Lester et al. 2006; Moreno et al. 2011; Han and Poliakoff 2012), soil decontamination (Librando et al. 2004; Saldaña et al. 2005; Sunarso and Ismadji 2009), advanced materials fabrication (Reverchon and Adami 2006; Pérez et al. 2010; Morre et al. 2011; Zhang et al. 2011), preparation of pharmaceutical (Domingo et al. 1997; Davies et al. 2008; Reverchon et al. 2009; Della Porta et al. 2011; Elizondo et al. 2011) and food products (Rubio-Rodriguez et al. 2008; Fernández-Ronco et al. 2011; Bernardo-Gil et al. 2011) or extraction of bioactive compounds from natural matrices (Martínez 2007; Casas et al. 2009; Langa et al. 2009a, b; Martín et al. 2011e).

The process design using supercritical fluids depends highly on the phase equilibrium scenario, strongly sensitive to changes in operating conditions. Therefore, phase equilibrium engineering plays a key role in the synthesis and design of these processes. This engineering is the systematic application of phase equilibrium knowledge to process development, including experimental data, data banks, phenomenological phase behaviour, thermodynamic analysis and mathematical modeling procedures for phase equilibrium process calculations (Herrero et al. 2010).

Although supercritical fluids have been used in several processes along their history and in several disciplines, the aim of this review is to summarize those techniques that have been used in the extraction, optimization and formulation of biopesticides, which will include: supercritical fluid extraction (SFE), supercritical antisolvent fractionation (SAF), supercritical antisolvent (SAS), supercritical solvent impregnation (SSI), particles from gas saturated solutions (PGSS) and supercritical assisted atomization (SAA).

Supercritical fluid extraction (SFE)

The SFE is the most used supercritical technique, and although it is somewhat new in time, it has already been deeply studied. Chemical, petrochemical and

food industries have been developing different processes related to this technique. Foods as decaffeinated coffee or tea, fruit juices with flavour enhancers or alcoholic drinks whose graduation has been reduced, have been obtained industrially by means of this technique (Brunner 2005; Ruiz-Rodríguez et al. 2012). However, the obtention of added value natural products by means of this safe and clean technique is the application that has to be highlighted among the uses of SFE.

SFE has become an alternative method to the traditional extraction ones such as hydrodistillation and organic solvent extraction, because it avoids the disadvantages of them. Hydrodistillation can cause hydrolysis and hydrosolubilization or can degrade thermolabile compounds, while the use of organic solvents in traditional extractions entails the inherent problems of working with these types of solvents (generation of Volatile Organic Compounds, sample contamination, expensive removal of the solvent, human toxicity) (Reverchon 1997). The only serious disadvantage of SFE is a high investment cost compared to traditional atmospheric pressure extraction techniques. However, the base process scheme (extraction plus separation) is relatively cheap and very simple to be scaled up to industrial level (Reverchon and De Marco 2006).

SFE consists in mixing inside a vessel a supercritical fluid (the solvent) with a matrix where the interesting compounds (the solutes) are. The viscosity, diffusivity and solvent power of the supercritical fluid allow the compounds to be solubilized in it. Afterwards, a correct depressurization of the supercritical phase allows the recovery of the solvent free compounds and the compounds free solvent. Furthermore, if an adequate configuration is used in the depressurization, several fractions can be obtained if the operational conditions of the separators are properly chosen.

The most widely used supercritical fluid for extraction is carbon dioxide; economic, inert, non toxic, environmentally friendly and generally recognized as safe by United States Food and Drug Administration and European Food Safety Agency. Furthermore, its operational conditions are moderate because of the critical temperature and pressure (31.1 °C and 7.39 MPa respectively), which avoids thermal degradation and excessive safety requirements. At industrial scale, the used CO_2 is recycled after the extraction process by means of a new compression, which also diminishes operational costs. As it has been mentioned before, its solvating capacity can be tuned by varying slightly the pressure and temperature conditions, so step extractions or consecutive separators allow for a simple fractionation. The principal disadvantage of CO_2 is its apolarity, which makes the CO_2 dissolve mainly apolar compounds. To overcome this limitation, a modifier, also called entrainer, (principally alcohols in a range of 1–10 %) of the supercritical fluid can be added, which lets the mixture dissolve more polar compounds.

At laboratory scale or pilot plant scale, several vegetable species have undergone extraction processes with supercritical CO_2 ($scCO_2$), with different results and applications (Pereira and Meireles 2009). Some factors influence the extraction and they have to be taken into account when carrying out a series of experiments; so evident as the temperature, the supercritical pressure, the CO_2 flow or the extraction time and some other not as evident as the particle size, the packing of the material in the extractor or the water content of the vegetable matrix.

Although SFE is a well known technique (14,023 references in scifinder®, key words supercritical fluid extraction), the biopesticides obtention with such technique is not so common (26 references in scifinder®, key words supercritical fluid extraction + natural pesticide, 724 references, keywords supercritical fluid extraction + pesticide, although the majority of them refers to the determination of pesticide residues in soils or food). However, some examples available in literature can be seen and will be reviewed in this paper.

SFE of pyrethrins

One of the applications of the biopesticide extraction with supercritical fluid is the pyrethrins extraction from plants of the genre *Chrysanthemum*. Pyrethrins (Fig. 1), the most widely used natural domestic insecticides, are extracted from pyrethrum flowers and are comprised of two groups of active compounds: pyrethrins I, with lethal effect, (including pyrethrin I, jasmolin I and cinerin I) and pyrethrins II, with knock down effect (including pyrethrin II, jasmolin II and cinerin II) which are known for being highly selective on insects (Wolansky and Harrill 2008). They are harmful for fishes, although they are much less

harmful for mammals and birds than other synthetic insecticides (Yamamoto 1970). They are not persistent, as they are easily decomposed when exposed to sunlight (Casida 1980). Conventionally, pyrethrins are extracted with organic solvents (hexane, methanol, petroleum ether…) (Ban et al. 2010), but several authors have already studied the SFE of pyrethrins.

Sims patented the liquid carbon dioxide extraction of pyrethrins (Sims 1981), while Otterbach compared pyrethrum extract obtained by ultrasonic extraction, Soxhlet extraction using hexane, and $scCO_2$ extraction, and observed that the $scCO_2$ process yielded better quality extracts in terms of colour and pyrethrin content (Otterbach and Wenclawiak 1999).

Pan et al. (1995) conducted the SFE of dry pyrethrum flower powder to obtain pyrethrins in the range of 8.3–2.48 MPa at 40 °C. The most effective extraction occurred at 8.3 MPa, achieving 140 ± 18 mg of pyrethrins I and 55 ± 9 mg of pyrethrins II per 100 g of dry pyrethrum flower powder. The results showed that extraction efficiencies of $scCO_2$ were much better than those of n-hexane. During the extraction process, the most efficient extraction period was the first 3 h of the experiment.

Della Porta and Reverchon (2002), extracting pyrethrins from pyrethrum, showed that pyrethrins were readily soluble in the $scCO_2$, so they could be extracted at 9.0 MPa and 40 °C, avoiding high pressures that could lead to coextraction of undesired compounds. In fact, they conducted a second extraction step at 20.0 MPa and 40 °C, showing that pyrethrins yield did not increase, compared to that of the extraction at 9.0 MPa and only undesired compounds were extracted.

Kiriamiti et al. (2003b) studied the effect of pressure, temperature, particle size and pre-treatment of raw material upon quality and quantity of pyrethrum flowers extracts obtained with carbon dioxide. They used both supercritical and subcritical CO_2 in the range of 7.0–25.0 MPa and 20–40 °C, relying on Stahl, who saw that there was no decomposition of pyrethrins in pressurized CO_2 if the temperature was increased from 20 to 40 °C (Stahl and Schutz 1980). They achieved a similar extract to the one obtained by hexane Soxhlet extraction, excepting that the ratio of pyrethrins I to pyrethrins II was lower and with less pigments. At 40 °C the amount of extract was found to be independent of pressure above 10.0 MPa. Pyrethrin content in the crude extract was shown to be higher at 20 °C than at 40 °C and decreased with a decrease in pressure. The effect of the particle size was investigated, yielding the biggest particles a lower quantity of extract with less pyrethrin. The extract obtained from smaller particles at 40 °C, contained more undesired product, finding that the best selectivity was achieved at subcritical conditions (operating at 20 °C). They also established that the seed part of the whole flower contained more crude extract and pyrethrins than the flower part, so a pre-treatment of unground flowers by washing with $scCO_2$ improved the quality of $scCO_2$ extract, because a part of the undesired waxes was eliminated by the pre-treatment. A simpler procedure of eliminating the waxes with hexane and then purifying the obtained extract by means of SFE was also proposed by Kirimiati et al. (2003a) in a subsequent paper.

Marongiu et al. (2009) accomplished the SFE of three sardinian chrysanthemum flowers, *Chrysanthemum coronarium* L., *Chrysanthemum segetum* L. and *Chrysanthemum flosculosus* L., the last one endemic to the region. Their volatile fractions were extracted at 9.0 MPa and 50 °C, their compositions compared to the ones obtained by hydrodistillation, and their antibacterial and antimycotic activities were contrasted with those of the essential oils obtained by hydrodistillation, and to the SFE extracts of *Chrysanthemum cinerariifolium*, a commercial species rich in pyrethrins. They tried to extract pyrethrins at 30.0 MPa and 50 °C, finding that the Sardinian plants did not contain any pyrethrin, while the commercial pyrethrin rich plant yielded 1.1 % (w/w), with a pyrethrin I to pyrethrin II ratio of 1.3. Moreover, they found out that some of the extracts had antifungal and antibacterial activity, but their antimicrobial activity was not selective nor specific. All the supercritical extracts of the local plants were active on plant pathogens (*Botrytis cinerea* and *Rhizoctonia*), while some of their hydrodistilled showed no activity. *Chrysanthemum cinerariifolium* supercritical extract, on the contrary showed no activity over those plants pathogens.

SFE of azadirachtins

Other pesticidal compounds obtained by means of SFE are the azadirachtins, extracted mainly from the seeds of neem tree, *Azadirachta indica*. Azadirachtins are tetranortriterpenoids formed by a group of closely

related compounds including azadirachtin, salannin, gemudin and nimbin. Azadirachtin (Fig. 1) is used as a natural pesticide and is considered as a gold mine, due to its feeding deterrency for many insects, its growth disruptancy for most insects and its very low toxicity for vertebrates (Morgan 2009). Among others, it has shown inhibitory effect on vitellogenin during oogenesis of arthropods (Jonsson and Piper 2007), acceleration of the hatching rate and mortality of *Hyalomma anatolicum excavatum* larvae (Abdel-Shafy and Zayed 2002) and decreased blood-feeding in *Dermacentor variabilis* (Landau et al. 2009) (Fig. 1).

Johnson and Morgan (1997) studied the selective extraction of azadirachtins and oil from neem seeds using $scCO_2$ with and without methanol as entrainer. The extraction with $scCO_2$ for 30 min could not remove nor the totality of the oil, nor the azadirachtins, while when prolonging the extraction to 150 min, all the nimbin and salannin were extracted, leaving some azadirachtin unextracted. When operating at 34.4 MPa with percentages of methanol of 20 %, most of the azadirachtin was extracted, while an optimum for extracting nimbin and salannin was found at 20.65 MPa and 6 % MeOH. Working at reduced pressures (13.7 MPa) they were also able to extract the whole nimbin and salannin, but 20 % of MeOH was used in this case.

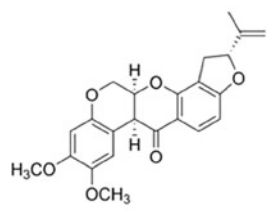
Ambrosino et al. (1999) used sub and supercritical CO_2 in the range of 20–40 °C and several pressures to obtain azadirachtins from raw or previously pressed neem seed kernels. The highest azadirachtins recovery was obtained with $scCO_2$ at 29.5 MPa and 40 °C, reaching values of 8,810 mg azadirachtins per kg of oil and 2,291 mg azadirachtins per kg of seeds.

Tonthubthimthong et al. (2001) studied the selective SFE of nimbin from neem seeds. They worked in the range of 10.0–26.0 MPa, 35–60 °C and 0.24–1.24 ml/min, finding that the best extraction conditions in their studied range occurred at 35 °C, 23.0 MPa and 1.24 ml/min, obtaining 0.18 mg nimbin per gram of neem seed per hour. In fact, a more extensive study conducted by the same group (Tonthubthimthong et al. 2004) reached to the conclusion that methanol was not found to be an effective modifier for extracting nimbin as the marginal increase in extraction yield using methanol as modifier was not substantial, compared to the added difficulty and cost of handling and separating a toxic modifier.

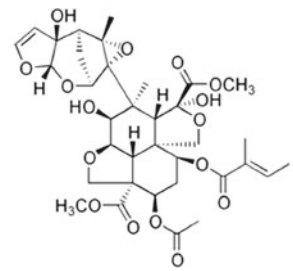
Today's trend within SFE is to try to obtain azadirachtins with a higher yield and a higher recovery. To that extent, studies of the solubility of azadirachtin in $scCO_2$ (Ismadji et al. 2011) and models to optimize the SFE of nimbin (Zahedi et al. 2010a, b) have been accomplished in order to improve the operational conditions that could increase both the recovery and the yield. In spite of the difficulties related to innovation in the pesticides market, several attempts of commercializing supercritically obtained extracts of azadirachtins from neem seeds have been carried out, including Essences srl, (Salerno, Italy) and ACRA (Milano, Italy). The latter has tried the sustainable production of a neem based insecticide with the cooperation between third world countries and Europe (ACRA 2012).

SFE of rotenone

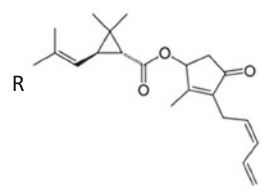
Rotenone is other natural compound that can be extracted by SFE. Rotenone (Fig. 1), whose insecticidal potential is known since ancient times, is a molecule that can be obtained from several tropical plants such as *Derris elliptica*, *Lonchocarpus nicou* or *Tephrosia vogelii*. The amazonic tribes threw rotenone rich extracts into water and fished manually the fishes that



Rotenone



Azadirachtin



Pyrethrin I (R=CH_3)
Pyrethrin II (R=CO_2CH_3)

Fig. 1 Pesticidal compounds obtained from natural matrices by means of SFE

were poisoned, capturing them once they got to the surface paralyzed or even dead. Besides being a piscicide, it is also used as a wide spectrum insecticide against pests as the potato beetle (*Leptinotarsa decemlineata*) or the common fruit fly (*Drosophila melanogaster*). It was once allowed as pesticide in the organic agriculture by the EU (European Commission 1991) due to its natural origin, its safety to non-target organisms, its low resistance development and its short persistence, but it has been restricted (European Commission 2007) due to the fact that a link between rotenone and Parkinson's disease has been discovered (Tanner et al. 2011). However, its SFE is a valid example of extracting and developing a supercritical insecticide.

Li et al. (2005) and Huang et al. (2006) have obtained rotenone from *Tephrosia vogelii*. The former worked at 27.58 MPa −60 °C adding methanol as modifier and achieved the extraction of 98 % of rotenone compared to that extracted with a chloroform maceration. The latter made a systematic study in the ranges of 22–28 MPa and 30–60 °C. The highest rotenone concentration in the extract was obtained at 30 °C and 24 MPa, while the highest yield of rotenone respecting to the quantity of dry material was obtained at 60 °C and 22 MPa (4.49 mg rotenone per gram of dry material). In order to improve the extraction, 10 % of ethyl acetate was added as modifier at 60 °C and 22 MPa, obtaining an extract with 7.96 % rotenone and a yield of 5.99 mg rotenone per gram of dry material.

D'Andrea et al. (2007) proposed the extraction of rotenone from the roots of *Derris elliptica* (Wallich) Benth. They carried out a study at different pressures (9–44 MPa), temperatures (40–60 °C) and CO_2 to feed material ratios (10–100 g/g). From all the studied conditions, the most efficient extraction occurred at 44 MPa, 60 °C and a CO_2 to feed material of 100 g/g. In these optimum conditions, the extract purity and the rotenone yield were 64.2 and 11.25 % respectively, while the Soxhlet extraction (methanol:dichloromethane 1:1 (v:v)) accounted for values of 27.7 and 8.36 %.

SFE of volatile oils

Apart from the aforementioned examples, the SFE of constituents of volatile oils and natural extracts is one of the most studied fields in the biopesticides development. This is so as the appearance of resistance against complex natural products is unlikely or very low, because they have different components with various modes of action (Imdorf et al. 1999; Rossini et al. 2007). Essential oils, for instance, show antifungal (Mishra and Dubey 1994), nematicidal (Pandey et al. 2000), antibacterial (Burt 2004), repellent (Nerio et al. 2010) and insecticidal properties among others (Regnault-Roger et al. 2012). Some of the SFE experiments aimed at the extraction of natural compounds tested as biopesticides are gathered in Table 1. In Table 1, 19 studies handling with supercritical extractions of natural extracts appear. In these studies, 24 species have undergone SFE in order to obtain bioactive fractions, and their activities have been tested over several pest organisms. The extracts showed diverse compositions and the pesticidal actions evaluated were different (insecticidal, fungicidal, herbicidal, antibacterial…). The supercritical conditions were as follows: pressures ranged from 8 to 40 MPa, while the used temperatures went from 30 to 80 °C, depending on the studied plant. Yields varied from 0.40 to 14 %. In 11 of those studies, four different cosolvents (methanol, water, acetone, ethanol) were used with proportions from 2.4 to 11.8 %, being ethanol the most used cosolvent.

It has to be noticed, however, that several experiments to extract volatile and non volatile compounds with pesticidal properties from natural matrices are not gathered in the table, as their pesticidal activities have not been tested in the same research. For instance, some biopesticides that have been approved recently by the EPA, listed in a review of Cantrell et al. (Cantrell et al. 2012), include extracts or single compounds that have already been obtained by SFE.

The former contain canola oil (Dunford and Temelli 1997; Pederssetti et al. 2011), black and white pepper oil (Ferreira et al. 1999; Perakis et al. 2005; Zhiyi et al. 2006; Dou et al. 2010), fish oil (Rubio-Rodríguez et al. 2012) or catnip oil (Louey et al. 2001), while the latter are comprised by indole that could be extracted from *Tabernaemontana catharinensis* (Pereira et al. 2004) or *Catharanthus roseus* (Verma et al. 2008), L carvone from *Lippia alba* (Braga et al. 2005), *Carum carvi* (Baysal and Starmans, 1999), or *Mentha spicata* (Almeida et al. 2012), lysophosphatidylethanolamine from antler velvet (Zhou and Li 2009), methyl eugenol from *Anemopsis californica* leaf oil (Medina et al. 2005), allyl isothiocyanate from *Wasabia japonica matsum* (Li et al. 2010), piperine from *Piper nigrum* (Sankar, 1989) or verbenone from *Lavandula viridis* (Costa et al. 2012).

Table 1 Biopesticides extracted by means of supercritical fluid extraction

Vegetable matrix	Main compounds obtained	Activity	Organism	T (°C)	P (MPa)	Co-solvent (%)	Yield (%)	Reference
Armoracia rusticana	Isothiocyanates	Insecticidal	*Sitophilus zeamais* *Rhizopertha dominica* *Tribolium ferrugineum* *Liposcelis entomophila*	45	25	11.8 (H_2O)	6.10	Wu et al. (2009)
Artemisia absinthium	Z epoxyocimene, $C_{10}H_{18}O_2$, absilactone type sesquiterpene	Antifeedant Phytotoxic	*Spodoptera littoralis* *Myzus persicae* *Rhopalosiphum padi* *Lactuca sativa* *Lolium perenne*	40	9–18	0–2.5 % EtOH	n.d	Martín et al. (2011c)
Artemisia sieberi	Camphene, cineol	Fungicidal Mosquito repellency	*Anopheles*	30–65	10.1–30.4	2.40–11 (MeOH)	1.6–14	Ghasemi et al. (2007)
Chamaecyparis lawsoniana	t-cadinol, t-muurolol	Antifungal	*Gloeophyllum trabeum* *Trametes versicolor*	60	20	No	3.27	Du et al. (2010)
Chamaecyparis nootkatensis	Nootkatone, t-cadinol						3.22	
Juniperus virginiana	Cedrol						3.29	
Citrus sinensis	l-limonene, palmitic and oleic acids	Antimicrobial	*Staphylococcus aureus* *Escherichia coli*	40–50	10–30	0–8 EtOH	0.61–3.0	Benelli et al. (2010)
Coriandrum sativum	Linalool	Herbicidal	*Zea mays*	40	9	No	n.d	Santoyo et al. (2006)
Santolina chamaecyparissus	1,8 cineole, cmaphor		*Triticum durum*	40	8			
Satureja montana	Carvacrol, thymol		*Pisum sativum*	40	9			
Thymus vulgaris	Thymol, p-cymene		*Lactuca sativa* *Portulaca oleracea* *Vicia sativa*	40	9			
Daucus carrota	Geranyl acetate, β-caryophyllene	Antibacterial Fungicidal	*Staphylococcus aureus* *Enterococcus faecalis* *Bacillus subtilis* *Bacillus cereus* *Listeria monocytogenes* *Rhodococcus equi* *Escherichia coli* *Salmonella enteritidis* *Pseudomonas aeruginosa* *Candida albicans*	40–50	9–10	No	0.91–1.17	Glišić et al. (2007)

Table 1 continued

Vegetable matrix	Main compounds obtained	Activity	Organism	T (°C)	P (MPa)	Co-solvent (%)	Yield (%)	Reference
Echinacea angustifolia	R-cyclopentadecanone	Antifungal	*Botrytis cinerea*	45	30	No	n.d	Li et al. (2011)
Helianthus annuus	n.d	Herbicidal	*Triticum aestivum L*	50	38	2.5–4.8 H_2O	0.2–1.6	Casas et al. (2008)
Hydrocotyle wilfordi	Bis(2-ethylhexyl)-phthalate	Toxicity	*Plutella xylostella*	50	35	No	5.32	Hu et al. (2008)
Origanum majorana	α-terpinene, p-cymol	Antimicrobial	*Aspergillus niger*	50	45	No	3.8	Vági et al. (2005)
		Antibacterial	*Trichoderma viride*					
			Penicillium cyclopium					
			E. coli					
			B. cereus					
			P. fluorescens					
Origanum vulgare	Carvacrol, trans-sabinene hydrate, cis-piperitol, borneol, terpinen-4-ol, linalool	Antimicrobial	*Staphylococcus aureus*	40	15	7 EtOH	n.d	Santoyo et al. (2006)
		Antibacterial	*Bacillus subtilis*					
		Antifungal	*Escherichia coli*					
			Pseudomonas aeruginosa					
			Candida albicans					
			Aspergillus niger					
Rosmarinus officinalis	Alpha-pinene, 1,8-cineole, camphor, verbenone, and borneol			60	25	4 EtOH	n.d	Santoyo et al. (2005)
Persea indica	Ryanodol	Antifeedant	*Spodoptera littoralis*	40–50	10–20	0–2.5 EtOH	0.40–1.13	Martín et al. (2011b)
Rosmarinus officinalis	α -pinene, camphor	Antibacterial	*Geobacillus stearotermophillus*	40	11.5–40	No	1.02	Ivanovic et al. (2012)
			Bacillus cereus					
			Bacillus subtilis var.niger					
			Enterococcus faecium					
			Salmonella enteritidis					
			Escherichia coli					
Salvia officinalis	α -thujone, camphor						2.13	
Thymus vulgaris	Thymol, p-cymene						1.23	
Satureja hortensis	δ-terpinene, carvacrol	Acute toxicity	*Musca domestica*,	50	12–28	0–4.3 acetone	3–4	Pavela et al. (2008)
			Spodoptera littoralis,					
			Culex quinquefasciatus					
			Leptinotarsa decemlineata					
Satureja hortensis	δ-terpinene, carvacrol	Insecticidal, antifeedant	*Leptinotarsa decemlineata*	50	12–28	0–4.3 EtOH	3–4	Pavela et al. (2009)
Thymus vulgaris	δ-terpinene, p-cymene					0–4.3 acetone	1.6–3.3	

Table 1 continued

Vegetable matrix	Main compounds obtained	Activity	Organism	T (°C)	P (MPa)	Co-solvent (%)	Yield (%)	Reference
Stellera chamaejasme	Squalene, 9,12-octadecadienoic acid	Contact, systemic toxicity	*Tetranychus cinnabarinus*	49	15	No	3.75	Liang et al. (2012)
Syzygium aromaticum	Eugenol, eugenyl acetate	Germination inhibitor	*Shirvodi* wheat variety	80	19	No	n.d	Darabi et al. (2011)
Tanacetum parthenium	Camphor, camphene	Mortality, antifeedancy and growth inhibition	*Spodoptera littoralis*	50	12–28	0–4.3 acetone	2.5–3.8	Pavela et al. (2010)

Plant material, main compounds extracted, action tested, target organism and extraction conditions are included, together with the authors

Some patents have been already licensed with the topic of SFE of volatile oils showing diverse uses (Santos and Meireles 2011); there are also different patents handling with the SFE of biopesticides, such as the SFE of cis-abienol from *Abies sachalinensis* (Tatsuro and Mitsukatsu 1996). The process takes place at 9.8 MPa and 40 °C for 60 min, obtaining an extract containing 13.60 % of cis-abienol (compared to the hexane extract, containing just 1.31 %). Another patent handles with the SFE of *Chenopodium ambrosioides*, process that provides an insecticide synergist formed by its essential oil or its supercritical extract (Hui et al. 2009). A third patent includes bioinsecticide derivatives extracted from plants with specific chemotypes of *Artemisia absinthium* by organic or supercritical CO_2 extractions (Gonzalez Coloma et al. 2012).

Apart from EPA approved biopesticides, there is also a category of minimum risk pesticides included in the biopesticides category that are exempt from registration under section 25(b) of the Federal Insecticide, Fungicide and Rodenticide Act (US Environmental Protection Agency 1947) which include oils (hydrodistilled and/or pressed oils) of several species. As the extracts obtained by SFE are analogous to these oils, research has already been conducted in order to obtain, by means of SFE, extracts with similar properties and compositions to those considered of minimum risk. Among them, the extraction of oils from seeds (soybean, cottonseed…) counts already with an SFE official method (Firestone 1998). Other volatile oils (comprising hydrodistilled and pressed oils) have also been obtained by SFE: cinnamon (Zhao and Liang 2006; Marongiu et al. 2007; Miao and Deng 2011), clove (Della Porta et al. 1998; Yazdani et al. 2005; Guan et al. 2007; Darabi et al. 2011), citronella (Wu et al. 1994; Silva et al. 2011), lemongrass (Carlson et al. 2001; Rozzi et al. 2002), mint (Barton et al. 1992; Díaz-Maroto et al. 2002; Almeida et al. 2012), peppermint (Goto et al. 1993; Castillo et al. 2003; Sovová et al. 2006), rosemary (Santoyo et al. 2005; Zermane et al. 2010; García-Risco et al. 2011a; Ivanovic et al. 2012), garlic (del Valle et al. 2008), geranium (Peterson et al. 2006; Gomes et al. 2007) or thyme (Pavela et al. 2009; Grosso et al. 2010a, b; García-Risco et al. 2011b). In these minimum risk pesticide category there are also single compounds that have been extracted from natural matrices by means of SFE such as eugenol (Geng et al. 2007; Tongwei et al. 2010) or geraniol (Moldão-Martins et al. 2000; Machmudah et al. 2009).

SFE is, by large, the most used supercritical technology to obtain biopesticides from natural matrices. In fact, it has become an existing alternative to the traditional extraction methods, as it has been described in the explained examples. Advantages such as the easy separation solvent–solute, the tunable density allowing a selective fractionation, the fast operation, the mild operating conditions and its *green* potential have converted this technique into a way in which biopesticides can be obtained. On the other hand, the high operational costs (counterbalanced however in most of the cases by the quality and purity of the extracts) and the inherent inertia of the productive sector are the obstacles that have to be avoided in order to further develop the obtention of biopesticides by means of SFE.

Supercritical antisolvent fractionation/extraction (SAF/SAE)

Apart from being used as extractive agents, supercritical fluids can be used as antisolvents in the so called Supercritical Antisolvent Fractionation (SAF) or Supercritical Antisolvent Extraction (SAE). Once again, the mainly used supercritical fluid is CO_2, being used as antisolvent, dissolving the organic solvent in which a mixture is contained, sweeping away undesired compounds and allowing thus the enrichment of interesting compounds.

The fractionation with supercritical CO_2 uses the apolar nature of the supercritical solvent to fractionate the compounds of interest present in a multicomponent solution. It consists of the continuous contact between $scCO_2$ and the liquid mixture in a pressurized precipitation vessel. A spray of the liquid solution is produced in the supercritical medium to enhance the mixing of the two fluids and, if the process is performed at optimized conditions, the liquid solution can be fractionated by $scCO_2$, precipitating part of the solutes as solid powder at the bottom of the high pressure vessel. CO_2 and the residual organic mixture can be recovered by decompression in a separator downstream from the precipitation vessel, operated at a lower pressure. In the precipitator, the more polar compounds that have not been swept away by the CO_2 are found, while in the separator, the swept compounds by the mixture $scCO_2$ + organic solvent can be recovered (Reverchon and De Marco 2006). The key of this antisolvent process is the equilibrium in the extractor vessel, i.e., the conditions in which the antidissolution takes place. The liquid solution and the $scCO_2$ have to be miscible in the working conditions avoiding the insolubility gap, taking into account that the compounds dissolved in the organic solution could raise the critical point. An incorrect selection of the working conditions would lead to a two phase behavior that could ruin the process.

The supercritical antisolvent processes present several advantages over classical antisolvent liquid techniques such as the easy separation of the supercritical solvents from precipitating products, their high diffusivity or their miscibility with many organic solvents, due to the well known characteristics of the supercritical fluids (Rodrigues et al. 2011).

SAE/SAF methods have mainly found applications in the fractionation of compounds from natural matrices. Some examples can be found in bibliography such as the fractionation of propolis (Catchpole et al. 2004), the selective obtention of polyphenols and anthocyanins from ethanolic solutions of freeze-dried grape residues (Floris et al. 2010), the refining of phospholipids from egg yolk (Aro et al. 2009) the fractionation of *Ginkgo biloba* extracts (Zhao et al. 2011) or the carnosic acid fractionation from rosemary ethanolic oleoresins (Visentín et al. 2011).

SAE/SAF techniques have been used scarcely up to date in the production of biopesticides, so there is still a great research potential in this field. Nonetheless, Martín et al. (2011a) have obtained ryanodol rich extracts parting from ethanolic solutions of *Persea indica*, a macaronesian endemic tree. Ryanodol has already shown its insecticidal activity (Gonzalez Coloma et al. 1993) in both traditional and SFE extracts (Martín et al. 2011b). A further enrichment of ryanodol by means of SAF has also shown better insecticidal activities than the extracts obtained either by SFE or by Soxhlet extraction.

A similar procedure that uses CO_2 as antisolvent, but in gas phase under the critical point, is the Gas Antisolvent, which has also rendered enriched extracts in interesting compounds. Phytochemicals like carotene from mango leaves, α-hydroxycitric acid from kokum, or licochalcone-A from licorice have been purified by this method (Mukhopadhyay and Patel 2009). This last compound is known for showing antimalarial (Chen et al. 1994) and antileishmanial (Chen et al. 1993) activities.

Supercritical Antisolvent processes have been developed to try to overcome the drawbacks presented

by traditional antisolvent methods. Supercritical antisolvent methods are versatile, operational at mild conditions and they avoid the use of great amounts of organic solvents. In fact, they are so versatile that they can be used in the encapsulation and/or micronization of compounds, topic that will be handled in the next section. Moreover, antisolvent methods constitute an alternative when the interesting compounds in a matrix are too polar to be extracted by means of SFE. Antisolvent processes have been thoroughly used in the nutraceutical, medical and pharmaceutical industries, due to the high added value of the final compounds and due to the intrinsic requirements that have to be fulfilled in these industries (particle size distribution, safety, good manufacturing practices, controlled delivery of the active principle). In spite of these known advantages, these processes still have to be implemented in the field of biopesticides.

Supercritical micronization and encapsulation methods

Beyond extraction (SFE) and fractionation (SAE/SAF) of natural compounds with pesticidal properties, supercritical fluids can also contribute advantageously to the formulation of biopesticides. Some of the limitations of biopesticides are their low solubility in water, their high volatility and their high reactivity with the ambient. In order to overcome these drawbacks, natural products can be formulated as composites or capsules which are nowadays produced by several traditional techniques, classified in physical processes (spray-drying, spray-chilling, extrusion, air suspension coating…) or in chemical processes (coacervation, liposomal entrapment, molecular inclusion….) (Desai and Jin Park 2005).

Supercritical fluids have been developed as an alternative to these traditional encapsulation processes taking advantage of their previously commented properties (tunable density, easy separation solute–solvent, mild operating conditions …). When working with $scCO_2$, those moderate conditions are used due to its low critical temperature and pressure. This allows the processing of thermolabile compounds and as it is an inert medium it also allows the processing of easily oxidable compounds. Furthermore, the use of supercritical fluids reduces or eliminates the use of toxic or contaminant organic solvents and by means of a simple depressurization, there is no need of carrying out an extra separation step, as the product is recovered without solvent. Several reviews (Jung and Perrut 2001; Meure et al. 2008; Cocero et al. 2009; Martín et al. 2010) enumerate and describe supercritical micronization and encapsulation techniques. Some of them, like Supercritical Antisolvent (SAS), Supercritical Solvent Impregnation (SSI), Particles from Gas Saturated Solutions (PGSS) and Supercritical Assisted Atomization (SAA) have been used in the field of biopesticides and will be reviewed briefly, while other techniques such as Supercritical Fluid Emulsion Extraction (SFEE)(Della Porta et al. 2010), Supercritical Assisted Injection in a Liquid Antisolvent (SAILA) (Campardelli et al. 2012), or Concentrated Powder Form (CPF)(Grüner et al. 2003) have not appeared up to date in literature handling with biopesticides development.

Supercritical antisolvent (SAS)

This technique is based on the use of $scCO_2$ as antisolvent and has been mainly used to micronize pharmaceuticals and biomedical antibiotics (Martín and Cocero 2008; Martín et al. 2010). Some examples can be found in bibliography such as the encapsulation of green tea (Sosa et al. 2011) or rosmarine antioxidants (Visentin et al. 2012), or the micronization of antibiotics or pharmaceuticals such as rifampicin (Reverchon et al. 2007), minocycline hydrochloride (Cardoso et al. 2008), ampicilin (Montes et al. 2011) or ibuprofen (Martín et al. 2009) from organic solutions.

Although both techniques SAF/SAE and SAS use $scCO_2$ as antisolvent, the objective, operating conditions and the characteristic of the product are different. SAF/SAE aim to separate an extract into fractions with different composition that can be liquid, solid or a paste. In SAS, the objective is to produce a free flowing powder of particles in the micron and submicron scale. In this case, if a polymer is added to the solution or extract, the encapsulation or coprecipitation of the compounds can be achieved.

The coprecipitation of a synthetic herbicide (diuron) loaded in amorphous microparticles of a biodegradable polymer (l-polylactic acid) is an example of the use of this technique (Taki et al. 2001). Long needle-like crystals with a mean length of 500 μm were obtained.

Supercritical solvent impregnation (SSI)

This technique allows the impregnation of carriers (protecting compounds) with active substances by dissolving the substance in a supercritical fluid and then contacting the resulting fluid mixture with the carriers to be impregnated (Kikic and Vecchione 2003). If the operational parameters are correctly chosen, the loading and the depth penetration can be varied. This method has been thoroughly used to obtain diverse materials such as mesoporous silica (MCM-41) impregnated with α-tocopheryl acetate (Belhadj-Ahmed et al. 2009) or chitosan impregnated with lactulose (Díez-Municio et al. 2011).

In the field of biopesticides, the supercritical impregnation with lavandin (*Lavandula hybrida*) essential oil of modified starch has been accomplished (Varona et al. 2011). This method achieved similar loadings to those obtained by using methods such as PGSS or PGSS-drying, however, their impregnation efficiency was lower for the same load. The distribution coefficient of essential oil between the starch and the supercritical phase and the essential oil load depended on the density of the CO_2.

The impregnation of l-lactide random copolymers with repellents and antibacterial agents (Japanese cypress oil, D-limonene, hinokitiol, trans 2-hexenal) using SSI has also been attempted (Tsutsumi et al. 2009, 2011, 2012). The mild working conditions during the impregnation due to the supercritical fluid allowed the incorporation of these thermolabile compounds, resulting in new controlled release materials.

A similar technique has been used to mix a synthetic fungicide (Imazalil) and a carrier (β-cyclodextrin) in presence of $scCO_2$ in an autoclave to make an inclusion complex taking advantage of the gaseous nature of CO_2 when depressurizing it (Lai et al. 2003). Although this fungicide is not a biopesticide, its mixing technique can result interesting for biopesticides.

Particle from gas saturated solutions (PGSS)

It is a two step process in which the first one comprises the saturation of the solute with carbon dioxide in a static mixer operating at high pressures. The second step consists in the expansion of the saturated solution of gas through a nozzle. The Joule–Thomson effect causes the particle formation due to a fast and pronounced reduction in temperature (Weidner 2009).

Varona et al. (2010) used this technique to encapsulate lavandin essential oil in polyethylene glycol (PEG). The encapsulation efficiencies of this oil with biocidal activity reached values of up to 66 %. They also developed a modification of the process, PGSS-drying, in which the coating material was fed to the static mixer in an aqueous solution. However, the encapsulation efficiencies reached a range of 6–55 %.

Varona et al. (2013) used both techniques (PGSS and PGSS-drying) also to encapsulate the oil of lavandin, but using other carriers such as soybean lecithin, n-octenyl succinic anhydride modified starch or poly-caprolactone. The antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Bacillus cereus* of the lavandin oil was enhanced by the encapsulation, due to the protection and control release of the oil. Among the tested carriers, soybean lecithin was the most efficient as it was able to form liposomes which can interact with cells. PGSS-drying particles showed a higher antibacterial activity than those formed by spray-drying with a similar essential oil load.

Pemsel et al. (2010) used this technique to encapsulate the *Cydia pomonella* granulovirus in a formulation containing 77 % fat (commercially obtainable palm oil-based fat), 12 % virus, 9 % surfactant (lecithin-based surfactant) and 2 % UV protectant (modified titanium oxide or a benzophenone derivative). Encapsulation is needed as the granulovirus is very sensitive to UV and it has a very low uptake by the *Cydia pomonella*. The obtained particles showed a spherical morphology (maximum diameter 23 μm), the bioassays proved that the granulovirus was encapsulated and there was no loss of virulence compared to commercial formulation.

Supercritical assisted atomization (SAA)

It is a similar technique to the PGSS, but in this case, the $scCO_2$ acts as co-solute and as pneumatic agent responsible for the atomization (Reverchon 2002). The encapsulation procedure is based on the double atomization of a quaternary mixture ($scCO_2$, organic solvent, biopolymer and active principle) inside a precipitator chamber, after being put in contact in a packing filled mixer. This technique has been successfully used in the atomization of pharmaceuticals and other substances. The micronization of ampiciline microspheres covered by hydroxypropylmethylcellulose (HPMC) has been studied by

Reverchon and Antonacci (Reverchon and Antonacci 2007). The granulometry depended on the concentration of HPMC in the initial solution. The SAA technique has also been used for the production of microparticles from thermolabile compounds like bovine serum albumin (Adami et al. 2011) or lysozyme (Adami et al. 2009).

In the field of pesticides, an attempt has arisen to encapsulate rotenone due to its instable nature and its formerly condition of biopesticide. The used carriers were PEG, polyvinylpyrrolidone and sodium alginate. The morphology of the obtained microspheres and the encapsulation yield depended on the carrier and on the working conditions. The effective loading of the microspheres and coacervates was analysed by means of HPLC, obtaining values near to 100 % (Martín et al. 2011d).

In general, the encapsulation processes using CO_2 have very promising applications due to the simplicity, cleanliness and encapsulation efficiencies. The particle size (down to the submicron scale), a system easily compliant with the Good Manufacturing Practices and the favourable technical and economic conditions for large scale production are additional advantages in their application. However, as in the case of supercritical antisolvent methods, this encapsulating methods have been mainly developed in the pharmaceutical, nutraceutical and medical industries and there is still a great field of interest in the biopesticide encapsulation.

General overview

Supercritical fluids are being studied in a wide range of applications as they possess several interesting properties which make them ideal solvents. Their tunable density, the high diffusivity and penetrability mixed with their solvent power, the easy separation solute solvent and their versatility, makes them attractive to not only the academy, but also to the industry. Furthermore, there are additional advantages when using CO_2 as supercritical solvent, such as its low cost, its mild operational conditions, its Generally Recognized as Safe nature (GRAS) and its inert character.

In the production of biopesticides, a potentially interesting field for the development of methods with supercritical fluids, three sections have been distinguished in this review: Supercritical Fluid Extraction (SFE), Supercritical Antisolvent Extraction or Fractionation (SAE/SAF) and Supercritical Micronization and Encapsulation (consisting of various techniques).

SFE is by far the most used supercritical methodology to obtain and optimize biopesticides. It is employed as an alternative to traditional methods such as hydrodistillation or organic extraction, because it overcomes the drawbacks of them (avoids the thermal degradation, hydrolysis or hydrosolubilization of the compounds in the former, or the inherent inconveniences of using organic solvents of the latter). SFE has been successfully used to extract bioactive compounds from natural matrices, obtaining extracts similar to the hydrodistilled or organically extracted. In fact, the supercritical extracts are not only comparable to the classical ones, but they can achieve a better quality, as the desired compounds can be preferentially extracted. The desired compounds can be partially fractionated by means of consecutive separators, extraction steps or use of entrainers. In most of the studies, the SFE extracts are chemically compared to the ones obtained by traditional methods, but their activity (in this case, the biopesticidal activity) has not been measured, so an effort should be made in order to systematically perform routine pesticidal tests. As a general rule, if the hydrodistilled or organic fractions from a plant show pesticidal activity, the supercritical extract will show also pesticidal activity if the supercritical extraction conditions are properly selected. However, this rule has to be taken cautiously, as the activity can be even higher (or smaller) if there are synergistic effects with compounds present in only one type of the extracts. That is the fundamental reason why the activity of the supercritical extracts should be inspected to further increase the knowledge about the SFE of biopesticides and convert this knowledge into industrial exploitation. Nonetheless, various patents handle with the production of biopesticides by means of SFE and several studies point out the adequacy of developing SFE as a routine method in the obtention of biopesticides.

SAE/SAF methods have been to date less applied to the obtention of biopesticides. The interesting compound has to be previously extracted by other solvent (preferentially an organic one), so one of the advantages of the use of supercritical fluids, the absence of organic solvent, cannot be applied. However, supercritical antisolvent methods have shown several advantages over traditional antisolvent techniques, including mild operation conditions, a non oxidant medium (if the supercritical fluid is CO_2), fast operational times and a controlled particle size distribution

if the technique is used as a encapsulating tool. The antisolvent techniques have been widely used in nutraceuticals, pharmaceuticals and material science, however, in the field of biopesticides, there is still much research to conduct. In spite of this, some attempts have been accomplished in the production of biopesticidal extracts by supercritical antisolvent techniques.

Supercritical micronization and encapsulation techniques comprise different methods such as supercritical antisolvent (SAS), supercritical assisted atomization (SAA), particle from gas saturated solutions (PGSS) or Supercritical Solvent Impregnation (SSI) among others. They present several advantages over traditional encapsulation methods such as the simplicity, submicron particle size control, high encapsulation efficiencies and economically viable scalability. In spite of this, as in the case of Supercritical Antisolvent techniques, other disciplines such as pharmaceutical, nutraceutical or material science have been studying these processes deeper. However, the supercritical encapsulation of biopesticides is still a good field to perform more experiments due to the versatility that a supercritical fluid offers.

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