



Original Articles

Use of botanical insecticides for sustainable agriculture: Future perspectives

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ABSTRACT

Recent decades have witnessed major growth in the use of agrochemicals worldwide, – for maximizing the food production for a rapidly growing human population. However, the indiscriminate use of these substances especially the pesticides has led to the accumulation of toxic residues in food, soil, air, and water, as well as the development of resistance in pests. Moreover, pesticides affect soil enzymes, which are essential catalysts that govern soil quality. In order to meet the food security, it is necessary to produce more food, sustainably and safely, in a diminishing area of available arable land and with decreased water resources. Given this situation, there is an increased interest in the use of alternative substances to synthetic agrochemicals that present less risk to the environment and human health while increasing the food safety. Promising results have been obtained using compounds derived from aromatic plants for the control of agricultural pests. Such compounds of botanical origin can be highly effective, with multiple mechanisms of action, while at the same time having low toxicity towards nontarget organisms. However, the large-scale application of these substances for pest control is limited by their poor stability and other technological issues. In this backdrop, the present work discusses perspectives for the use of compounds of botanical origin, as well as strategies employing the encapsulation techniques that can contribute to the development of systems for use in sustainable agricultural practices.

1. Introduction

Human population is increasing at an alarming rate (i.e., 70 million per year) and if this trend continues, there will be 10 billion people in the world by the end of the century (Gerland et al., 2014; Tilman et al., 2002; United Nations, 2013). In order to feed such a population, it will be necessary to double or even triple agricultural production in the coming years. Since most of the cultivable land is already being used, this growth must come from higher yields in the existing production areas (Archana Singh, 2014; Fountain and Wratten, 2013; Kumar, 2013; Tilman et al., 2002). With the advent of the Green Revolution, agriculture started to generate higher yields, although the growth in productivity of most crops has now stabilized (a phenomenon known as yield stabilization), and one of the main contributing reasons for this is the damage caused by pests and diseases (Archana Singh, 2014; Grassini et al., 2013). Approximately 67,000 species of organisms are known to affect agricultural crops, and without preventive protection using agrochemicals, 70% of agricultural production could be lost (Archana Singh, 2014; Donatelli et al., 2017; Ross and Lembi, 1985). Although the use of agrochemicals has benefited agricultural

production, indiscriminate use (intensive and extensive) has led to many problems, including environmental damage (contamination of water, air and soil resources), toxicity to nontarget organisms, toxicity to humans associated with the presence of agrochemical residues in food, and decreased effectiveness of the chemicals following the development of pest resistance (Aktar et al., 2009; Fountain and Wratten, 2013; Kumar, 2012).

Agrochemicals can reach the soil due to direct applications, such as for weed control and following seed treatment, as well as indirectly by spraying of the aerial parts of plants, the falling of treated foliage or fruits, and the movement of contaminated water on the surface and within the soil profile (Chaplain et al., 2011; Chowdhury et al., 2008; Cycon et al., 2017; Gevaio et al., 2000). Once accumulated in the soil, these chemicals can be transported by leaching and surface runoff and they can undergo chemical processes such as hydrolysis, photolysis, and chemical degradation, as well as they can interact with the living fraction of the soil (the microbiota) and be biodegraded (Arias-Estévez et al., 2008; Chaplain et al., 2011; Kookana et al., 1998; Meite et al., 2018; Salazar-Ledesma et al., 2018; Shaheen et al., 2017). As a result of these processes, pesticides and/or their metabolites (which may be

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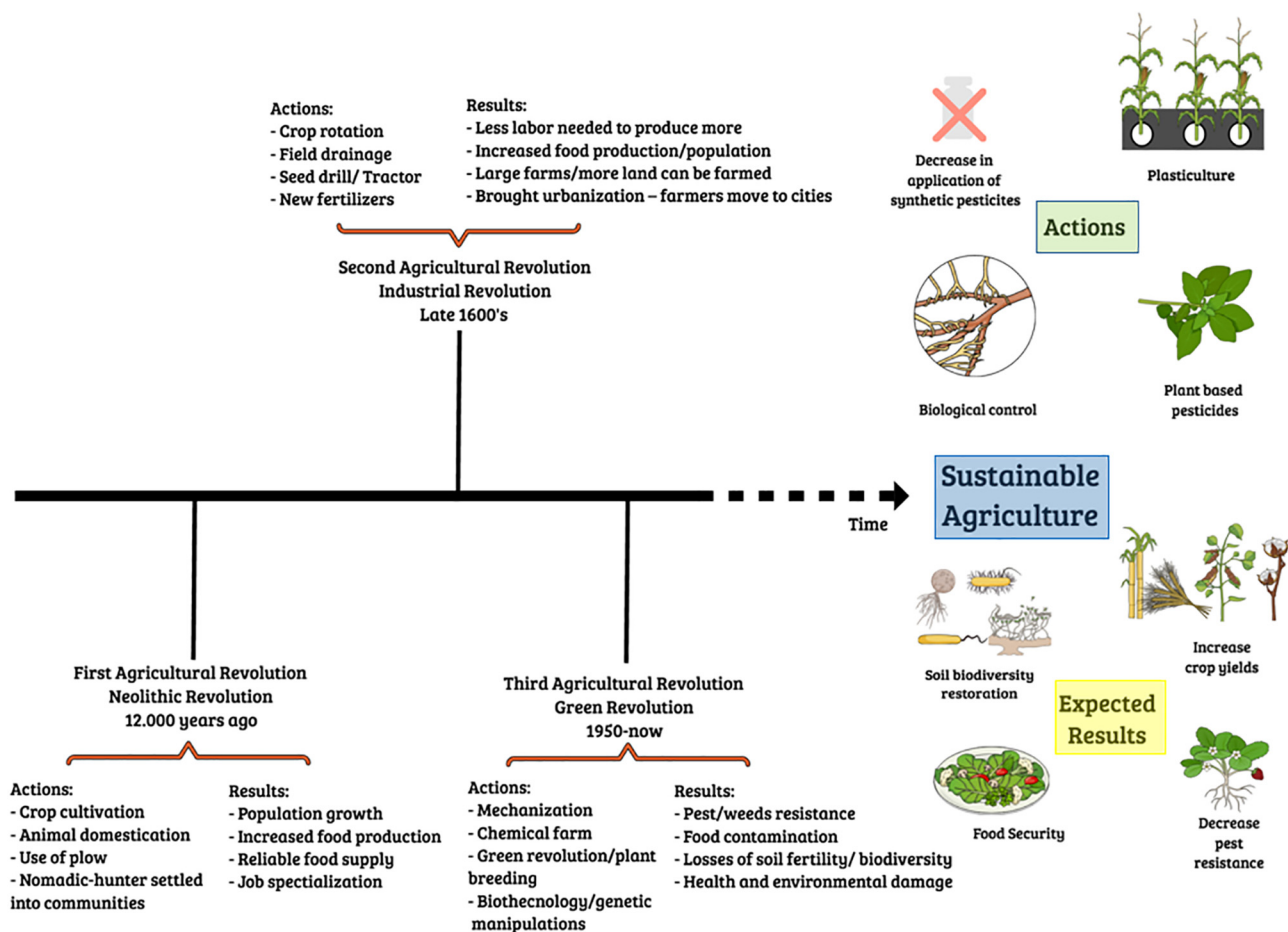


Fig. 1. Schematic representation of agricultural development and potential gains from implementation of sustainable agriculture.

more or less toxic than the parent compounds) can reach hydric resources (surface and subterranean waters), become bioaccumulated through the food chain, be completely mineralized, or persist for long periods in the soil (Chaplain et al., 2011; Gevaio et al., 2000). The intensive use of agrochemicals increases their persistence in the soil and thereby negatively affecting the soil microbiota. The microorganisms that compose this microbiota respond in different ways to the different types of pesticides, and may exhibit increased or inhibited growth and metabolism (Chaplain et al., 2011; Chowdhury et al., 2008; Cycon et al., 2017). Many studies have shown that pesticides cause qualitative and quantitative changes in the soil microbiota (Duah-Yentumi and Johnson, 1986; Hartmann et al., 2015; Komorowicz et al., 2010), alteration of nitrogen cycling (Damin and Trivelin, 2011), changes in soil enzymatic activity, and disruption of the symbiosis between mycorrhizae and root nodules in legumes. These factors lead to alterations of soil fertility and, consequently, plant growth (Malik et al., 2017).

Since 2008, more than 80% of soybean and maize grown in the United States are genetically engineered. Corn seeds are modified in two genes: one kills insects that feed on seeds and the other allows seeds to tolerate glyphosate while soybeans contain only the gene that confers resistance to glyphosate. According Perry et al. (2016), farmers who used the insect-resistant seeds used significantly less insecticide (about 11.2% less when compared with to farmers who did not use genetically modified maize). It was observed also a reduction around 1.3% of herbicide applications. However, farmers who used soybean genetically modified seeds used 28% more herbicides than the farmers who did not use genetically modified seeds. These authors also attribute this increase to the proliferation of glyphosate-resistant weeds. Despite the decrease in insecticide use, continued growth in herbicide use poses a significant environmental problem as large doses of the chemicals can

harm biodiversity and increase water and air pollution. (Kniss, 2017) evaluate the how mammalian toxicity of herbicides has changed in United States in the last 25 years especially regarding the widespread use of genetically modified crops. According to this author there is a strong evidence that herbicides applications has increased in maize, soybean and cotton genetically modified crops. Nevertheless, this author also found an increasing in herbicides uses in non-genetically modified crops (such as rice and wheat). These finding indicates that there is a general trend towards increased use of herbicides independent of the use of genetically modified plants. In addition, the authors suggested that the dependence of current agriculture on genetically modified crops and herbicides use has resulted in a decrease in the development of other potential solutions.

Soil degradation is now one of the greatest environmental challenges, especially in agriculture (Pimentel and Burgess, 2013; Squire et al., 2015). The intensification of agriculture after the Green Revolution resulted in widespread degradation of soils in the forms of erosion, compaction, pesticide contamination, loss of organic matter, increased salinity, and loss of biodiversity, among others (Kibblewhite et al., 2008; Schiefer et al., 2016; Turpin et al., 2017). Therefore, it is essential that sustainable agriculture should be able to recover soil quality by means of strategies such as the use of biopesticides and biofertilizers, crop diversity and rotation, and the use of microbial consortia, in order to meet the growing demand for food (Verma et al., 2015; Zhang et al., 2016). The search for effective and environmentally safe techniques for controlling pests has intensified, with the main strategies being biological control using natural enemies present in the field, as well as the use of natural products such as those derived from plants. Botanical pesticides offer a good alternative to traditional chemicals for use in crop protection systems (Bissinger and Roe, 2010;

Nerio et al., 2010; Kumar, 2012; Fountain and Wratten, 2013; Kumar, 2013; Campos et al., 2014; Pavela and Benelli, 2016). A variety of different strategies can be adopted for the development of sustainable agriculture. Therefore, the present study considers the potential of botanical pesticides as tools in pest control, with the aim of maintaining the long-term productivity of crops, while at the same time reducing environmental degradation.

About 12,000 years ago, a new process of instrument manufacture began to develop, resulting in the Neolithic revolution (Fig. 1). Some of these neolithic societies began to sow plants and keep animals in captivity, in order to multiply them and use their products. After some time, these selected and exploited plants and animals were domesticated, and thus these predator societies were progressively transformed into societies of cultivators and breeders. This passage from predation to agriculture is known as the Neolithic Agricultural Revolution (Scanes, 2018). The second Agricultural Revolution (Fig. 1) refers to the period of change in the agriculture that occurred between the mid-1600s and the late 1800s. Before the revolution, the open-field system of cultivation was used which caused cattle overgrazing, uncontrolled breeding, and spread of animal diseases. Mechanization and scientific principles were adopted, which led to increased productivity and efficiency. As agricultural outputs became increasingly more efficient, fewer workers were required, more food was on hand, and industries cropped up as a result of the agricultural revolution (Demont et al., 2001; Hess, 2016). Technological innovations in agriculture to achieve higher productivity through the development of bio-engineered seeds that worked in conjunction with chemical fertilizers and agrochemicals, heavy irrigation and mechanization in the field to increase productivity was called the Green Revolution (Fig. 1). Although initially used to improve crop production, overuse of chemicals has now started affecting the environment and human health (Evenson, 2003; Pingali, 2012). These chemicals have drastic effects on non-target organisms and affect animal and plant biodiversity, aquatic as well as terrestrial ecosystems. In addition, one of the major problems of pesticide overuse is the development of resistant species to pesticides commonly used to control agricultural pests (Bernardes et al., 2015; Chowdhury et al., 2008; Kaur and Garg, 2014). Thus sustainable development represents in many ways a critique and contrast to the successes of the Green Revolution. In this way, sustainable agriculture is the way to feed the world (Caira and Ferranti, 2016; Martin-Guay et al., 2018).

Industrialized agriculture and sustainable agriculture (Fig. 1) differ in terms of the use of land and agrochemicals, crop yields, and environmental impacts. The traditional agricultural management model is characterized by high dependence on inputs of materials such as pesticides and fertilizers, many of which cause environmental contamination (Pretty and Pervez Bharucha, 2015; Seufert et al., 2012). The sustainable agriculture model is based on improved efficiency of the use of agrochemicals by means of integrated pest management (IPM), substitution of materials, and the application of alternative technologies with low energy consumption and plant/animal integration (Alam et al., 2016; Lechenet et al., 2014; Seufert et al., 2012).

2. Botanical pesticides

The main botanical pesticides are essential oils produced as secondary metabolites in plants. These oils play an important role in the life cycles of plants, acting as defenses against pathogen and herbivore attacks, or attracting pollinators and seed disseminators (Isman, 2000a, 2006; Pavela and Benelli, 2016; Regnault-Roger et al., 2012). Essential oils (Fig. 2) are responsible for the different flavors and aromas of aromatic plants (Nagegowda, 2010). These oils consist of complex mixtures of volatile and lipophilic compounds, with typically around 20–60 substances, of which two or three are considered major compounds present at high concentrations, while the other substances are present at trace levels (Bakkali et al., 2008; Burt, 2004). The

compounds present in the essential oils can be classified into two chemical groups, according to their metabolic synthesis pathways: (i) low molecular weight phenylpropanoids, and (ii) terpenoids (monoterpenes and sesquiterpenes). Monoterpenes are synthesized in the plastids via the methylerythritol phosphate pathway, while sesquiterpenes are synthesized in the cytosol via the mevalonate pathway (Aharoni et al., 2005; Nagegowda, 2010; Regnault-Roger et al., 2012).

Botanical pesticides, in the form of isolated substances or complex mixtures, exhibit a range of biological activities, acting as repellents, insecticides, fungicides, nematocides, and bactericides (Isman, 2006). Studies have found that in several species of mosquito, including species of agricultural importance, botanical pesticides inhibit food ingestion, growth at various stages of development, and egg laying (Aharoni et al., 2005; Nagegowda, 2010; Pavela, 2011; Regnault-Roger et al., 2012). However, there is poor understanding of the mode of action of these substances, which appear to differ according to the individual compounds (Table 1). In bacteria and fungi, the action of essential oils is generally associated with their ability to disrupt the cell walls and cytoplasmic membranes of the organisms. This results in cell lysis and loss of intracellular components, or increased absorption of inorganic phosphate (PO_4^{3-}) and consequent leakage of potassium (K^+) (Devi et al., 2010; Lambert et al., 2001; Tian et al., 2012; Turgis et al., 2009). There is evidence that botanical pesticides can present different mechanisms of action in insects and mammals, acting especially in the nervous system, affecting γ -aminobutyric acid (GABA) gated chloride channels, acetylcholinesterase, nicotinic acetylcholine receptors (nAChR), octopamine and tyramine receptors, and sodium channels, among other possible mechanisms (Pavela and Benelli, 2016; Regnault-Roger et al., 2012).

Monoterpenes isolated from essential oils have been found to be capable of binding to ionotropic GABA receptors in insects, rodents, and other mammals. Positive allosteric modulators of mammalian GABA_A receptors include camphor, carvone, linalool, menthol, and thymol, among other monoterpenes (García et al., 2006; Hall et al., 2004; Krasowski et al., 2002). Homozygous GABA receptors of *Drosophila melanogaster* were found to be positively modulated by thymol (Priestley et al., 2003). All of these compounds have been shown to increase the GABA-induced chloride current at recombinant GABA receptors in different models. In addition to receptors, botanical pesticides can affect enzymes present in the nervous system, such as acetylcholinesterase. Some compounds, such as geraniol, linalool, γ -terpinene, and fenchone have been observed to bind to the active site of the enzyme, resulting in reversible competitive inhibition. Others, such as camphor, estragole, and S-carvone have shown non-competitive inhibition, binding to the free enzyme or to the enzyme-substrate complex at locations different to the active site (Dickens and Bohbot, 2013; El-Wakeil, 2013; Lambert et al., 2001; Ahmed et al., 2011).

In insects, tyramine and octopamine receptors are coupled to G-protein and are important targets for botanical pesticides. Studies using *Periplaneta americana* showed that eugenol affects the octopaminergic system, leading to the activation of octopamine (a neuromodulator) receptors (Enan, 2001, 2005a,b). An increase in adenylate cyclase activity was observed at low doses of eugenol and octopamine, while high doses of eugenol decreased the activity of this enzyme. Similar to eugenol, compounds including carvacrol, α -terpineol, pulegone, and 20 other monoterpenes were found to bind to the octopamine receptors of *Periplaneta americana*, with high sensitivity. Receptors for tyramine, which is a precursor of octopamine, were also involved in the mechanism of action of some monoterpenes, such as carvacrol, α -terpineol, and thymol, in *Drosophila melanogaster* cells presenting tyramine receptors. Thymol acted to increase the intracellular cAMP levels, whereas carvacrol and α -terpineol decreased this intracellular second messenger, hence modulating intracellular calcium levels (Enan, 2001, 2005a,b).

Botanical pesticides whose mechanisms of action involve GABA receptors may be more effective, due to the speed of the effect, since

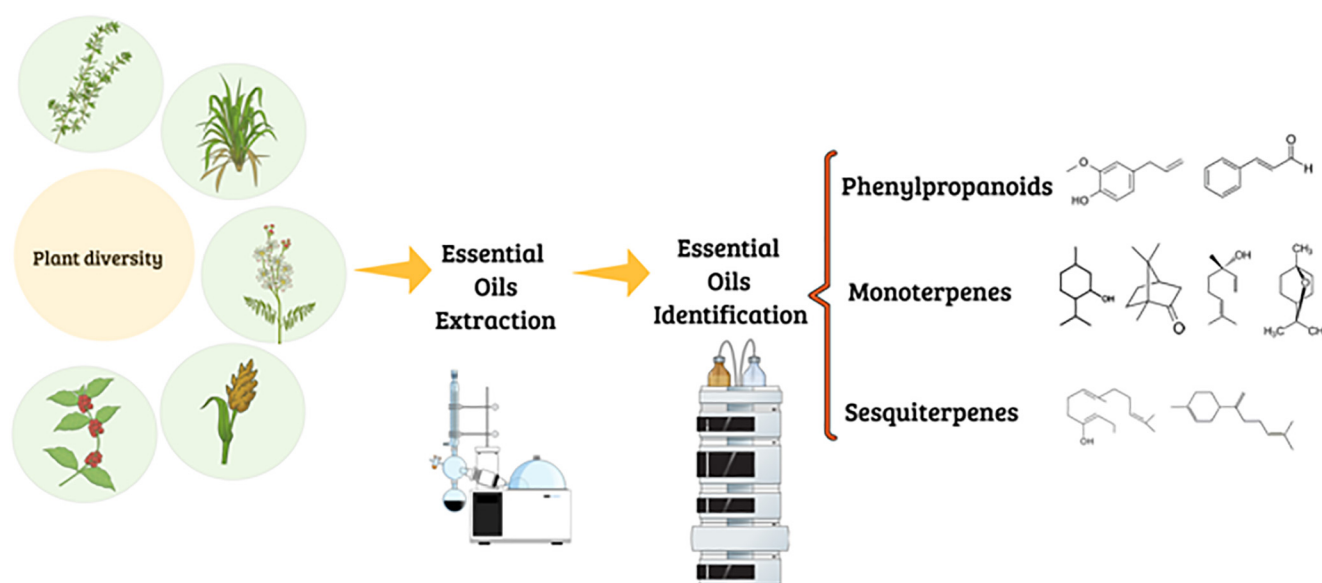


Fig. 2. Essential oils from plants obtained by extraction processes, and identification and quantification of the active components. The different compounds include the phenylpropanoid, monoterpene, and sesquiterpene classes.

Table 1
Mechanisms of action of some botanical pesticides.

Compound	Botanical species ^a	Mechanism of action ^b	References
Pyrethrin	<i>Chrysanthemum cinerarifolium</i>	Agonists of voltage-sensitive sodium channels (GABAergic system)	Wakeling et al. (2012) and Soderlund and Bloomquist (1989)
Thujone	<i>Artemisia absinthium</i>	Reversible modulator of GABA _A receptors	Höld et al. (2000)
Thymol	<i>Thymus vulgaris</i>	Stimulates GABA _A receptors	Enan (2005a)
Azadirachtin	<i>Azadirachta indica</i>	Inhibits the activity of acetylcholinesterase	Senthil Nathan et al. (2008)
Linalool	<i>Aniba roseodora</i>	Competitive and reversible inhibition of acetylcholinesterase activity	Perry et al. (2000) and Ryan and Byrne (1988)
Carvacrol	<i>Origanum vulgare</i>	Binds to nicotinic acetylcholine receptors	Tong et al. (2013)
Eugenol	<i>Syzygium aromaticum</i>	Stimulates octopamine receptors	Price and Berry (2006)
Menthol	<i>Mentha piperita</i>	Positive allosteric modulator of the GABA _A receptor	Hall et al. (2004)
α-Terpineol	<i>Citrus sinensis</i>	Reduces intracellular levels of second messenger cAMP (tyramine receptors)	Enan (2001)
1,8-Cineol	<i>Rosmarinus officinalis</i>	Antagonist of octopamine receptors	Dayan et al. (2009) and Fischer et al. (2013)
Cinnamaldehyde	<i>Cinnamomum zeylanicum</i>	Antagonist of octopamine	Dayan et al. (2009) and Fischer et al. (2013)
Nicotine	<i>Nicotiana sp.</i>	Agonist of acetylcholine	Copping and Duke (2007) and Isman and Paluch (2011)
Rotenone	<i>Derris sp.</i>	Mitochondrial cytotoxin	Copping and Duke (2007) and Isman and Paluch (2011)
Citronellal	<i>Cymbopogon nardus</i>	Antagonist of octopamine	Dayan et al. (2009) and Fischer et al. (2013)

these receptors are mainly present in the peripheral nervous systems of insects, especially at neuromuscular junctions. In contrast, those compounds that act on receptors attached to G-protein (octopamine and tyramine receptors) have lesser effects, due to the complex signaling cascades of these pathways (El-Wakeil, 2013; Ahmed et al., 2011).

Other botanical substances, such as pyrethrins, rotenone, nicotine, and azadirachtin, among others, have insecticidal activities that are well documented in the literature (Bennett and Wallsgrove, 1994; Campos et al., 2016; Isman, 2000a, 2006; Pascual-Villalobos and Robledo, 1998; Regnault-Roger, 1997). However, with increasing interest in pest control employing substances that are safer in the environment, recent research has shown that essential oils or their constituent compounds, such as carvacrol and linalool, are not only able to repel insects (Tambwe et al., 2014), but also present insecticidal action following direct contact or entry into the insect respiratory system (Beier et al., 2014). Both carvacrol and linalool have proven fungicidal activity against several important pathogens (Engel et al., 2017; Guimarães et al., 2015; Herman et al., 2016; Hsu et al., 2013; Keawchaoon and Yoksan, 2011; Müller et al., 2009; Peana et al., 2004a,b; Silva Brum et al., 2001; Tong et al., 2013).

It is already known that the performance of essential oils and/or their components may vary according to the susceptibility of a particular species, i.e., essential oils are not effective for all species of agricultural pests (Khani and Asghari, 2012; Khani and Rahdari, 2012; Lee et al., 2003; Negahban et al., 2007). In addition, the chemical composition as well as the functional groups (position and nature) present in the essential oils plays an important role in the insecticidal and/or repellent activity (Kumbhar and Dewang, 2001; Mossa, 2016). This biological activity can be potentiated by modifying the chemical structure of the monoterpenoids present in essential oils (Kumbhar and Dewang, 2001; Mossa, 2016). In this sense, the relationship between performance and chemical composition, regarding the importance of functional groups can be studied through biorational design of the derivatives (Kumbhar and Dewang, 2001; Mossa, 2016).

3. Botanical pesticides: R&D, gaps, and market

Microorganisms are known to play a key role in soil quality and health. In this way, the microbial biomass as well as the enzymatic activity are potential indicators of soil quality, since they are directly

correlated with the soil biology and for rapidly responding to changes due to anthropogenic and environmental action. Stimulating or inhibitory effects may be observed after the application of essential oils and/or their compounds alone, in microorganisms (Stamou et al., 2017; Vokou, 2007) and soil enzymes (Papathodorou et al., 2014; Stamou et al., 2017). There may be an increase or decrease in the microbial population, alter the microbial community profile and influence the activity of various microbial taxa (Kadoglidou et al., 2011; Abdel Rasoul, 2012; Vokou et al., 2002). However, it has also been shown that these compounds affect the soil enzymes in a selective manner, i.e., at the recommended dose, have no effect on soil structure and microbial biomass (Papathodorou et al., 2014; Spyrou et al., 2009). Thus, these compounds cause lower impacts to soil organisms and enzymatic activity when compared to chemical pesticides being then used to control agricultural pests.

Antonious (2003) evaluated the soil urease activity caused by pyrethrin and Neemix formulations. According to this author application of these compounds resulted in a transitional effect on urease activity. However, this effect was beneficial since they were neither drastic nor prolonged enough to be considered toxic to soil microorganisms. This author also found that the application of botanical insecticides could reduce the urea fertilizer mineralization to some extent. Stamou et al. (2017) evaluated the mutual effect of arbuscular mycorrhizal fungi (AMF) and essential oil in the soil microbial community. The results found that both AMF and essential oil operate as selective forces during fungal pre-symbiotic phase. Experiments carried out with essential oil only showed microbial community dominated by actinomycetes and micro eukaryotes while experiment with both treatments revealed the emergence of new microbial communities due to the divergent effects of both treatments. However, a synergistic effect of these treatments was observed for enzymatic activity of asparaginase and glutaminase. In this sense, the soil microbiota as well as soil quality can be benefited by the association of beneficial microorganisms and essential oils for sustainable agriculture. However, factors such as concentration, form of application, as well as application phase (in relation to the development of the microorganism) should be better studied in order not to harm the beneficial effects of this association.

In recent years, there is an exponential growth in the number of academic publications regarding the use of botanical pesticides as a tool for pest control, applying the integrated pest management (IPM) approach. Furthermore, many laboratories worldwide have intensified research into essential oils and their constituents, with the aim of exploiting their pesticidal properties (Grumezescu, 2017). However, despite these advances, there are still only few commercially available products based on plant essential oils or their isolated constituents (Table 2). According to Isman and Grieneisen (2014), the major factors limiting the wide scale exploitation of botanical pesticides are i) due to the lack of practically applicable results in many of the published studies ii) lack of the availability of good quality botanical pesticides at affordable prices; iii) strict legislation; iv) short persistence of the compounds in the environment, due to rapid degradation; v) extraction of oils from plants grown under different climatic conditions, resulting in different compositions in terms of active agents, with potentially weaker effects in pest control and likelihood of variability among batches.

Therefore, issue of sustainability of botanical resources represents one of the main barriers to advances in the commercial availability of these products. Production on a commercial scale requires a large biomass of the source plant, necessitating its production on an agricultural scale (Isman, 2006). However, the increasing demand for production of food and energy crops hinders the cultivation of plants containing essential oils, making it difficult to obtain sufficient quantities for commercial purposes, unless the plants are highly abundant in nature (Sola et al., 2014a). A further difficulty lies in the reproducibility of botanical pesticides, mainly due to natural genetic variations of the species, as well as different cultivation conditions (considering

geography and climate, among other factors) (Ndakidemi et al., 2016). In addition to the problems of cultivation, a key issue in the marketing of botanical products concerns the confidence of agriculturalists. Since many botanical compounds do not show any immediate effects and also have low residual action, many potential users are reluctant to substitute conventional products by botanical pesticides (Isman et al., 2011).

Even if it is possible to resolve all the issues described above, current regulatory barriers also present a major obstacle to the commercialization of these naturally occurring substances. In much of the world, legislation makes no distinction between synthetic pesticides and biopesticides (including botanicals). As a result, these products need to pass through long and costly registration processes, often accompanied by expensive toxicological and environmental assessments (Pavela, 2014; Pavela and Benelli, 2016). Therefore, the fact that many of these products may be destined for use in organic agriculture and by small producers means that it is often not possible to obtain the financial resources required to cover the costly processes involved in registration of new products (Hernández-Moreno et al., 2013).

In this context, the successful exploitation of emerging technologies seems to offer a way to overcome many of the difficulties that hinder the large scale production and commercialization of the botanical pesticides (Pavela and Benelli, 2016). For example, plant biotechnology research shows that genetic manipulation of certain field crop species will make it possible to produce large quantities of natural compounds originally isolated from other plant species (Daviet and Schalk, 2010). The nano/microencapsulation of natural compounds in different matrices has been shown to be an effective way of overcoming stability problems, increasing the effectiveness of the compounds due to: i) increased solubility; ii) protection against premature degradation (by high temperatures, photodegradation, and biodegradation); and iii) increased residual activity due to sustained release (de Oliveira et al., 2014; Mossa, 2016). The wall material of nanoparticulate system is selected according to the physicochemical properties of the active agent and required usage of the final formulation. However, according Kah and Hofmann (2014), among the different nanoparticulate system produced for agricultural applications, polymeric nanoparticles are those with greatest potential for development and practical application in agriculture. For this purpose, polysaccharides represent very attractive molecules, as they are biocompatible, biodegradable, low cost and high availability and can undergo various chemical modifications (Campos et al., 2015; Posocco et al., 2015; Raemdonck et al., 2013). Currently, nanotechnology has been shown to be a potential tool in the field of agricultural entomology (Kumar et al., 2017). Companies are already involved in the development of nanoformulations, for example, Syngenta started marketing the Karate® ZEON that is a broad-spectrum pesticide consisting of the insecticide lambda-cyhalothrin nanoencapsulated to regulate the insect population in rice, peanut, cotton and soybean crops. Many nanoformulations loading botanical pesticides has proven biological activity against pre and post harvest crop pests (Ebadollahi et al., 2017; Khoobdel et al., 2017; Negahban et al., 2014, 2012; Yang et al., 2009). In addition, progress has been also made in unblocking the marketing of products based on botanical pesticides. The recent classification of some botanical products as “low risk” by the European Food Safety Authority has contributed to decreasing the regulatory requirements for these products (Marchand, 2015).

4. Botanical insecticides and nanotechnology: is it a real new possibility?

It is increasingly accepted that traditional approaches to integrated pest management (IPM) are insufficient to combat pests and increase food productivity, and that there are adverse effects of intensive and extensive use of pesticides on animal and human health, nontarget organisms, and soil fertility. Alternative options have been sought to

Table 2
Examples of commercially available products based on botanical pesticides.

Active ingredient	Application	Commercial product	Company
Oil of neem (Azadirachtin)	Insecticide	Margosom®	Agri Life (India)
		AZA-Direct R®	Gowan Company (USA)
		AzeraTM®	MGK (USA)
		Azamax®	UPL Ltda. (Brazil)
		Molt-X®	BioWorks Inc. (USA)
		Neemix 4.5®	Certis (USA)
		Azatin XL®	OHP Inc. (USA)
		NeemAzal T/S®	Trifolio-M (Germany)
		Fortune Aza 3%EC®	Fortune Biotech (USA)
		Shubhdeep NeemOil®	King AgroFood (India)
		AjoNey®	I.H.N. (Mexico)
Essential oil of garlic (<i>Allium sativum</i> L.)	Insecticide	EcoA-Z®	EcofloraAgro (Colombia)
		L'EcoMix®	
		CapsiAlil®	
<i>Citrus sinensis</i> L. oil (limonene and linalool)	Insecticide/repellent	Demize EC®	Paragon Professional Pest Control Products (USA)
Essential oil of thyme (<i>Thymus vulgaris</i>)	Insecticide/repellent	Prev-Am®	Oro Agri SA Ltd. (South Africa)
		EcoVia WD®	Rockwell Labs Ltd. (USA)
Rotenone	Insecticide	5% Rotenone ME®	Beijing Kingbo Biotech Ltd. (China)
		Rotenone Dust®	Bonide Products Inc. (USA)
Nicotine (<i>Nictiana tabacum</i> L.)	Insecticide	Nico Dust®	Nico Orgo Manures (India)
		Nico Neem®	
		10% Nicotine AS®	Beijing Kingbo Biotech Ltd. (China)
Carvacrol/essential oil of oregano (<i>Origanum vulgare</i>)	Insecticide/animal feed supplement	By-O-reg + ®	By-O-reg + (USA)

combat these problems, by developing pesticides that are more effective and do not persist in the environment (Arora and Mishra, 2016; Chandler et al., 2011; Park and Tak, 2016; Parsa et al., 2014). In order to reduce the adverse effects of conventional pesticides, plant-based biopesticides (such as essential oils) can be employed as an alternative or complementary tools in integrated pest management, benefiting from their desirable characteristics, as discussed above (Archana Singh, 2014; Bakkali et al., 2008; Isman, 2000b; Pavela and Benelli, 2016; Regnault-Roger et al., 2012). However, problems related to low aqueous solubility, high volatilization rates, and oxidation when exposed to the environment need to be resolved before these compounds can be employed in integrated pest management (Pavela and Benelli, 2016; Regnault-Roger et al., 2012).

The combination of two or more alternative pest control methods in production systems can enhance the effects and extend the range of target organisms, affecting different species or different stages of development of the same species. The use of botanical pesticides in association with bioinsecticides based on microorganisms offers a promising technique for the control of agricultural pests. In this approach, botanical pesticides cause stress in pests, hence facilitating their attack by disease organisms, whose toxins act more rapidly and consequently increase the mortality rates of the pests (Ansari et al., 2012; Ezhil Vendan, 2016; Raja, 2013; Wezel et al., 2014).

Among alternative methods, nanotechnological techniques can provide effective tools to overcome many difficulties. Benefits include protection of the compounds against degradation and losses by volatilization, easier handling, sustained release, and specific targeting of the active agents (Bilia et al., 2014; de Oliveira et al., 2014; Donsi et al., 2014; Marques, 2010; Pavela and Benelli, 2016; Regnault-Roger et al., 2012; Werdin González et al., 2014). In addition, such nanoformulations can be more effective than non-encapsulated substances (Anjali et al., 2012, 2010; Werdin González et al., 2014).

There has been a steady increase in published studies concerning the encapsulation of essential oils and/or their constituents in matrices including natural or synthetic polymers, lipids, and proteins, among others, according to the desired characteristics (Chen et al., 2009, 2015; de Oliveira et al., 2014; Gabriel Paulraj et al., 2017; Guimarães et al., 2015; Keawchaon and Yoksan, 2011; Negahban et al., 2007, 2012, 2014; Yang et al., 2009). However, it should be noted that most of these studies have focused on the development of methods for the

encapsulation of these compounds for food and pharmaceutical purposes (Pavela and Benelli, 2016; Rodríguez et al., 2016).

Synergistic effects obtained using combinations of different compounds can result in enhanced biological activity, compared to the activities observed for the individual compounds. The use of this strategy can enable application of lower dosages of the active agents, hence reducing both the cost of pest management and the environmental risks (Akhtar and Isman, 2013). Furthermore, the use of mixtures of compounds is less likely to lead to resistance and behavioral adaptation of insects (Akhtar and Isman, 2013; Pavela and Benelli, 2016). However, there are few reports concerning the action of different essential oils and/or their major components in the control of agricultural pests (Koul et al., 2013; Kumrungsee et al., 2014).

Although the combination of nanotechnology and botanical pesticides could be a promising tool for integrated pest management, further studies are required in relation to i) the use of encapsulation technology to encapsulate mixtures of different essential oils and/or their constituents; ii) the toxicological evaluation of nanoformulations, including effects on nontarget organisms; iii) effects of sublethal concentrations on target and nontarget organisms; iv) regulation of the use of nanomaterials and botanical pesticides in agriculture; v) selection of natural matrices for the production of nanoparticles and scalable nanoformulations; vi) comparative cost-benefit studies of nanoformulations and current commercial formulations; and (vii) evaluation of the fate and behavior of nanoformulations in the environment (Archana Singh, 2014; Fraceto et al., 2016; Isman and Grieneisen, 2014; Regnault-Roger et al., 2012; Servin and White, 2016).

Nanotechnology is described by the European Union as one of the six key technologies required for global sustainable development (European, 2012). It has been used in many branches of science, including pharmaceutical sciences, materials science, physics, chemistry, and medicine. In agriculture, there have been advances in nanotechnology applied in animal husbandry, insect control, and soil treatment (Chen and Yada, 2011; Salamanca-Buentello et al., 2005), as well as in the production, storage, processing, packaging, and transportation of agricultural products (Campos et al., 2014; Fraceto et al., 2016; Mukhopadhyay, 2014; Sekhon, 2014).

Nanotechnology can provide many benefits in sustainable agriculture (Chaudhary and Misra, 2017; Kumar et al., 2017; Prasad et al., 2017), including i) control of pests and diseases using nanoformulations

that enable the sustained release of pesticides, improving their effectiveness and decreasing the concentrations required to achieve the desired effects; ii) sustained release of fertilizers to increase plant growth while reducing losses in runoff and decreasing water pollution problems such as eutrophication; iii) nanoparticle-mediated transfer of genes or DNA, assisting in the development of species resistant to pests and/or diseases; iv) use of nanomaterials to develop biosensors able to detect signs of diseases and/or predators, as well as identification of lack of nutrients and water; and v) new economically viable methods for the removal of pollutants from the soil and for water treatment (Araújo et al., 2015; Duhan et al., 2017; Fraceto et al., 2016; Iavicoli et al., 2017; Mukhopadhyay, 2014; Nair et al., 2010; Rai and Ingle, 2012; Sekhon, 2014; Torney et al., 2007; Verma, 2017).

Although there are various uncertainties regarding the use of nanotechnology and botanical pesticides in agriculture, cordial efforts should be made to convince the policy makers to seriously provide a market for such products by reducing many existing regulatory barriers (Amenta et al., 2015; Chandler et al., 2011; Jain et al., 2016; Sola et al., 2014b). In nanotechnology, the uncertainties are not related to the risks themselves, but the impossibility of calculating them (dos Santos and Gottschalk Nolasco, 2017; Pyrrho and Schramm, 2012). There are risks associated with nanotechnology in a complex and yet difficult to define scenario, but which, however, cannot be underestimated (Maynard, 2014; Stokes, 2013). Among them, we can emphasize the identification and management of the impacts of nanomaterial during the production chain; monitoring the cycle of persistent nanoparticles in the environment; and the complexity in the definition of acceptable levels of particles present in working conditions, environmental exposure and consumer of nanoproducts (Simone et al., 2009; Strand and Kjølberg, 2011; Tavares et al., 2015). Within this context, there is a question: what are the global strategic directions for a specific regulation for the use of nanotechnology? To date, there is no specific international regulation for commercially available products incorporating nanoparticles at some stage of industrial processing. Another point to be made is the lack of reliable international standard protocols for assessing the human and environmental toxicity of nanoparticles (dos Santos and Gottschalk Nolasco, 2017; Retzbach and Maier, 2015; Stokes, 2013; Strand and Kjølberg, 2011).

Due to the improvement in the quality and cost-effectiveness of nanotechnological products and processes, as well as the social benefits added to this technology, companies have developed strategic business plans and policies in research, development and innovation with the aim of bringing industrial competitive advantages in several areas (dos Santos and Gottschalk Nolasco, 2017; Riccardi, 2015). Importantly, effective cooperation is needed between academic research institutions and botanical pesticide producers in order to put into practice the results obtained at the laboratory scale. This is one of the keys to the success of integrated pest management, as both nanotechnology and biopesticides are tools that can be used in the development of sustainable agriculture, with the aim of providing significant improvements in food quality and safety, human health, and environmental preservation (Bilia et al., 2014; Pavela and Benelli, 2016; Regnault-Roger et al., 2012).

In addition to the nanotechnology associated with botanical pesticides, other technologies have been widely used in sustainable agriculture with the aim of reducing the population of insects that attack crops, such as the use of biological insecticides. Biological insecticides are excellent alternatives to bypass the environmental pollution derived from chemical insecticides, besides providing the most selective control of insects (Bravo et al., 2015; Narva et al., 2014). For the biological control of insect pests, the bacterium *Bacillus thuringiensis*, 1915 is considered the most interesting species being characterized by the production of protein crystals during sporulation, which have insecticidal activity (Proteins Cry) with high specificity against insect larvae of several orders. Transgenic cultures expressing Bt proteins require fewer applications of pesticides, reduce production costs, provide

selectivity and specificity against target pests, and natural enemies (Bravo et al., 2015; Narva et al., 2014; Savini and Fazii, 2016). However, in spite of these advantages, there is currently great concern for the widespread use of Bt crops since they can accelerate the selection of resistant organisms in target pest populations (Niu et al., 2016; Vachon et al., 2012). In this sense, the association of bio-insecticides, both botanical and biological, may be potential tools in the control of agricultural pests in sustainable agriculture.

As highlighted here, the nanoencapsulation and sustained release of botanical pesticides has becoming a promising strategy to efficiently protect these compounds from premature degradation, thereby increasing their biological activity as well as reducing negative impacts on the environment. It is believed that in the near future, the sustained release of botanical pesticides will become a key tool for sustainable agriculture, aimed at improving agricultural production in order to produce sufficient food for the growing world population. In addition, the use of these nanoformulations aims to reduce environmental impacts and reduce risks to human and animal health. Thus, efficient management of agricultural pests with these nanoformulations will result in less use of bioactive molecules to control pests and consequently reduce several problems associated with the intensive use of synthetic agrochemicals, as previously mentioned.

5. Future trends in sustainable agriculture

The use of synthetic pesticides remains the principal technique for the control of pests and diseases in conventional agriculture, but it is acknowledged that agricultural production will be seriously threatened if sustainable techniques are not adopted. Many studies have shown that the intensive use of synthetic chemicals leads to irreversible damage to the structure and ecology of soil (Dabrowski et al., 2014; Saruchi et al., 2016), with negative effects on the microbiota (Asad et al., 2017; Bending et al., 2007; Yang et al., 2017). In contrast, there have been few studies and little is known concerning the impacts of botanical pesticides on soil microbiota (Fig. 3). It is mistakenly believed that since botanical pesticides are obtained from natural sources, they are therefore not toxic towards nontarget organisms and are always safer than synthetic pesticides (Rousidou et al., 2013; Spyrou et al., 2009).

Botanical pesticides typically exhibit broad spectrum antimicrobial activity, in most cases being nonselective, so they can potentially affect the soil microbiota population (Bhat et al., 2012; Conti et al., 2014; George et al., 2010; Spyrou et al., 2009). Nonetheless, as discussed earlier, these compounds offer considerable advantages, compared to the synthetic compounds currently used, and are promising for use in sustainable agriculture (Chowdhury et al., 2015; Dar et al., 2014; Dubey et al., 2010; Karani et al., 2017; Khaliq et al., 2014; Xu et al., 2015). Their rapid breakdown in the environment, together with low accumulation in the soil organic matter, can help to decrease the degradation of agricultural soils (Ansari et al., 2012; Archana Singh, 2014; Blázquez, 2014; Carrubba and Catalano, 2009; Pavela and Benelli, 2016; Raja, 2013). Botanical pesticides have been shown to provide effective control of different species of agricultural pests, in many cases being more effective than synthetic chemicals, due to their varied mechanisms of action (Sola et al., 2014a,b; Tambwe et al., 2014; Oliveira et al., 2017; Štefanidesová et al., 2017). An important point is that the formulation of new commercial products (using, for example, nanotechnological techniques) could further enhance the performance of these natural compounds, reducing both the dosages required and their toxicity towards nontarget organisms, especially the soil microbiota (Chhipa, 2017; de Oliveira et al., 2014; Mattos et al., 2017; Mossa, 2016).

Although nanotechnological materials have been shown to provide superior performance in many areas of science, the processes used to produce them can result in the generation of hazardous wastes, while the raw materials may be non-renewable resources (Duhan et al., 2017;

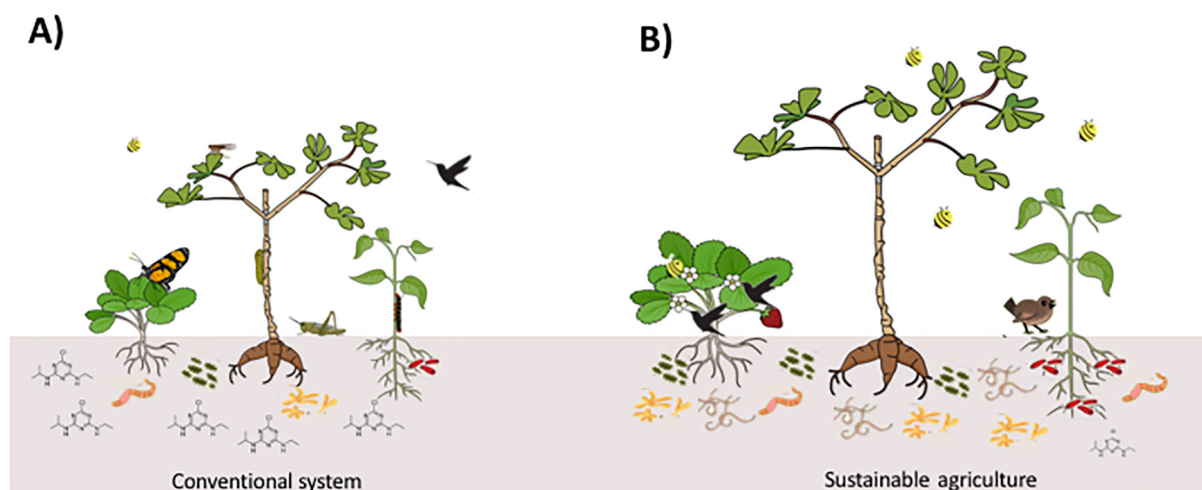


Fig. 3. Representation of a conventional agricultural system (A), based on the use of synthetic chemical compounds to control pests, with the development of pest resistance and decrease in the soil microbiota. (B) A sustainable agricultural system based on biological pest control, use of botanical insecticides/repellents, and application of new technologies. This scheme highlights the diversity of the soil microbiota, which is essential in sustainable agricultural practices, as well as potential improvements in plant development and consequently in food production.

Iavicoli et al., 2017; Mishra et al., 2017; Sinha et al., 2017). Hence, there have been considerable efforts to reduce the generation of toxic wastes and their disposal in the environment, as well as to develop production methods that are more energy efficient, in compliance with the principles of green chemistry. The aim of green nanotechnology (the combination of nanotechnology and the practices of green chemistry) is to develop and manufacture safer nanomaterials with zero or minimal generation of hazardous waste (de la Guardia, 2014; Lu and Ozcan, 2015; Nath and Banerjee, 2013; Pleissner, 2017). Green nanotechnology is one of the keys to successful implementation of sustainable agriculture in the 21st century, and has three basic principles: i) use of biocompatible and nontoxic solvents; ii) use of natural raw materials; and iii) use of energy efficient processes (de la Guardia, 2014; Lu and Ozcan, 2015; Nath and Banerjee, 2013).

For applications in sustainable agriculture, sustained release systems should preferably be manufactured using natural biodegradable polymers, instead of the synthetic polymers. Natural polysaccharides such as alginate, chitosan, and cyclodextrins, among others, have been extensively studied for the production of sustained release systems for use in agriculture, since they are biodegradable, biocompatible, and present low toxicity towards mammals (Campos et al., 2014). Chitosan is used in agriculture for the management of biotic and abiotic stress (Sharp, 2013; Wang et al., 2015; Xing et al., 2015). In addition to antimicrobial activity, chitosan is believed to enhance the systemic resistance of plants against pathogens (Katiyar et al., 2014; Sharp, 2013; Xing et al., 2015), and also to increase and regulate the growth, development, and yield of crops (Wang et al., 2015), and stimulate certain soil microorganisms (Cretoiu et al., 2013; Kamari et al., 2011).

Nanostructured systems can also be used to resolve a major issue in sustainable agriculture, namely the presence of contaminants in the soil, by detecting, monitoring, and removing these substances. This is especially important due to losses of productive agricultural areas following extensive soil degradation. The adoption of more sustainable agricultural practices is the only viable way of increasing productivity without causing negative impacts in the environment and on human health, and the use of botanical pesticides in agricultural systems can contribute to this goal. Further advantages could be gained by implementing techniques employing botanical pesticides in combination with nanomaterials produced in accordance with the principles of green chemistry. These promising systems offer effective and ecologically more sustainable ways for reducing the pest attack and consequently maximizing crop productivity. Nonetheless, it is clear that further work will be needed to obtain a better understanding of the fate and behavior

of these materials in the environment.

To make the nanoencapsulated botanical pesticides closer to application in field condition, some issues need to be addressed. Studies involving the toxicity of these systems for humans, soil microorganisms and plants need to be better studied and understood in order to predict the possible toxic effects of these systems when they are deposited in the ecosystem. In addition studies focused on the elucidation of how these systems behave in relation to climatic changes, soil composition and structure, interaction/absorption and translocation in plants are of extreme importance to understand how these nanoformulations behave under different conditions and with different degrees of severity. As for example, these nanoformulations will behave in the same way in a tropical climate when compared to a temperate climate? It is worth mentioning that these studies cannot be limited only in laboratory scale, through in vitro tests. After obtaining satisfactory results in vitro, these studies are expected to be carried out under field conditions in small scale or in greenhouses, in order to bring these products closer to commercialization.

Another important fact that needs to be analyzed by future studies in the sustained release of botanical pesticides is the association of two different compounds in the same nanoparticulate system. These compounds may be derived from the essential oil of the same or different species. It is already known that the association of different compounds originating from essential oils may have additive, synergistic or antagonistic effects in a particular pest (Akhtar and Isman, 2013; Singh et al., 2009; Tak and Isman, 2017; Yang et al., 2017). However, these studies were largely performed only with non-encapsulated botanical pesticides. It is of great importance to analyze if the nanoencapsulation of these compounds, as well as the sustained release of them do not alter the effect patterns in the pests. As for example, two compounds which exhibit antagonistic effects when associated may have synergistic or additive effects when nanoencapsulated? Synergistic effects between botanical pesticides are quite promising for the application of these compounds in agriculture. Since potentiation of the effect results in the use of lower concentrations of these compounds for the control of pests and, consequently, would delay further the emergence of species resistant to botanical pesticides.

Finally, another trend in the field of nanotechnology that should be widely studied for agricultural applications is the development of “intelligent” sustained release systems (Hussain, 2017), which change the pattern of release of the substance according to a given stimulus. In agriculture, for example, release systems that are sensitive to changes in pH, salinity, temperature, and others can be strong candidates for

increasing agricultural productivity.

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