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REVIEW

# Odorant binding protein as a management target for *Ceratitis capitata*: a window of opportunities for in vivo/in silico integration

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**Abstract**

*Ceratitis capitata,* known as Mediterranean fruit fly, represents one of the main problems to the agricultural production, due the ability to infest a wide variety of fruits, which makes it one of the most worrying pests globally. The infestation of host fruits by the insect compromises their quality and appearance, causing losses to their commercialization and consumption. In order to minimize this problem, fruit growers have adopted the indiscriminate use of conventional insecticides that raise environmental and public health concerns, in addition to promoting resistance in insects. Alternatively, semiochemicals have been explored as a management tool, attracting males and females into traps or promoting repellency in exposed fruits. In this context, in silico approaches, as Molecular Docking, Molecular Dynamics and the Virtual Screening procedures, offer opportunities to identify new molecular entities as potential ligands to Odorant Binding Proteins (OBP), that are involved in olfactory communication of *C. capitata*. In this review, we present a collection of data including the chemistry of olfactory communication of *C. capitata* and some computational tools that can be used in these studies, emphasizing their impact on the behavior of this and other associated insects. We also address theoretical ADME-Tox parameters as initial evaluation criteria to ensure human safety in the environmental applications, as well as the importance of molecular synergism for the effective management of the medfly.

## Introduction

The Mediterranean fruit fly, *Ceratitis capitata*, is recognized as one of the most worrying pests due to its ability to adapt to a wide variety of fruits (European and Mediterranean Plant Protection Organization 2022). Its remarkable ecological flexibility and evolutionary capacity make it an invasive and polyphagous pest, with significantly negative economic impacts on the commercialization and industrialization of fruits, in addition to direct damage during preharvest (Papanicolaou et al. 2016; Zucchi 2015). The main crops affected by larvae infestation, originating from eggs deposited in fruits by adult females of *C. capitata*, include mango, grapes, papaya, pitanga, guava and acerola, creating a way for opportunistic bacteria and fungi. This results in necrosis, rot and premature ripening of the fruits, affecting their appearance and making them unsuitable for commercialization (Santos et al. 2007). Therefore, the incidence of these flies is a global situation, requiring frequent applications of insecticides to control the pest (Bittencourt et al. 2006). However, the indiscriminate use of these products has negative impacts on the environment, leading to the search for attractive or repellent molecules as a new approach to managing the insect (Melo et al. 2010).

In the context above, Molecular Docking and Virtual Screening computational strategies can be used as interesting tools to identify new molecules that can be used in pest control methods (Ferreira et al. 2011a), as well as explain the mechanisms of action of knowled ligands. Molecular Docking strategies are composed by "search algorithms", able to

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predicting the best energy, conformation and orientation of a ligand in a specific site of a macromolecular biological target (Kitchen et al. 2004). This technique can be applied, for example, for the identification of molecules with potential affinity with proteins of *Ceratitis capitata* in Virtual Screening campagnes, using virtual libraries of compounds. An important target that emerges in this context is the Odorant Binding Protein (OBP), the structure located in the insect's antennae initially involved in olfactory communication and therefore an important target for species management.

OBPs play an important role in the olfactory system of insects, facilitating the detection of volatile molecules such as pheromones and compounds present in the environment (Rana et al. 2024). These proteins are present in the fluid of olfactory sensills, microstructures located mainly in the antennae and other sensory organs (Benton et al. 2009). With a compact structure, composed predominantly of six α-helices and stabilized by disulfide bridges, OBPs have a hydrophobic central cavity that allows the capture and transport of odorants through an aqueous medium to the olfactory receptors (Al-Jalely and Xu 2021). Their structural conformation protects them from environmental degradation, ensuring efficiency in the transmission of chemical signals (Vieira et al. 2007). In general, the transduction of the odorant signal begins with OBPs, which capture and transport odorant molecules to odorant receptors (ORs) in the membranes of olfactory neurons (Pelosi and Maida 1995).

This entire mechanism of action has some well-defined steps. At the beginning of the recognition process, proteins capture, through the pores of the antennae, odorant molecules present in the environment, interacting with them through Van der Waals forces, hydrophobic interactions, and, in some cases, hydrogen bonds (Leal 2013; Zhang et al. 2018). The binding capacity of OBPs is another notable aspect, being determined by the shape and composition of the hydrophobic cavity, which confers high affinity for specific odorants (Falchetto et al. 2019). Then, the odorant is transported by the OBP through the sensillary fluid, being protected from degradation until it reaches the ORs in the membrane of sensory neurons (Laughlin et al. 2008; Gomez-Diaz et al. 2013). ORs, in turn, are membrane proteins that activate a signaling cascade when an odorant binds to them. The activation of ORs leads to increased levels of cyclic AMP (cAMP), opening of ion channels and depolarization of the olfactory cell, generating an electrical signal that triggers the perception of odor and, consequently, the behavioral response of the insect (Breer 2003).

Near these receptors, odorant release is modulated by factors such as pH (neutral pH), which influences the affinity of the OBP and the subsequent release of the compound, allowing the odorant to bind directly to the OR, activating a signaling cascade that transmits the information to the insect's nervous system, activating the insect's behavioral response (Zhou 2010; Brito et al. 2016a). This interaction, modulated by factors such as pH, alters the structural conformation of the protein, promoting the controlled release of the odorant (Leal 2013; Rana et al. 2024). Despite the knowledge about the signaling cascade and how the general mechanism occurs, which will be discussed later, the detailed interactions between OBPs and ORs and the dynamics of this transduction are still open questions (Rihani et al. 2021). Future studies should use advanced techniques to clarify how these interactions and variations influence olfactory perception.

OBPs also perform essential functions that go beyond simply capturing odorants. These confer specificity to the olfactory system, allowing insects to discriminate a wide range of chemical compounds, important for certain behaviors such as searching for food, choosing mates for mating, detecting predators, flying, and identifying places for egg deposition (Falchetto et al. 2019; Rana et al. 2024). In addition, OBPs protect odorant molecules from degradation before their interaction with receptors and adapt to different environmental conditions, such as pH and temperature variations, ensuring effective performance in various ecological scenarios (Pelosi et al. 2014; Rihani et al. 2021; Gu et al. 2015). Therefore, the study of these proteins has great practical relevance for the detection of compounds with semiochemical activity and in the development of synthetic pheromones for pest control, chemical biosensors and more effective repellents (Campanacci et al. 2001; Venthur and Zhou 2018), since OBPs represent an essential interface between the external chemical environment and the sensory perception of insects.

Considering that affinity and efficacy events in molecular signaling (physiological response) depends on the structural attributes of a molecule, the Docking could help in identifying molecular architectures with attractive or repellent potential, after experimental confirmation at light of theoretical affinity predictions. In other words, knowing from basic pharmacology that high affinity can result in agonist or antagonist effect depending on the mobilized amino acids, the computational technique can help to elucidate the targeting of repellents or attractors depending on the phenotypic response subsequent to the predictions. In addition, to improve and validate Docking results, Molecular Dynamics (MD) simulations are often used as a subsequent step for ligand-target complexes (De Vivo et al. 2016). These simulations generate the trajectory of atoms over time, allowing the evaluation of the conformational temporal profile of the ligand–protein complex, including their flexibility and the influence of the explicit aqueous medium on the interaction (Alonso et al. 2006). These aspects are importants to accurately predict binding energies and geometries (De Vivo et al. 2016; Alonso et al. 2006). In this paper, an extensive review about the biochemical and phytochemical aspects involved in the olfactory communication of *C. capitata* are

discussed, emphasizing the window of opportunities widely open for integration with some Computational Chemistry techniques.

## Presentation and life cycle of *Ceratitis capitata*

The genus *Ceratitis*, belonging to the Tephritidae family, comprises approximately 100 cataloged species (White and Elson-Harris 1992; Virgilio et al. 2014). The *Ceratitis capitata* (Wiedemann) (Diptera: Tephritidae), whose presence dates back to the beginning of the twentieth century in Africa, spread to Mediterranean Europe, Central and South America through the intense global trade of fruits (Nava and Botton 2010; Metcalf 1995; Liquido et al. 1991). It is currently considered as one of the most worrying fruit pests, affecting around 400 fruit varieties (European and Mediterranean Plant Protection Organization 2022). Possessing great evolutionary flexibility in different environments (Papanicolaou et al. 2016; Zucchi 2015), it is an invasive and polyphagous pest, with negative economic impacts on pre-harvest fruit production (McPheron and Steck 1996). In this context, the genus *Ceratitis* stands out among the main global pests, together with five other genera: *Anastrepha, Bactrocera, Rhagoletis, Dacus* and *Toxotrypana* (Fazenda 2023). The genera *Ceratitis* and *Anastrepha* are the most economically relevant, since some of their species infest the majority of cultivated fruits (European and Mediterranean Plant Protection Organization 2022). In this regard, the insects becomes particularly destructive because it is capable of infecting around 200 varieties of fruits, from the moment the females pierce the fruits when laying their eggs, consequently allowing larval invasion and even opportunistic microbial invasion (Ouarhach et al. 2022). Insect pheromones are the main compounds that play an important role in intra- and interspecies communication, inducing specific behavioral responses in terms of sexual attraction, mating aggregation and aiding in the identification of the host fruit for egg deposition (Siciliano et al. 2014). After emerging, the adult *Ceratitis capitata* begins searching for the host fruit to reach sexual maturity, aiming to mate and lay eggs, starting a new cycle (Pereira 2003). The dimensions of the adult of this species vary from 4 to 5 mm in length and 10 to 12 mm in wingspan, with a predominantly yellow coloration, brown-violet eyes, a black thorax on the upper side with symmetrical white designs and a dark yellow abdomen, containing two grayish and yellow transverse stripes (Paranhos et al. 2008).

Considering its life cycle, the infestation process is initiated by the adult female of *C. capitata*, which lays its eggs in the host fruit, compromising its appearance, damaging the pulp and, consequently, reducing its quality for commercialization and consumption (Vargas et al. 2001; Vontas et al. 2011; Dias-Pini et al. 2022). Fruit flies are holometabolite insects, and iniciate their metamorphosis in the host fruits: from egg, becoming a larva that consumes the fruit and goes to the ground, converting into a pupa, until they become adults. (Thomas et al. 2001). Females, in the sexual maturation phase, lay eggs on the fruit skin, preferably in the maturation stages, in a period that varies from 9 to 16 days after emergence (Malavasi 2009). After 2 days, the eggs hatch, and the larvae, during 6 to 10 days, go through three stages inside the fruit, feeding and producing galleries, depending on environmental conditions (Duarte and Malavasi 2000). The larva, in its last stage, leaves the fruit and buries itself in the soil for the pupal stage, which lasts 10–15 days (Carvalho and Nascimento 2002). Then, the adult insect emerges (Malavasi 2009). After emerging, the *Ceratitis capitata* adult begins the search for food necessary to reach sexual maturity, aiming to mate and lay eggs, starting a new cycle (Pereira 2003). At this stage, insects seek protein food and sugars for their sexual maturation by lodging themselves in the foliage of plants, mainly in the shaded area where the fruits are (Senar 2016). Mating occurs when the insects reach sexual maturity and, after copulation, the female begins to search for fruits to lay eggs (Raga and Sato 2016). It is at this moment that a new biological cycle of the species begins. The dimensions of the adult in this species vary from 4 to 5 mm in length and 10 to 12 mm in wingspan, with a predominantly yellow color, violet-brown eyes, a black thorax on the upper side with white symmetrical designs and a dark yellow abdomen, containing two stripes grayish and yellow transversals (Paranhos et al. 2008).

The life cycle duration of these flies is significantly influenced by abiotic and biotic factors, such as temperature, relative humidity, physiological conditions and types of host fruits (Arredondo et al. 2010). The availability and population density of hosts constitute biotic factors that impact population dynamics, oviposition preference and the biology of these organisms (Montes et al. 2011). Furthermore, *C. capitata* demonstrates a remarkable ability to adapt to different hosts and, in the absence of the primary or preferred host, resorts to secondary hosts, facilitating its persistence in available hosts (Leite et al. 2019). The primary host refers to the fruit in which the fly completes its life cycle in a short period, while the secondary host is the alternative fruit, used in the absence of the primary host, which can interfere unfavorably in the different stages of development of these tephritidae (Carvalho and Nascimento 2002). It is important to highlight that, in polyphagous insects, discrimination and selection of the appropriate host represent unpredictable behaviors, especially when these insects turn to other plants in the absence of their primary hosts (Aluja and Mangan 2008). Thus, the biological and demographic cycles of *C. capitata* populations have been explored in different hosts,

seeking a more in-depth understanding of the different life strategies adopted by this insect (Costa et al. 2011; Zanardi et al. 2011; Leite et al. 2019).

## Economic importance and problematics involved

China, India and Brazil are the main fruit producers globally (Vidal 2023). Fruit flies are considered key pests in fruit farming, being responsible for annual losses of approximately one billion dollars worldwide, due to the damage caused and high control costs (Bittencourt et al. 2006; Marques 2023). They prefer juicy fruits, such as papaya, melon, peach, mango, guava and grapes (Haji and Alencar 2000). In grapevines, fruit flies are considered one of the main pests (Haji et al. 2009). In 2023, grape production reached 1,660,124 tons on 74,744 hectares, in Brazil (IBGE 2023a) Considering this economic importance, the risk caused by fruit flies deserves attention and its proper management could further optimize production (Nava and Botton 2010). Their damage in orchards not only makes export difficult, but also leads to the implementation of more stringent quarantine barriers by importing countries (Manrakhan et al. 2022).

The main control method is the chemical, through the application of synthetic insecticides, organophosphates and pyrethroids, whether in the form of toxic bait or spraying (Raga and Sato 2016). However, the indiscriminate use of these pesticides, their toxicity and non-biodegradability of some of them, have significant environmental impacts, in addition to being associated with several diseases (Melo et al. 2010). Given this scenario, as a proposed solution to the problem, alternatives have emerged in Integrated Pest Management (IPM), including the use of biological sources, biopesticides and semiochemicals, among others (Goulart et al. 2015).

Research aimed at understanding the reception of pheromones in *C. capitata*, for example, has indicated the possibility of developing new applicable attractants or repellents, replacing pesticides (Jang et al. 1989; Siciliano et al. 2014; Falchetto et al. 2019). In particular, non-toxic molecules known as semiochemicals, which are signaling compounds used in insect communication, produced and released in extremely small quantities, have the potential to improve control strategies such as monitoring, mass collection and sexual confusion, contributing to environmental preservation (Arioli et al. 2013). Furthermore, the characterization of these molecules involved in the behaviors of fruit flies sheds light on the understanding of their biology and ecology, providing a solid basis for the development of new pest control tools specific to each species, exploring and interfering in the chemical perception (Scolari et al. 2021).

## Olfactory sensitivity

Several approaches to reducing insect pest population levels rely on modulating their behavior. (Camelo et al. 2007). The interpretation of environmental chemical signals plays a crucial role in the survival of these organisms, triggering diverse behavioral responses (Brito et al. 2016). Insects utilize a wide range of semiochemicals, such as pheromones and plant volatiles, to regulate essential behaviors such as identifying food sources, oviposition sites, suitable hosts, discriminating host plants, detecting pheromones, and locating mating partners. (Siciliano et al. 2014; Solari et al. 2018). Plant volatiles, which are complex mixtures of up to hundreds of compounds, play a crucial role in biosignaling of these behaviors (Fraser et al. 2003). Similar to plant volatiles, pheromones, commonly synthesized by male fruit flies, constitute a set of multicompound substances with different volatilities, allowing the transmission of complex messages for feeding, reproduction and defense (Vilela and Della Lucia 2001). In some cases, sexual signaling and pheromone emission begin in the presence of host plant volatiles (Papadopoulos et al. 2006), while in others, host plant volatiles synergistically amplify the response of a given sex to the sexual pheromones of opposite sex (Schmidt-Busser et al. 2009).

Over the years, studies have been dedicated to characterizing the chemical composition of pheromones and identifying their biologically active compounds (Alfaro et al. 2011; Light et al. 1988; Vaníčková et al. 2012; Siciliano et al. 2014). In the case of *C. capitata*, the pheromone compounds involved in sexual intercommunication can be classified as primary constituents ((*E,E*)-α-farnesene and geranyl acetate), intermediates (myrcene and linalool), and secondary or trace constituents (such as o (*E*)-β-farnesene and 2,3-butanediol) (Sollai et al. 2018). These compounds regulate the reproductive behavior of fruit flies through molecules released by males (Díaz-Fleischer and Aluja 2003).

Among the tephritid species studied, it is known that virgin males release substances to attract males and females to specific locations close to host plants, where mating and, subsequently, oviposition occur in fruits (Leal and Zucoloto 2008). Volatile compounds can influence the reproductive behavior of males in three distinct situations: increasing calling frequency, enhancing the attraction of females and serving as precursors of chemical signals released by males (López-Guillén et al. 2011). In the case of females, the odors released by males and host fruits function as olfactory cues for locating partners and selecting potential hosts for oviposition (Siderhurst and Jang 2006). The perception of these semiochemicals occurs in antennal olfactory sensilla, present in both males and

females, and which, even in small quantities, are noticed at great distances, depending on the wind speed (Gallo et al. 2002). Therefore, understanding the olfactory sensitivity of *C. capitata* may be valuable for developing more targeted control strategies using biologically active molecules (Reddy and Guerrero 2004). This alternative is considered acceptable in agriculture, compared to other forms of control, making the use of semiochemicals an attractive and viable strategy (Hassanali et al. 2008), as the use of natural or synthetic insect pest pheromones can significantly reduce the use of insecticides, thus minimizing the environmental impact (Ghini and Bettiol 2000).

## General aspects of odorant binding protein (OBP)

OBPs are small, water-soluble extracellular transport proteins (Zhou et al. 2010). These biochemical structures, responsible for the odors transport, are located in the insect antennae, specifically in cuticular structures called "sensilla" (Klein 1987). Sensillas have pores that allow the passage of odorous substances that then come into contact with the sensilla lymph, a cytoplasmic liquid where OBP as carrier proteins are highly abundant (up to 10 mM) (Vogt and Riddiford 1981; Vogt et al. 1989). Surrounded by the sensillary lymph are the dendrites of olfactory sensory neurons, which are nerve cells specialized in processing and transmitting odorous stimuli (Fan et al. 2011; Leal et al. 2013). In this environment, OBPs bind to hydrophobic odorant substances and transport them to OR, located in the membranes of dendrites (Pelosi 1994; Biessmann et al. 2010; Pelletier et al. 2010). By transporting volatile compounds under ideal pH conditions to the ORs, the olfactory message is converted by ORs into behavioral responses (Zhou et al. 2010) (Fig. 1). Detailing the signaling cascade, the ORs are G-protein-coupled receptor (GPCR). Each receptor is specialized to binding specific classes of odorants or pheromones. Upon binding the ligand, the OR undergoes a conformational change that activates the associated G-protein, releasing an α-subunit that activates adenylyl cyclase, an enzyme that catalyzes the conversion of ATP into cyclic AMP (cAMP). The increase in cAMP levels leads to the activation of Protein Kinase A (PKA), that can phosphorylate a variety proteins within the olfactory sensory neuron. The cAMP production also leads to the opening of cation channels, allowing $Na^+$ and $Ca^{2+}$ ions to flow, depolarizing the olfactory sensory neuron and generating an action potential. The depolarization is the initial electrical signal in the process of odor detection (Fan et al. 2011).

Additionally, several studies, performed on different species of insects, revealed that these proteins play not only the role of passive transporters of odorants, but are also involved

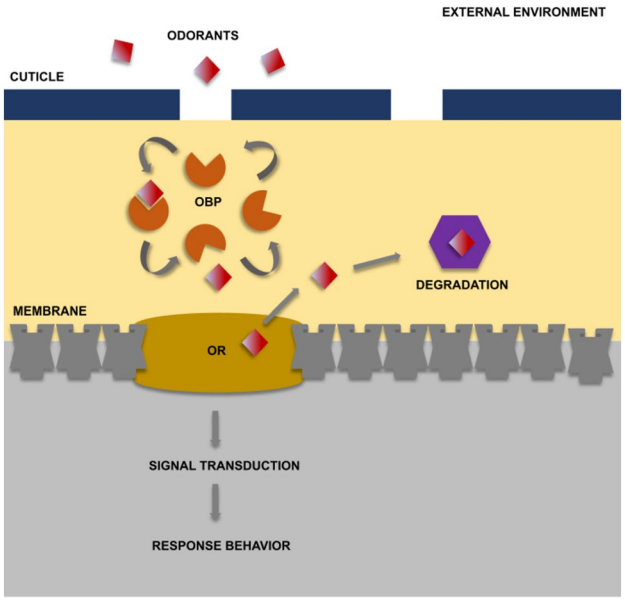



**Fig. 1** Schematic representation of the recognition of volatile compounds by the odorant protein. Source: Adapted from Sanchez-Garcia et al. (2009)

in the discrimination of semiochemicals, functioning as the first molecular filter in the selection process (Chang et al. 2015; Leal 2005; Yin et al. 2015). The OBP primary sequence of insects, for example, determines the binding site specificity for different ligands, as evidenced by several molecular structures obtained through X-ray crystallography and NMR spectroscopy (Tsitsanou et al. 2012). Considering the main interest of this review, the OBP of *Ceratits capitata* is deposited in the online Protein Data Bank (PDB ID: 6HHE), of which the three-dimensional structure was determined from studies involving X-ray diffraction. (Falchetto et al. 2019). In this sense, the number of candidate genes for a structural approach targeting the olfactory system continues to grow consistently, especially after the completion of genomic sequencing of several insect species, such as *Drosophila melanogaster* and *Anopheles gambiae* (Adams et al. 2000; Holt et al. 2002).

The three-dimensional architecture of insect OBPs generally has a molecular weight ranging from 15 to 20 kDa and is composed of a domain of six α-helices, which form a hydrophobic cavity (González-González et al. 2019; Sun et al. 2018a, b; Vogt 2002). This cavity is stabilized by three disulfide bridges, which interconnect conserved cysteines, conferring stability to the structure (Leal et al. 1999). In the case of the *C. capitata* OBP, there is a distinct structural characteristic: the presence of a seventh α-helix in the C-terminal region (Fig. 2). This additional helix plays a crucial role in defining the central hydrophobic binding cavity of the odorant molecule, allowing greater stability of the bound molecules compared to OBPs from other insects, which

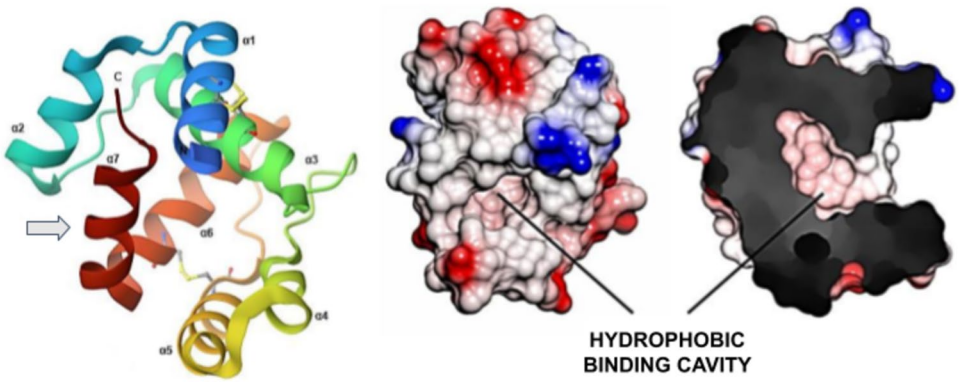



**Fig. 2** Three-dimensional structure of the odorant protein from *Ceratitis capitata* and the representation of the hydrophobic binding cavity, where the ligand interacts with the target macromolecule. The arrow is indicating the seventh alpha-helix in red of the protein. Source: Adapted from Falcheto et al. (2019)

typically have only six α-helices. Furthermore, the seventh α-helix enables the closure of the cavity when the odorant compound binds to the protein, a phenomenon influenced by the pH of the hemolymph, which ensures the stability and functioning of the protein (Falchetto et al. 2019).

Furthermore, the OBP is genetically more expressed in females and plays a crucial role in intersexual olfactory communication (Falchetto et al. 2019). In *C. capitata*, the male synergistically releases the intersexual communication pheromone in trace quantities, with the aim of attracting the female for mating, at the same time, it also attracts males, thus facilitating the encounter with females (Siciliano et al. 2014). This process results in increased pheromone concentrations, making it more effective in attracting a greater number of females under specific physiological conditions (Prokopy and Hendrichs 1979; Jang et al. 1989). The increase in concentrations is strongly influenced by the sexual maturity of males, with the glands responsible for pheromone production becoming more active in the reproductive phase (Heath et al. 1993). Pheromone production in males is also regulated by circadian rhythms, with peaks in release occurring during the hours of the day most conducive to mating, usually in the late afternoon. This synchronization maximizes the chances of reproductive success, ensuring that males release pheromones at times of greatest female activity (Landolt and Sivinski 1992). In addition, environmental factors such as the presence of receptive females and lighting conditions influence the amount of pheromone released. Males adjust their release in response to external stimuli, such as the perception of pheromones from other males, increasing competition for female attention (Jang and Light 1996).

As already mentioned, the predominant compound in the pheromone released by *C. capitata* males is (E,E)-α-farnesene (Gonçalves et al. 2006; Jang et al. 1989; Merli et al. 2018). This component demonstrates a remarkable specificity and affinity with the Odorant Binding Protein (OBP) when compared to the five main compounds of the Mediterranean fly pheromone (Falchetto et al. 2019). Therefore, the six volatiles that make up the male sex pheromone of *C. capitata* are: α-farnesene and geranyl acetate (major components), linalool and β-myrcene (intermediate components), β-farnesene and 2,3-butanediol (minor/trace components) (Sollai et al. 2018).

These compounds play a crucial role in several complex behaviors, such as cutting, aggregation, associative learning, search for and acceptance of food, in addition to host plant recognition by insects (Biolchini et al. 2017). (E,E)-α-farnesene is also an active component in antennal and behavioral pheromones in other tephritid species, such as *Anastrepha ludens* and *Anastrepha suspended* (Rocca et al. 1992). More specifically, (E,E)-α-farnesene is a volatile compound released by plants, especially in ripe fruits, and acts as an attractant for insects such as fruit flies, guiding them to food sources or egg-laying sites (Bruce and Pickett 2011). In contrast, some male insects emit alpha-farnesene as signs of sexual attraction or to mark territory, demonstrating the versatility of the compound in different biological contexts (Schwab et al. 2008). However, it is important to highlight that male fruit flies do not produce alpha-farnesene; they obtain the compound from the plant. The (E,E)-α-farnesene found in ripe fruits is used by males of some species of fruit flies as a component in their sexual pheromones (He and Zhang 2012). They collect (E,E)-α-farnesene and other volatile compounds from fruits to incorporate into their own pheromone emissions, which help attract females for mating (Witzgall et al. 2008). This behavior highlights the importance of the interaction between the compound produced by the plant and the mating strategy of insects.

Fruit flies detect alpha-farnesene through highly sensitive OR on their antennae, which can capture very low concentrations of the compound (Bruce and Pickett 2011). This high sensitivity is crucial for flies to locate the source of the odor, playing a vital role in their survival and reproductive success (Cha et al. 2012). In addition, the activation or deactivation of olfactory receptors (OR) on fruit fly antennae is influenced by the concentration of volatile compounds, the age of the insect and its physiological state (Schwab et al.

2008). The effectiveness of (E,E)-α-farnesene as an attractant for fruit flies, for example, depends on its concentration. Very low concentrations may not activate ORs, while very high concentrations may cause repulsion or temporary desensitization. The ideal concentration range to attract fruit flies generally varies from parts per billion (ppb) to parts per million (ppm), balancing attraction and avoiding receptor saturation (Cha et al. 2012).

Considering this information, the manipulation of chemical communication emerges as a promising option to optimize control strategies for Mediterranean fly populations (Keil 1999). Insects' sense of smell plays a crucial role in understanding plant-host interactions, intersexual communication between male and female, and oviposition promoted by females (Gadenne et al. 2016). Therefore, to contain the populations of these insects, control methods that use sexual pheromone compounds in the agricultural sector can be employed (Zarbin et al. 2009), aiming to increase the effectiveness of capture systems for these flies (Tan et al. 2014).

In this scenario, structural bioinformatics and chemoinformatics stand out as crucial tools for the in silico identification of promising ligands capable of interfering with the olfactory system of *C. capitata*, especially in females, which play an essential role in the fruit infestation process (Carey and Carlson 2011; Suckling et al. 2013; Pelosi et al. 2014).

## Compounds that bind to odorant protein

Compounds that interact with OBPs, triggering behavioral responses, are often found in fruit extracts and absorbed by males to compose the pheromone (He and Zhang 2012; Witzgall et al. 2010; Jacobson et al. 1973). These compounds, absorbed by males, play a vital role in intersexual communication, while those released by the fruits themselves facilitate the location of host plants, being essential for insects to meet their nutritional needs and find suitable sites for oviposition (Visser 1986; Knudsen et al. 1993). Male fruit flies, *Ceratitis capitata*, use specialized organs called accessory glands to absorb and process the volatile substances that make up the pheromone (Jang and Light 1996). In addition, males also have specialized structures called peritrema, which help in the emission of pheromones and in the detection of chemical substances in the environment (He and Zhang 2012). Geranyl acetate, (E,E)-α-farnesene, linalool (Baker et al. 1985; Jang et al. 1989), limonene, (E)-β-ocimene, indole (Cossé et al. 1995) and myrcene (Ohinata et al. 1977) are examples of volatile compounds absorbed and released by these structures (Jang and Light 1996).

Female fruit flies, in turn, detect these pheromones using ORs located on their antennae (Jang and Light 1991). Antennae are highly specialized sensory organs, equipped with olfactory neurons capable of capturing and processing chemical signals such as pheromones, which trigger specific behaviors, such as attraction for mating (Witzgall et al. 2010). These responses are in agreement with findings reported for *C. capitata* and other tephritid species, where some key components of the male sex pheromone (geranyl acetate and (E,E)-α-farnesene) and host plant volatiles elicit behavioral changes in females (Fein et al. 1982; Jang et al. 1989; Jang and Light 1996; Light et al. 1988a; Robacker et al. 1986; Robacker and Hart 1987; Pers et al. 1984). Siciliano et al. (2014) also points out that *Ceratitis* females have a greater sensitivity to recognize the compound (E,E)-α-farnesene (Siciliano et al. 2014). Corroborating this information, this compound and other similar ones are also identified in the pheromones of other genera, such as *Anastrepha*, which belongs to the Tephritidae family (known as fruit flies) (Belliard et al. 2022).

In the species *Anastrepha fraterculus*, the compound limonene was identified in the sexual pheromone released by the male, directly influencing the responses of females and altering their way of reacting to homospecific and heterospecific pheromonal mixtures (Cáceres et al. 2009; Břízová et al. 2013). This same species also revealed the presence of α-pinene and (*E,E*)-α-farnesene in the antennae of females (Milet-Pinheiro et al. 2015). A comparative study of the volatile compounds released by *Anastrepha suspensa* and *Anastrepha ludens* identified five new compounds in the pheromonal mixture, including (*E,E*)-α-farnesene and limonene (Rocca et al. 1992). In *Anastrepha striata*, linalool, myrcene, limonene, (*Z*)-β-ocimene, (*E*)-β-ocimene, terpineol and (*Z,E*)-α-farnesene were found (Cruz-López et al. 2015a). Finally, the chemical composition of the pheromone from *Anastrepha obliqua* males indicated that linanol came from the host, being found exclusively in aeration extracts and not in salivary gland extracts (Gonçalves et al. 2013).

Thus, through these studies it is possible to observe that different species of fruit flies present similarities in the composition of the pheromonal mixture with *C. capitata*, and can, consequently, promote these communications and be used as standards in the selection of new attractive molecules or repulsive (Falchetto et al. 2019).

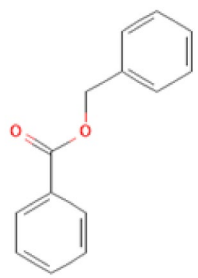
## Natural compounds that interfere with the olfactory sensitivity of insects

Some studies highlight the influence of natural substances on the olfactory sensitivity of insects, in general. Thus, the correlation of other species with *C. capitata* is possible in some extension, because insect OBPs share some common characteristics in terms of size, the constitution of alpha helices, highly conserved disulfide bonds and an internal cavity for binding volatile compounds (Falchetto et al. 2019). This may be a challenge in the search for selectivity, but it

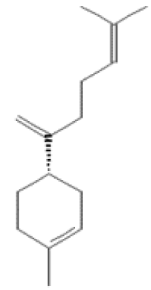
also encourages more detailed research to find small amino acid changes, pockets or specific prominences in the odorant receptor topology that may allow more specific interactions in a specific species. Furthermore, thinking about future application, it is important to study the environmental mapping of the most frequent insects in geographic regions of pest management. Despite these contradictions, regarding the molecular characterization of this review, we have that the benzyl benzoate compound, for example, provided greater attraction for *C. capitata* males compared to trimedlure (reference attractant) (El-Metwally et al. 2019). It is an aromatic ester that has a balsamic, herbal and oily smell (Menenses et al. 2020), present in clove oil. The same compound was also tested in *Drosophila melanogaster* (fruit fly) larvae, indicating an attractive olfactory response (Khurana and Siddiqi 2013). Rocca et al. (1992), carrying out a comparative study of the volatile compounds released by *Anastrepha suspensa* (Caribbean fruit fly) and *Anastrepha ludens* (Mexican fruit fly), identified five new compounds in the pheromonal mixture, including β -bisabolene and (E,E)-α-farnesene, with intense attractive activity. Aluja et al. (2020) also point out that of the 14 components present in the pheromone of *A. ludens* and *A. obliqua* males, β-bisabolene acted in conjunction with the other molecules, modifying the behavior of the larvae of these tephritid polyphagic pests. In a quantitative analysis of pheromone blends in males of *A. suspensa*, β-bisabolene, together with solid suspension, anastrephin and epianastrephin, stood out as one of the main components of the pheromone, playing a significant role as an attractant for females. (Ponce et al. 1993). Similarly, in another study, in the pheromone of *A. suspensa* males, in addition to the presence of α-farnesene, β-bisabolene was also found, promoting intersexual communication (Lima-Medonça et al. 2014). In agreement, essential oils from citrus fruits with β-bisabolene were attractive in stimulating oviposition by *C. capitata* females in the host fruit (Ioannou et al. 2012). (+)-α-curcumene, an aromatic sesquiterpene, was reported to stimulate the antennae of female *Aedes aegypti* together with other sesquiterpenes (β-sesquiphellandrene, zingiberene and β-bisabolene) extracted from ginger essential oil (Zingiber officinale, Zingiberaceae) (Campbell 2009). *Ceratitis capitata* and *A. aegypti* are from the order Diptera, which makes it possible to correlate work on these two species (Luu-Dam et al. 2021). Liu et al. (2022) also highlight the presence of α-curcumene as a volatile compound extracted from a northeastern Chinese plant (*Rhododendron dauricum*), acting on insect OBPs. The germacrene B present in the composition of the oil from the leaves of *Commiphora leptophloeos* (imburana) was recognized as a source of compounds with repellent and larvicidal activities against the dengue mosquito (Silva et al. 2015). Furthermore, in essential oils extracted from tangerine (*Citrus reticulata*) and tea tree (*Melaleuca alternifolia*), germacrene B also has repellent activity against *Drosophila suzukii* (spotted wing fly) (Bedini et al. 2020) (Fig. 3).

β-longipinene showed a repulsive response in antennae of female *Aedes aegypti* when used in a synthetic mixture containing 1-octen-3-ol, (-)-isolongifolene, (+)-longifolene and 3-caryophyllene with 100 ng of each substance (Zhang et al. 2011). α-copaene isolated from clove oil was 5 to 6 times more attractive than trimedlure, the main commercial attractant for *C. capitata* males, confirming the interaction of this substance with the odorant protein (Lull et al. 2023). Vaníčková et al. (2012a) found α-copaene in the mixture of *C. capitata* sexual pheromones promoting an attractive response. The volatiles in ginger root oil, which mainly contain α-copaene, also modified the behavior of several species of fruit flies of the genus *Anastrepha*, named as *Anastrepha fraterculus, A. ludens, A. obliqua* and *Anastrepha serpentina* (Wiedemann) (Dip., Tephritidae) (Ruiz et al. 2021). α-copaene was also one of the main volatile constituents found in guava, along with α-caryophyllene promoting attractive olfactory responses in the fruit fly genus *Bactrocera* (Jaleel et al. 2021). In contrast, this same compound showed no evidence of repellency to *A. aegypti* mosquitoes (Dekker et al. 2011). Regarding α-humulene, Silva et al. (2015) revealed that the presence of this compound caused changes in the behavior of *A. aegypti* and presented high repulsive activity at low concentrations (5 ppm). Jaleel et al. (2019) reported that through olfactometer tests, the mixture of β-caryophyllene and α-humulene was of good attractiveness to females of *Bactrocera correcta* (Asian fruit fly). In *C. capitata*, males when exposed for three days to the aroma of α-humulene performed significantly fewer matings than males that were not exposed, consequently exhibiting a signaling suppressive activity in intersexual communication (Shelly and Nishimoto 2015). In contrast, males of *A. fraterculus* (South American fruit fly) when exposed to a mixture of seven compounds released by guava, including α-humulene, increased their courtship behavior, accentuating the mating process (Bachmann et al. 2015).

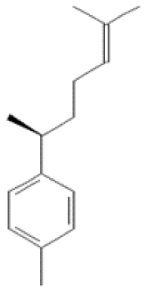
β-chamigrene was found among the volatiles of orange, lemon, bergamot and apple fruits, together with limonene, attracting *C. capitata* females to the host fruit discovery behavior and in the fruit's susceptibility to oviposition infestation (Antonatos et al. 2023). The essential oil of *Melaleuca alternifolia* had α-selinene, α-humulene and α-copaene in its composition and triggered olfactory responses to the emissions of these volatiles in *C. capitata* males (Tabanca et al. 2020). The essential oil of *Magnolia citrata*, composed of α-selinene, α-humulene, β-caryophyllene and other molecules, exhibited moderately strong attraction for males of *C. capitata* (Luu-Dam et al. 2021). The essential oil of *Cupressus funebris* (Chinese weeping cypress) showed repellent activity against adult yellow fever mosquitoes, *A. aegypti*, having in its



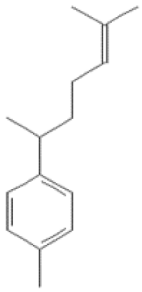
Benzyl benzoate



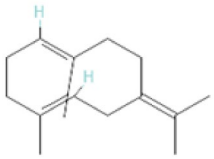
β-bisabolene



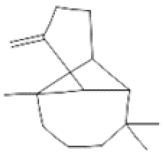
(+)-α-curcumene



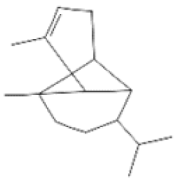
α-curcumene



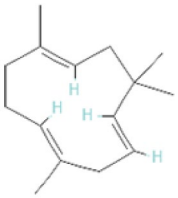
Germacrene B



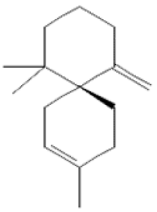
β-longipinene



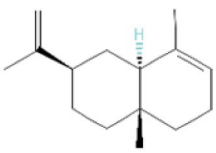
α-copaene



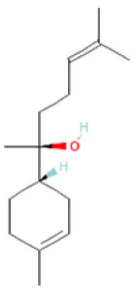
α-humulene



β-chamigrene



α-selinene



(-)-α-bisabolol

**Fig. 3.** 2D attractive and repellent compounds (Source: PubChem)

composition the sesquiterpene β-chamigrene, as well as α-selinene, γ-bisabolene, among others (Carroll et al. 2011). α-selinene also triggered antennal responses in *A. aegypti* females, together with α-humulene, determining them, therefore, as active compounds present in the essential oil of the leaf of *Commiphora leptophloeos* (imburana do sertão) (Silva et al. 2015).

(-)-α-bisabolol is a monocyclic sesquiterpene natural product, also called levomenol, colorless viscous oil with a pleasant aroma, weak floral odor with a tertiary hydroxyl group and a six-membered ring, two trisubstituted unsaturations, has the minimum formula $C_{15}H_{26}O$ and molecular weight of 222.37 g (Nemoto et al. 1993). In nature, it occurs in enantiomeric (+) and (-) forms, with only the (-) enantiomer having biological activities (Megwer and Schornow 2001). Furthermore, regarding the control capacity promoted by this compound, in a research involving six constituents of an essential oil, (-)-α-bisabolol indicated significant repellency to the eastern fruit fly, *Bactrocera dorsalis*, when applied separately in the Y-tube olfactometer (Jaffar and Lu 2022). This species is also a fly from the Tephritidae family like *C. capitata*, possibly pointing to the action of this compound as a repellent against Mediterranean fruit flies. Four terpenes including (-)-α-bisabolol showed affinity with the odorant protein (AaegOBP1) of *A. aegypti*, also demonstrating protective-repellent activity comparable to DEET (N,N-diethyl-3-methylbenzamide) (Portilla-Pulido et al. 2020). (-)-α-bisabolol extracted from the essential oil of German, Roman and Chinese chamomile flowers also promoted repulsive activity for *A. aegypti* with an action similar to DEET (Ali et al. 2023).

DEET is the most used insect repellent in the world and is characterized by blocking the electrophysiological responses of olfactory sensitivity to attractive odors, mainly in *Anopheles gambiae* and *Drosophila melanogaster* (Ditzen et al. 2008). In an affinity study, it was possible to indicate that the interaction of DEET with the OBP takes place in the hydrophobic cavity, the characteristic binding region of insect OBPs (Tsitsanou et al. 2012). Unlike an attractive substance that, when transported by the OBP to the OR, promotes the activation of the biosignaling process, DEET, when transported to the OR, blocks it, preventing the recognition of another molecule, which consequently causes, the removal of the insect (Ditzen et al. 2008). Despite the repellent effect, the main concern with widely used synthetic compounds is the insect's potential to develop resistance or insensitivity (Degenaro et al. 2013; Wagman et al. 2015), as well as concerns related to possible toxicity and carcinogenicity for mammals (Legeay et al. 2016). Thus, in recent years, research into new insect repellents has focused on natural products, as some plant-derived repellents target multiple odor receptors (Thireou et al. 2018). Therefore, (-)-α-bisabolol emerges as a promising repellent compound, with the potential to integrate control formulations, effectively replacing DEET.

Nesterkina et al. (2018) also highlighted the importance of the hydroxyl group in the repellent activity of the compounds, highlighting the lack of repellency of ρ-Cymene, devoid of the OH- group, unlike menthol, which exhibited repellent activity very close to that of DEET. This highlight reinforces the role of (-)-α-bisabolol, which has repellent activity, due to the presence of the OH- group in its composition, contributing to the effectiveness of its repellency. Over time, repulsive activity has been associated with the structural aspects of compounds, mainly in relation to functional groups, as evidenced by older and well-established works. Garson and Winnike (1968), for example, pointed out that compounds containing amides, imides, phenols, alcohols, hydroxy ethers, glycols and hydroxy esters were active repellents, while the original hydrocarbons were weak repellents. Bunker and Hirschfelder (1925) and Roadhouse (1953) corroborate this information, highlighting that the presence of the amide and phenol group are one of the main chemical groups that promote repellency. Christophers (1947) further reported that the repellent activity of alcohol groups, along with aldehydes and phenols, raised the hypothesis that the repulsive activity was related to the positioning of the -OH groups. Given this, it can be said that these compounds that interfere with the olfactory sensitivity of insects, whether in an attractive or repellent way, can boost the identification of compounds, through virtual screening, that bind to the odorant protein of *C. capitata*, acting as excellent potential for the management of these flies.

## Molecular docking and virtual screening

Virtual screening is an in silico method used to examine large databases of compounds, aiming to select molecules with high affinity in target proteins, for subsequent in vitro biochemical evaluation (Ferreira et al. 2011). Through its search and selection mechanisms, virtual screening has established itself as an effective, fast and economically viable technique, allowing the reduction of the number of compounds that require experimental evaluation (Ferreira et al. 2011). There are several approaches to virtual screening, and choosing the most appropriate one depends on the availability of information (Pinto et al. 2022). The strategies of this method are related to molecular database investigation tools, which make use of computational models and algorithms to filter compounds based on desired characteristics (Schneider 2010).

To achieve this, the strategies adopted for screening are based on the structure of bioactive ligands (LBVS—Ligand-Based Virtual Screening) or on the structure of the biological receptor (SBVS—Structure-Based Virtual Screening)

(Guido et al. 2008). In the last process, virtual screening employs molecular docking, a technique for predicting the preferred binding orientation of a molecule to a receptor by calculating binding energies (Morris and Lim-Wilby 2008). This computational approach makes it possible to couple thousands or even millions of compounds to a target protein, identifying potential inhibitors or modulators of signaling pathways (Trott and Olson 2009; Lee et al. 2015; Kurcinski et al. 2019). This is made possible by optimizing docking algorithms, allowing ligands to access the target protein and revealing favorable binding sites and potential adverse interactions (Mikovski et al. 2018).

The results of the docking-based screening are scored based on several criteria. The first consists of the Binding Energy Score, which evaluates the strength of the interaction between the ligand and the target, usually calculating variation in energy of the system when the ligand is bound to the target, providing the changes in enthalpy and entropy (Morris et al. 2009). The second is the Affinity Score, which reflects the affinity and stability of the ligand for the target, which can be associated with the dissociation constant (Kd). A lower score generally indicates a better affinity (Morris et al. 2009). The third is the Fit or Fit Score, which evaluates the spatial geometry of the ligand in the binding pocket of the target, often considering the overlap with a standard geometry. The RMSD (Root Mean Square Deviation) is the common metric for this score, used to measure the distance between the ideal position and the calculated position of the ligand (Goodsell and Olson 2000). The fourth and final criterion is the Specific Interaction Score, which indicates the specific interactions between functional groups of the ligand and the amino acid residues of the target protein, such as hydrogen bonds, ionic interactions and hydrophobic interactions (Jones et al 1997).

The assembly of molecular libraries is also a crucial step in compound screening, involving the creation of a diverse set of molecules to test interactions with a specific target. The assembly of these libraries can be done in several ways. Chemical Compound Libraries consist of the set of chemical molecules that may include small compounds, peptides or other chemical entities, and can be assembled by direct chemical synthesis, combinatorial, or by purchasing ready-made compounds from specialized suppliers (Graaf and Benson 2011). Virtual Compound Libraries can be assembled using molecule generation algorithms and molecular modeling techniques to create a diverse set of structures, thus obtaining a set of molecules generated by computational simulation, as fragments or derivatives of known compounds (Bender et al. 2021). Natural Substance Libraries can be made by direct extraction from natural sources or by chemical synthesis based on known natural structures, forming collections of compounds derived from natural sources, such as plants or microorganisms (Newman and Cragg 2007). In addition to these, it is possible to assemble Peptide or Protein Libraries and DNA or RNA Libraries that respectively collect a set of peptides or proteins, and a set of DNA or RNA sequences, often used to study genetic interactions or gene functions (Krumpe and Mori 2007; Wu et al. 1999).

In molecular docking, two computational steps are established: (i) the molecular docking algorithm, which evaluates the different conformations and degrees of freedom of the ligand according to the properties of the interaction site, generating a list of poses that best complement the cavity, and (ii) the scoring functions, which perform approximate calculations to evaluate the electrostatic complementarity and van der Waals interactions between the ligand and the receptor (Gohlke and Klebe 2002). In this sense, Autodock VINA is the most widely used molecular docking program today, employing the grid box concept to identify the binding site and reduce the analysis time for each molecule (Eberhardt et al. 2021). The grid-based method calculates and stores the energy potentials between ligand atoms at various points in the interaction cavity region of the molecular target (Trott and Olson 2009). This pre-calculated data is stored in libraries by AutoGrid and then AutoDock VINA uses it to speed up interaction calculations (Kitchen et al. 2004). On the other hand, there are now a wide variety of paid and free online programs and platforms available for performing molecular docking and, with this tool, virtual screening. Among the most cited programs, we can highlight the GOLD (Jones et al. 1997), Dock (Gschwend and Kuntz 1996), Molegro (Bitencourt-Ferreira et al. 2019), SwissDock (Grosdidier et al. 2011), DockThor (Guedes et al. 2024), among others.

In pioneering work with the organism *Bactrocela dorsalis*, Jayanthi et al. (2014) proposed a useful virtual screening protocol for this oriental fruit fly, combining molecular docking algorithm with molecular dynamics simulation technique in identifying potential ligands for its OBP modeled via homology. Despite using a relatively very short equilibration time by current standards (700 ps), they achieved an excellent correlation between in silico and in vitro affinity data, showing that this association would be promising, including specific isoforms of OBPs, for other organisms.

Considering the particularities and objectives of virtual screening and molecular docking, both are important tools for: 1- Selecting molecules that act as pesticides on specific targets, seeking selectivity; 2- Elucidate classes of compounds with greater affinity for biological targets for subsequent in vitro/in vivo application; 3- Explain the molecular mechanism of action of compounds with previously determined activity. Examples of these applications in the context of pest control and management, extending to *C. capitata*, can be found in the works of Renthal (2024), Wang et al.

(2024), Liggri et al. (2023), Tiwari and Sowdhamini (2023) e Thireou et al. (2018).

## In silico ADME-Tox parameters

ADMETox (Absortion, Distribution, Metabolism, Excretion and Toxicology) parameters for bioactive compounds are considered nowdays as extremely important, because they help to evaluate the viability and safety of a compound to be exposed to humans or animals before its introduction to the market (Yu and Adedoyin 2003). Knowledge about these parameters can save time and resources, avoiding the development of candidates for human, animal or environmental applications, preventing toxicity problems among others (Bandeira et al. 2023). Furthermore, it is estimated that research into the development of new products based on bioactive molecules entails costs in the order of millions of dollars, reinforcing the need to use methodologies that reduce the number of molecules that need to be evaluated on the bench (Tetko et al. 2006). Therefore, ADME-Tox parameters play a crucial role in the chemical products development process, contributing to the selection of more promising and safe candidates for humans and animals exposed (Yu and Adedoyin 2003). It is a fact that the platforms and software dedicated to evaluating ADMET-Tox properties have human beings as their main target. However, considering the context of molecules applied to insect management, the alerts provided by these theoretical filters can be quite valuable in predicting situations involving humans and animals exposed to environmental products. Still in this sense, the construction of platforms dedicated to the prediction of physicochemical properties aimed specifically at the interaction with insects presents itself as a field that is still unexplored and capable of important contributions. Characteristics such as the external coating of certain family or considerations about the process of distribution through the hemolymph and insect metabolism could be explored in the construction of useful predictive models.

Here are some of the main reasons why these parameters can be important considering the possibility of human exposure: A (Absorption), evaluates the ability of a compound to be absorbed in the human body by analyzing whether it is effective or not; D (Distribution) indicates whether the compound reaches some type of tissue such as the ability to cross biological barriers, such as the blood–brain barrier; M (Metabolism) highlights whether the given compound will undergo transformation when metabolized; E (Excretion), refers to the elimination of the compound by the body; and Tox (Toxicity) assesses whether the compound is safe to apply, analyzing whether it promotes adverse side effects (Geerts and Heyden 2011). Thus, the evaluations of these parameters in silico are defined as the set of computational tests, mathematical experiments and data science approaches for chemical compounds, which compile a set of predictions to provide toxicological activity, making the process more effective and safe screening for in vivo tests (Kavlock et al. 2008) (Table 1).

The ADME-Tox properties (absorption, distribution, metabolism, excretion and toxicity) of the selected compounds are predicted using the online platforms pkCSM (Pires et al. 2015) or SwissADME (Daina et al. 2017), with the purpose to determine whether a given molecule will pose a risk to humans when handled in the laboratory or applied to the fruit after an in vivo test. For this, a simplified canonical system of molecular input lines (SMILES) is used to represent all chemical structures submitted to the platform (Yamari et al. 2023) (Table 2).

## Molecular dynamics simulations

Molecular dynamics (MD) simulation is a computational technique that models the movement of atoms and molecules over time (Barbhuiya and Das 2023). This approach becomes particularly powerful when analyzing ligand-receptor interactions, taking into account both the flexibility of the ligand and the molecular target (Brooijmans and Kuntz 2003). Furthermore, it enables researchers to simulate the dynamic behavior, energy and interactions of individual atoms and molecules (Chen et al. 2018, 2023). This technique is classically based on the application of Newtonian laws, focusing on atomic movement over time, where the trajectory of molecules can be calculated based on variations in the energy and position of the atoms (Verli 2014). The behavior of each atom is analyzed based on the differential form of the equation of Newton's second law (Cunha 2013).

The Root Mean Square Deviation (RMSD) is a metric also frequently used in the area of computational chemistry, especially in molecular docking and molecular dynamics studies (Maruyama et al. 2023). In MD, RMSD is used to monitor how the conformation of a ligand changes over time during a simulation (Brüschweiler 2003). This can be valuable for understanding the flexibility of the ligand and how it adapts and stabilizes in the binding site over time (Verli 2014). The RMSD calculation is performed by the following formula: $RMSD = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(r_i - r_i^0)^2}$, where $r_i$ are the positions of the atoms in the simulated structure, $r_i^0$ are the corresponding positions in the reference structure, and N is the total number of atoms (Kuzmanic and Zagrovic 2010). The RMSD result is plotted as a function of time to evaluate the stability of the simulation (Maiorov and Crippen 1994). The graph may show initial phases of equilibration followed by a stable phase, or it may indicate significant fluctuations (Verli 2014). Small initial spikes in the RMSD can be

**Table 1** The main semiochemical molecules that act in interfering with the behavior of organisms close to *Ceratitis capitata*

| Molecule | Molecular formula | Function | Organisms | Behavior influenced | Synergy with other compounds | References |
|---|---|---|---|---|---|---|
| Benzyl benzoate | C14H12O2 | Attractant | *Ceratitis capitata* | Increased attraction to males | No | Menenses et al. (2020); El-Metwally et al. (2019) |
| | | Attractant | *Drosophila melanogaster* | Attractive olfactory response | No | Khurana and Siddiqi (2013) |
| β-bisabolene | C15H24 | Attractant | *Anastrepha suspensa, A. ludens, A. obliqua* | Attraction and behavior modification in larvae and females | Yes, with α-copaene | Rocca et al. (1992); Aluja et al. (2020); Lima-Medonça et al. (2014); Ponce et al. (1993); Ioannou et al. (2012) |
| (+)-α-curcumene | $C15H_{22}$ | Stimulant | *Aedes aegypti* | Antennal stimulation | No | Campbell (2009) |
| α-curcumene | C15H22 | Attractant | *Ceratitis capitata* | Possible correlation with olfactory response | No | Liu et al. (2022) |
| Germacrene B | $C15H_{24}$ | Repellent, larvicide | *Aedes aegypti, Drosophila suzukii* | Repellent and larvicidal activity | No | Silva et al. (2015); Bedini et al. (2020) |
| β-longipinene | $C15H_{24}$ | Repellent | *Aedes aegypti* | Repulsive response in antennae | No | Zhang et al. (2011) |
| α-copaene | $C15H_{24}$ | Attractant | *Ceratitis capitata* | Superior attraction compared to other attractants | Yes, with β-bisabolene | Lull et al. (2023); Vaníčková et al. (2012a) |
| | | Attractant | *Anastrepha fraterculus, A. ludens, A. obliqua* | Behavior modification and attraction | Yes, with β-bisabolene | Ruiz et al. (2021) |
| α-humulene | $C15H_{24}$ | Repellent/attractant | *Aedes aegypti, Ceratitis capitata, Bactrocera correcta, A. fraterculus* | Repellent activity and modification in mating behavior | Yes, with α-copaene | Silva et al. (2015); Shelly and Nishimoto (2015); Bachmann et al. (2015); Jaleel et al. (2019) |
| β-chamigrene | C15H24 | Attractant/repellent | *Ceratitis capitata, Aedes aegypti* | Attraction to females, repellent activity | No | Antonatos et al. (2023); Carroll et al. (2011) |
| α-selinene | C15H24 | Attractant/repellent | *Ceratitis capitata, Aedes aegypti* | Activation of antennal responses, moderate attraction | No | Silva et al. (2015); Tabança et al. (2020); Luu-Dam et al. (2021) |
| (-)-α-bisabolol | C15H26O | Repellent | *Bactrocera dorsalis, Aedes aegypti* | Significant repellent activity | No | Jaffar and Lu (2022); Portilla-Pulido et al. (2020); Ali et al. (2023) |

**Table 2** Summary of the predicted functions by the platforms for each parameter

| Parameter | PREDICTION FUNCTIONS |
|---|---|
| A (absorption) | Water solubility<br>Caco2 permeability<br>Intestinal absorption (human)<br>Skin Permeability<br>P-glycoprotein substrate<br>P-glycoprotein I inhibitor<br>P-glycoprotein II inhibitor |
| D (Distribution) | VDss (human)<br>Fraction unbound (human)<br>BBB permeability<br>CNS permeability |
| M (Metabolism) | CYP2D6 substrate<br>CYP3A4 substrate<br>CYP1A2 inhibitior<br>CYP2C19 inhibitior<br>CYP2C9 inhibitior<br>CYP2D6 inhibitior<br>CYP3A4 inhibitior |
| E (Excretion) | Total Clearance<br>Renal OCT2 substrate |
| TOX (Toxicity) | AMES toxicity<br>Oral Rat Acute Toxicity (LD50)<br>Max. tolerated dose (human)<br>Hepatotoxicity<br>Skin Sensitisation |

expected during equilibration and if the RMSD stabilizes at a consistent value, the simulation is probably in equilibrium (Maruyama et al. 2023). Large continuous oscillations may indicate problems in the simulation (Shaw 2010).

It can be stated that MD seeks to reproduce, in the computational environment, conditions that are close to the natural environment at the macroscopic level (Gunsteren et al. 2006). Solvation is a crucial aspect to be considered in this type of simulation, since water plays a significant role in many biological reactions, influencing, for example, the hydration necessary for the functioning of some receptor proteins (Guerra et al. 2016). Thus, there is substantial relevance attributed to computer simulation models to reproduce the biological environment more accurately (Berendsen et al. 1984), offering insights into mechanical, thermal and chemical properties, as well as the effects of external factors, such as temperature and pressure (Zhang et al. 2022).

However, it is essential to note that MD simulations have limitations, requiring precise force field parameters, adequate computational resources and appropriate modeling assumptions (Barbhuiya and Das 2023). One of the main limitations lies in the inability to analyze ligands outside of a local minimum energy state (Brooijmans and Kuntz 2003). This considerably restricts the events that DM can analyze, especially when observing the behavior of the ligand in different temperature ranges, making it sensitive and dependent on robust energy minimization analysis algorithms (Brooijmans and Kuntz 2003).

One of the algorithms used to more accurately demonstrate the stability of the formed complexes is the application of the Molecular Mechanics Poisson-Boltzmann surface area method (MM-PBSA) (Xu et al. 2023). MM/PBSA is a method that calculates the binding energy between a protein and a ligand (Genheden and Ryde 2015), evaluating the energy terms of the DM force field and approximating the polar energy terms with the Poisson–Boltzmann (PB) equation ($G = E_{bond} + E_{VdW} + E_{ele} + G_{pol} + G_{np} - T.S$), and non-polar energy terms using the Solvent Accessible Surface Area (SASA) method (Gallo et al. 2022). This last algorithm makes it possible to identify how the surface area of a protein interacts with water molecules (solvent) (Mazola et al. 2015).

## Protein obtention, softwares and platforms in structure based molecular design

In silico methods are computational techniques that can be used to identify potential ligands for OBPs. Some platforms can be used to model or find deposited receptor structures, such as PDB (Protein Data Bank) and UniProt, which provide 3D structures of important target proteins (Berman et al. 2000; Wang et al. 2021). Homology modeling is another widely used technique, based on the premise that proteins with similar structures have similar functions (Hameduh et al. 2020). In this context, known olfactory proteins are used as models to build structures of new proteins of interest, comparing sequences with databases of proteins with known structures (Alfonso-Prieto and Capelli 2023). Tools such as MODELLER (Šali and Blundell 1993) and Swiss-Model (Waterhouse et al. 2018) are often used to predict the three-dimensional structures, facilitating the assessment of their odorant-binding capacity based on structural similarities. Alternatively, the structure can be modeled using AlphaFold 2 (https://alphafold.ebi.ac.uk/), platform that revolutionized the prediction of 3D protein structures, with amino acid sequences obtained from NCBI (Jumper et al. 2021).

Phylogenetic analysis is also a valuable method, comparing protein sequences between different species to identify potential odorant targets, exploring the evolutionary relationship and identifying groups of receptors with conserved functions. Tools such as Clustal Omega (Sievers et al. 2011) and MEGA (Tamura et al. 2021) are used to build phylogenetic trees and perform comparative analyses. Furthermore, machine learning and neural network methods have been gaining prominence in bioinformatics to predict interactions between proteins and ligands, using large data sets to efficiently identify new interactions (Dhakal et al. 2022;

Lemkul 2018). After training the models, they can identify new odorant-binding proteins based on recognized patterns, accelerating the discovery of interactions without the need for time-consuming laboratory experiments (Guo and Yamaguchi 2022).

Accuracy in protein structural determination is extremely important, since the 3D conformation and binding sites of the target molecules are necessary for the correct anchoring of potential ligands (Rodrigues et al. 2012). Techniques such as X-ray crystallography, Nuclear Magnetic Resonance (NMR), and cryo-electron microscopy (Cryo-EM) are responsible for assembling these structures with high resolution and reliability, allowing their use for screening and docking processes (Berman et al. 2000). X-Ray crystallography is the most widely used technique for determining protein structures (Ambrosio and Franchini 2017; Shi 2014). Analysis of the diffraction pattern generated by the passage of X-rays through the crystal allows the reconstruction of the atomic structure with high precision, and good resolutions are considered as smaller than 2 Å (Feiten 2022). In addition, NMR (Nuclear Magnetic Resonance) is also used to provide structural information on proteins in solution, but with a lower resolution than X-ray crystallography (Figueiredo and Marsaioli 2007; Cavanagh et al. 2007). The geometric information used in NMR to solve the three-dimensional (3D) structures of proteins resides in short interproton distance data (less than 5 Å) (Oschkinat et al. 1988). Cryo-EM (Cryo-Electron Microscopy), in turn, is a powerful method for resolving the three-dimensional structures of biological macromolecules, mainly due to technological advances that have made it possible to achieve lower resolutions (Yip et al. 2020). One of the main advantages of this technique is that it allows the study of larger protein complexes (Sawh-Gopal et al. 2023).

In contrast, in silico methods based on structure predictions, generated by homology modeling based on amino acid sequences (SwissModel, for example), have some limitations. These models generally present uncertainties in some fundamental regions, such as binding sites or the unreliability of amino acid rotation and arrangement, which can consequently result in incorrect interactions (Jumper et al. 2021). This can end up compromising the virtual screening process, since these limitations can influence the accuracy of molecular docking simulations, leading to the identification of false positive or non-biologically active compounds (Cheng et al. 2007). Therefore, the use of three-dimensional proteins already available in databases and obtained by the techniques mentioned above becomes more reliable to offer a solid basis for the identification of bioactive compounds (Dror et al. 2012; Jumper et al. 2021).

After obtaining the three-dimensional structure, the prediction of binding sites can be performed.There are algorithms capable of identifying probable odor binding sites, or the technique for experimental determination of the macromolecule already considers a standard complexed ligand. For example, tools such as SiteHound (Hernandez et al. 2009), GRaSP (Santana et al. 2020) and FPocket (Guilloux et al. 2009) analyze the three-dimensional structure of proteins to identify cavities that can serve as binding sites for molecular docking studies (Morris et al. 2009).

Once the protein structure has been obtained, using a completely in silico method or with the aid of experimental techniques, its subsequent processing can be carried out. Programs such as Chimera software (Petersen et al. 2004) can be used, for example, to remove water molecules from experimental techniques, if necessary. The virtual platform ABPS (Adaptive Poisson–Boltzmann Solver), in turn, can perform additional electrostatic analysis, adjusting the pH media and aminoacid protonation states for a more realistic simulation (Lee et al. 2002; Brito et al. 2016a; Jurrus et al. 2017).

A step towards validating docking strategies based on the structure of macromolecular targets is the obtention of the ROC (Receiver Operating Characteristic Curve) curve. For example, the Drug Design online platform (http://stats.drugdesign.fr/) is a free tool that can be used in the molecular modeling field. The ROC curve is a validation process, that indicate if a macromolecule and the docking algorithm used for screening has the capacity to differentiate molecules that promote a real biological response from compounds that bind and do not promote any type of response (Emperieur-Mot et al. 2016; Davis and Goadrich 2006). Therefore, true positive ligands, molecules that bind at the binding site and promote behavioral responses, must be initially identified through a literature review (Kim et al. 2023). These molecules may already come with their structure optimized to a minimal energy or this geometry can be obtained in programs such as ArgusLab or PyRx (Dallakyan and Olson 2014; Thompson 2004). Based on these defined true ligands, a library of, for example, 50 decoys (false positives) for each true ligand must be assembled using, for example, the DUD-E platform and after fitting all these false positives, 10 decoys corresponding to each real ligand, randomly selected, will be used to build the ROC curve (Mysinger et al. 2012). The AUC (Area Under the Curve) value closest to 1, obtained after building the curve, indicates that the fitting model has an excellent ability to differentiate true positive ligands from false positives (Emperieur-Mot et al. 2016). The molecular docking parameters for the aforementioned step and for the rest of the virtual screening can be defined in docking programs interface (Morris et al. 2009) and the docking itself can be performed. Softwares and platforms as AutoDock, Vina (Eberhardt et al. 2021; Trott and Olson 2009), SwissDock (Grosdidier et al. 2011) and DockThor (Guedes et al. 2024), are examples widely used.

Considering specifically the molecular docking in the virtual screening process, online molecular databases make this process possible. Some examples of databases also considering the specific interaction with odorant binding proteins, are: NuBBE (Nucleus of Bioassays Biosynthesis and Ecophysiology of Natural Products), which was created with the aim of bioprospecting new natural molecules with antifungal, antitumor, antioxidant, anticholinesterase, anti-inflammatory and antiparasitic potential (Pilon et al. 2017). The ZINC database, which is a free database with more than 230 million compounds in 3D format, ready for docking (Irwin and Shoichet 2005). LOTTUS, which is a database for storage, research and analysis of Natural Products (NPs), currently contains more than 200 thousand molecules extracted from plants (Rutz et al. 2022). Essential Oil (EssOilDB) and Essential Oil University (EOUDB), which are databases of molecules isolated from essential oils (Kumari et al. 2014a, b; Pappas 2024), and Pherobase, a platform composed of several databases that provide comprehensive information on more than 6500 pheromones and semiochemical compounds (El-Sayed 2024). In addition, one of the best known and most used is PubChem, operated and maintained by the National Center for Biotechnology Information (Kim et al. 2016).

Within the specificity of communication by semiochemicals, after virtual screening, the molecules can be selected as possible candidates based on criteria such as lowest binding energy and vapor pressure, which indicate the compound as volatile, an important character to interact with OBP (Mourão 2021; Gomes et al. 2022). The calculation of enthalpy of vaporization, boiling point and vapor pressure values of the most promising molecules found in each database can be performed (Pence and Williams 2010; Mucha et al. 2023). The visualization of the interactions for the most promising compounds from screening, complexed with target, can be made by softwares as BIOVIA Discovery Studio, PyMol and LigPlot+, that provide 2D diagrams of the interactions between the atoms of the ligands with amino acid residues of the protein, as well as can demonstrate this fit in a three-dimensional format (Schrödinger and DeLano 2020; BIOVIA 2015; Wallace et al. 1996).

Considering the Molecular Dynamics procedures, some of the main software used are: GROMACS 5.1.2 (Hess et al. 2008; Abraham et al. 2015), AMBER (Pearlman et al. 1995), CHARMM (Brooks et al. 2009), and GPUGRID (Rodríguez-Espigares et al. 2020). Below we will describe a minimal step-by-step process that can later be detailed and explored for a basic molecular dynamics routine, as per the guidelines in our laboratory.

The topological parameters for ligands, necessary for running molecular dynamics, can be acquired through online platforms, such as ATB (Automated Topology Builder) (Stroet et al. 2018). ATB is a web-accessible server that provides topologies and parameters for a wide variety of molecules, ideal for application in molecular simulations, computational design of compounds, and refinement of structures obtained by X-ray diffraction (Malde et al. 2011). Another procedure necessary in the dynamic simulation, often neglected by docking, is the solvation. The complexes are solvated with water molecules in a box (cubic, monoclinic, orthorombic, etc.), considering periodic boundary conditions to treat the surface problem (Berendsen et al. 1984). This method allows the simulation of a more realistic biological aqueous environment and closer to the real interaction situation through the influence of water molecules in the system (Jorgensen et al. 1983; Namba et al. 2008).

Also within the simulation, the Particle Mesh Ewald algorithm is used as another parameter, in this case, to treat long-range electrostatic interactions (Darden et al. 1993). The method requires charge neutrality of the molecular system to accurately calculate the Coulomb interaction, which consists of the electrostatic interaction between electrically communicated particles (Kolafa and Perram 1992). The bond lengths can be maintained in equilibrium using the P-LINCS algorithm (Hess et al. 2008). This method is called parallel linear constraint solver (P-LINCS), which allows the restriction of all bonds in macromolecules, protecting the energy conservation properties and promoting improvements in the restriction of decoupled angle constraints (Hess 2007). It is worth noting that this entire system must be carried out by controlling energy minimization, through the application of other joint algorithms such as NVT (Constant temperature, constant volume) and NPT (Constant temperature, constant pressure), in conjunction with the modified Berend-sen thermostat and a Parrinello–Rahman barostat, to control pressure and temperature during the simulation (Parrinello and Rahman 1981). In detail, Berend-sen consists of an algorithm to resize particle velocities in molecular dynamics to control the simulation temperature (Berendsen et al. 1984). While the Parrinello–Rahman barostat considers that the inertia tensor of the simulation cell is spherical and constant in time, considering the irrotational fluctuation movements of the cell (Podio-Guidugli 2010).

Finally, the average value of the binding energy for all complexes can be estimated calculating the free energies of the monomers and the ligand–protein complex in each stage submitted to the simulation (Kollman et al. 2000). For example, the MM/PBSA method can be used through the 'g_mmpbsa' script (Kumari et al. 2014a) (Fig. 4).

## In vivo, in vitro, in silico perspectives

Techniques for testing repellent or attractive compounds in fruit flies, such as *Ceratitis capitata*, include laboratory (in vitro) and field (in vivo) experiments. In the laboratory, flies


**Fig. 4** Diagram of the main stages of OBP identification, Docking, Virtual Screening, and Molecular Dynamics simulation using computational methods

are exposed to different concentrations of the compounds in controlled boxes, called choice boxes or wind tunnels, in order to observe their behavior in response to the compounds (Scolari et al. 2021). Confirmation of whether or not attraction occurred, or whether the compound was repellent or not, is assessed by the amount of time and frequency of the flies' visits to the sources of the molecules (Tabanca et al. 2019). In field experiments, the compounds are applied in traps or devices, and effectiveness is measured by the capture of flies, as well as by proven changes in the population in areas that were treated versus those that were not (Manoukis et al. 2015). Therefore, it can be said that these methods make it possible to determine the attractive or repellent properties of compounds in pest management.

There are some limitations associated with the field use of the compounds as discussed in this review, one of which is the short period of protection provided by the molecule, especially when its volatility is high and the application is directly on the fruit (Thireou et al. 2018). To overcome this issue, it is important to develop slow release formulations (Ghayempour and Montazer 2016), add fixatives to extend the protection time (Tawatsin et al. 2001) and create devices for continuous spatial release (Dame et al. 2014), which represent potential modifications to extend the effectiveness of these molecules. A strategy proposed by Drapeau et al. (2009) to increase repellent activity over time involves the use of microemulsions with surfactants associated with highly volatile compounds against *A. aegypti*.

It is important to highlight that, depending on the type of compound or activity provided, synergism between molecules is a crucial factor to be considered in the management of *C. capitata.* Mixtures made with up to six compounds imitate the actions of pheromones, which are also made up of a set of molecules (Milet-Pinheiro et al. 2015). This alternative is even more effective when volatiles are combined with known pheromone constituents, as the synergism between these semiochemicals has been shown to produce more efficient mixtures in controlling insect pests (Reddy and Guerrero 2004a). The synergism of mixtures, unlike the individual application of compounds, promotes a higher level of perception, achieved only by the joint action of these volatiles, forming what researchers call a "complete bouquet" that is detected by the insect, inducing the desired behavior when a mixture is applied (Cruz-López et al. 2015a).

Furthermore, each mixture is interpreted as a new signal, so the addition or removal of a component from the formulation can result in a new mixture, triggering a completely different behavioral response from the previous one (Beyaert et al. 2010). Therefore, it is clear that natural compounds are not ephemeral, and the chemistry behind the joint formulation of these molecules is crucial to prolong the effectiveness of control and ensure its total effectiveness (Carroll et al. 2011). In some cases, as mentioned in the studies above, it is also possible to test the use of the compound in isolation, which can vary significantly depending on the type of assay used for these analyzes (Jaffar and Lu 2022; Ali et al. 2023).

The insect's great capacity for chemical recognition makes the in silico exploration of molecular criteria for ligand-target affinity a challenge and, at the same time, a fruitful way to identify interaction patterns and propose new promising scaffolds. Furthermore, chemical characteristics intrinsic to each compound as well as blends of molecules with known attractive or repellent properties can be studied through artificial intelligence and pattern recognition algorithms, generating models with orthogonal variables that can be useful in the development of products for pest management.

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