Chapter 18
Molecular Modeling Approaches to Investigate Essential Oils (Volatile Compounds) Interacting with Molecular Targets

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18.1 Introduction to Molecular Modeling

The term molecular modeling comprises two words, "molecular' and 'modeling'. The term 'molecular' itself denotes the fact that molecules are involved, wherein, the second term 'modeling' indicates the process of representing various molecular structures numerically and correlating or expressing them so as to correlate with their biological activity or to model or mimic the behaviour of molecules (Verma et al. 2010). This has been done with the help of various quantum and classical physics equations (Vanommeslaeghe et al. 2014).

Since last decade, a new drug designing approach called CADD (Computer-aided drug design) has emerged as crucial technique for the drug discovery processes including identifying potential hits and development of a potential lead (Abdolmaleki et al. 2017) . Some of key examples are dorzolamide (carbonic anhydrase inhibitor); captopril (the angiotensin-converting enzyme); ritonavir, and indinavir (anti- human immunodeficiency virus (HIV), etc. It is proven that CADD approach utilizes more target-based searches as compared with traditional approach of finding hits (Pinto et al. 2019). Thus, this technique is not only

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capable of explaining various molecular basis involved for pharmacological activities but also useful to predict plausible bioactivities of various synthesized derivatives. (Vucicevic et al. 2019).

It is also important to note that molecular modeling techniques look at biological processes at the molecular level while trying to understand the root cause of underlying disease conditions (Sun and Scott 2010).

Usually, this technique has been classified into two categories as (1) direct drug designing (the fact that 3Dimensional structure of the receptor is known) and (2) indirect drug designing (where, 3D structure of the receptor is not known and based on active and in-active ligand sets, a hypothetical receptor site would be assumed) (Santos et al. 2020). It is well evident that such techniques have a common feature depicting the atomistic level description of whole system (Leelananda and Lindert 2016). This involves two fundamental approaches (1) a molecular mechanics approach and (2) a quantum chemistry approach. Molecular modeling techniques have wide range of applications such as their use in drug discovery, computational biology, materials science, and in drug designing. The pharmaceutical field has been largely benefited from this technique. Considering the recent pandemic of COVID-19, such techniques would play important role in identifying possible hits against such virus within short span of time (Wang et al. 2017; Prajapat et al. 2020; Gurung et al. 2021).

18.2 Molecular Modeling Methods

18.2.1 Molecular Descriptors

Molecular descriptors are usually physicochemical properties. Such properties would contribute towards biological activity of molecule (Redžepović and Furtula 2021). This was also defined by Todeschini and Consonni as: "The molecular descriptor is the final result of a logic and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into a useful number or the result of some standardized experiment."(Alves et al. 2020; Pinzi et al. 2021) Although many physicochemical properties have been studied by medicinal chemists, only three of them are highly important and those are (1) hydrophobic (e.g., partition coefficient (P)), (2) steric and (3) electronic properties (e.g., Hammett substitution constant) or descriptors (Grisoni et al. 2018; Costa et al. 2020).

18.2.2 SAR and QSAR

In general, biological properties of compounds are dependent on their chemical structure. Furthermore, it is believed that structurally similar molecules would show similar properties (Huang et al. 2021b). Thus, the understanding of such relationships has given rise to a concept called structure–activity relationship (SAR). The structure activity relationships (SAR) are basically a qualitative expression. However, same relationship when established in a mathematical form by utilizing a set of molecular properties or descriptors along with their corresponding bioactivities would give rise to **Q**uantitative **S**tructure–**A**ctivity **R**elationship models (QSAR models) (Idakwo et al. 2019; Almeida et al. 2021). QSAR models are regression based or classification-based models. QSAR regression models relate two variables; (X) 'prediction variable' (physico-chemical properties or theoretical molecular descriptors) to the potency of the response variable (Y). Statistically robust and validated QSAR models can be also be used for predicting biological activity of newer chemical structures (Halder et al. 2018).

Quantitative structure–activity relationship models (QSAR models) can be expressed in the form of a mathematical model:

Biological Activity = *f* (physiochemical properties and/or structural properties) + error

In order to quantify the activity of a set of molecules, one need to usually have Half maximal inhibitory concentration (IC_{50}) or inhibition constant (Ki) measures. QSAR models, unlike various pharmacophoric models can be useful to see how particular features to drug molecule can have positive or negative effects upon introductions (Zhong et al. 2018). The selection of a proper set of molecular descriptors governs successful QSAR model development. Furthermore, its ability to predict biological activity has also been taken into consideration while deciding best QSAR model among various developed QSAR models. Various statistical measures would be applied to decide best QSAR model (Gupta et al. 2018). For the development of a good predictive QSAR model, one need to have enough biological activity data (training data), otherwise QSARs cannot perform well. MLR (multivariable linear regression) and Machine learning approaches (neural networks (NN) and support vector machine (SVM)) methods can be also used for building successful QSAR models. MLR methods can only be used when there is linear relationship between descriptors and activity (Achary 2020; Hadrup et al. 2021). Principal component analysis (PCA) technique would simplify the complexity of selecting molecular descriptors and building QSAR models by removing descriptors that are not independent. Various statistical validations were reported by various researchers (Sharma and Bhatia 2020). Although, good QSAR models have better predictivities still they should be used cautiously and applied only to the particular set of compounds with varied structural features on similar scaffold (Fukuchi et al. 2019).

18.2.3 Molecular Docking

The study of how two molecular structures would fit into each other, usually drug molecule and receptor or enzyme or proteins is called as 'molecular docking'. In a simpler way, it is a technique used to see or predict binding interactions of small molecules with target forming a complex that may indicate inhibition or enhancement of biological activity (Saikia and Bordoloi 2018; Pinzi and Rastelli 2019). Such behaviour of ligands (small molecules) can be established with molecular docking simulations by predicting affinity between the small molecules and proteins (Ramos et al. 2020). Based on such behaviours, docking can be classified into three types viz., (1) protein-ligand docking; (2) protein–nucleic acid docking; and (3) protein–protein docking (Torres et al. 2019; Mohammad et al. 2021). The protein-ligand docking is comparatively simple than protein-protein docking. As proteins are flexible in nature, their conformational space is so wide and thus making protein-protein docking more complex. Docking simulations are based on varieties of search algorithms like e.g., genetic algorithms (GAs), distance geometry methods, MC methods, fragment-based methods, Tabu searches, etc. (Li et al. 2019; Castro et al. 2021). Docking methodology typically includes three main steps as depicted below:

1. Retrieving X-ray co-crystallized structure from the protein data bank (PDB), and identifying active site. (Protein Preparation)
2. Ligand Preparation (Drawing of chemical structures and converting into 3D form, generating least energy conformers, etc.)
3. Docking of ligand into active site via Grid generation or site mapping.

Several docking engines have been reported over last decades which include *Glide, GOLD, AutoDock, iGEMDOCK, DOCK,* etc. Identifying correct binding site, re-docking validation and setting up of input files for docking are crucial steps in the molecular docking to get suitable acceptable results (Pagadala et al. 2017; Liu et al. 2018b).

18.2.4 Molecular Dynamics Simulations

Molecular dynamics simulation (MDs) is extensively used molecular modeling tool for understanding protein motions and conformational space (Van Der Spoel et al. 2005; Neves Cruz et al. 2020). There are many famous and widely used MD simulation software packages available such as GROMACS, AMBER, NAMD, Desmond, etc. One must note that for it has typical timescale ranges from nanoseconds to microseconds (Salomon-Ferrer et al. 2013; Lima et al. 2020). Basically, MD simulation is computer-based method to analyse physical movements of atoms. MD simulation typically finds its application in material science, chemical science, and in biophysics (Moradi et al. 2019). Apart from several MD simulation success

stories, the application of MD simulation is still limited due to two main challenges: (1) the force field used and (2) high computational demand. For example, if someone wants to run a 1 microsecond simulation for a smaller system of 25,000 atoms using 24 processors, it will still take several months to complete the same (Liu et al. 2018a). Moreover, force fields are also approximations of the quantum-mechanical reality. The MD simulation is poorly suitable for systems, where quantum effects are important (Venable et al. 2019).

18.2.5 Binding Free Energy Calculations

In order to estimate binding affinity of the binding affinity of target–ligand complexes, binding free energy calculations are used. Binding affinity calculations can be used to understand the effects of target mutations. Moreover, the drug potency can be correlated directly with binding affinities (Gohlke and Case 2004; Cournia et al. 2017; Leão et al. 2020; Neto et al. 2020).

$$\Delta \mathbf{G}_{\mathbf{bind}} = \Delta \mathbf{G}_{\mathbf{complex}} - \left(\Delta \mathbf{G}_{\mathbf{protein}} + \Delta \mathbf{G}_{\mathbf{ligand}} \right)$$

Where,

$\Delta\ G_{bind}$ = the free energy of binding,
$\Delta\ G_{complex}$ = the free energy of the protein–ligand complex,
$\Delta\ G_{protein}$ and $\Delta\ G_{ligand}$ = the free energies of the protein and ligand, respectively.

Rigorous approaches are considered as most accuratHe approaches to calculate binding free energies. The FEP (free energy perturbation) methods and thermodynamic integration (TI) methods are the two important rigorous binding free energy approaches. The FEP methods were introduced by Zwanzig in the 1950s. Such method uses molecular dynamics and Monte Carlo simulations. Another method called BEDAM (binding energy distribution analysis method) is also used to calculate binding free energy calculations. It is well understood that the free energy is overall sum of all local energy minima (Wang et al. 2019; Kuhn et al. 2020).

18.2.6 In-silico ADMEtox Properties

After obtaining hit molecules, lead optimization would be carried out. During the lead optimization, various parameters should be taken into consideration like drug safety, pharmacokinetic properties and ADME profiles (absorption, distribution, metabolism, and excretion/elimination) (Bueno 2020; Araújo et al. 2020). Thus, carrying out ADME analysis is a crucial step. It is important to note that affinity changes with atom modifications. Considering drug absorption, permeability and

solubility are two most important factors for the enhancement of drug potency. Henceforth, in-silico ADME analysis is important for predicting solubility and membrane permeability (Farouk and Shamma 2019; dos Santos et al. 2020). The experimental measurement of solubility is quite tedious, while in-silico solubility calculations are faster. One of published review on computational approaches explains various approaches to predict drug solubility. Human intestinal absorption is important while considering bioavailability of drug. Thus, the Lipinski's 'Rule of 5' (there should not be more than 5 H-bond donors, Log P is over 5, more than 10 H-bond acceptors, and the molecular weight is over 500) would be taken into consideration (Li 2001; Alqahtani 2017). The calculation of the Lipinski's 'Rule of 5' via computational methods would help medicinal chemists to design drug molecule with high bioavailability. QikProp, admetSAR, FAF-Drugs2, etc. are some of widely used ADMET calculation programs. For generating ADME models and calculations, 'VolSurf' package can be utilized. Qikprop, a program by Schrodinger is able to calculate large number of physically significant physicochemical properties, toxicity indicating descriptors for small molecules (Huang et al. 2021a). Even though many experimental verifications are required to assess the pharmacokinetic properties and toxicity of molecules, in-silico ADMET analysis offers several benefits by reducing the actual costs. The assessment of ADME properties is a key step in drug screening. However, one must take into consideration of several limitations of computational methodologies and thus, would use such techniques with caution (Stouch et al. 2003; Durán-Iturbide et al. 2020).

18.3 Investigation of the Mechanism of Action of Volatile Compounds

18.3.1 Background

Medicinal plants have been used to treat human diseases since antiquity as the world's greatest biochemical and pharmacological living reservoirs. Natural products originating from plants are an important option in the quest for therapeutic agents because they contain a diverse range of bioactive chemical components (Fowler 2006; de Carvalho et al. 2019). Phytochemicals have biological pre-validation concerning drug-like properties: their basic scaffolds can be seen as natural structures in drug discovery because they have interacted with diverse enzymes and proteins during their biosynthesis (Bezerra et al. 2020a; Barbosa et al. 2021). They thereby fall into the biologically relevant chemical region, which is predetermined for interaction with drug targets. Computational chemistry, in conjunction with bioinformatics, has aided in the development of new drugs with various biological activities (Kellenberger et al. 2011; Maier 2015).

Natural products are, unfortunately, disadvantaged since their isolation is difficult and time-consuming, and because of their high structural complexity and relatively large molecular weight their total synthesis is not as favorable for large-scale manufacture (de Oliveira et al. 2020). In addition, these traits can transmit poor absorption, distribution, metabolism, discharge, and toxicity profiles (ADMET) (Hazzaa et al. 2020). Molecular docking is a computer-based technology that predicts the positioning (orientation and configuration) of the ligand (drug or molecule of therapeutic interest) at a target site of interaction and helps comprehend the biological activity of volatile compounds. Thus, for therapeutic compounds, molecular docking serves as a predictive model that can help with *in vivo* pharmacological activity evaluations (Meng et al. 2011; Bezerra et al. 2020b). Plants that produce volatile compounds are classified into more than 17,500 species of plants from many angiosperm families, e.g., *Rutaceae*, *Alliaceae*, *Lamiaceae*, *Apiaceae*, *Poaceae*, *Asteraceae*, and *Myrtaceae* (de Paulo et al. 2020). They are well-known for their ability to produce commercial and therapeutic volatile compounds. Volatile compounds are complex chemicals with a strong odor that are produced as secondary metabolites by aromatic plants (Michel et al. 2020). Methyl-d-erythritol-4-phosphate (MEP), mevalonic acid, and malonic acid pathways are responsible for the synthesis of volatile oils in the cytoplasm and plastids of plant cells. They are found as liquid droplets in the roots, stems, fruits, flowers, bark and leaves of the plants, and are generated and preserved in secretory cavities, glands, and resin conduits which are some of the complex secretory structures (Arsenijevic et al. 2021). Volatile oils are exceedingly complex combinations of predominantly terpenoids phenylpropanoids, and terpenes, while comprising two or three major components at a level of 20–70% (Ferreira et al. 2020). The other components are aromatic and aliphatic constituents, all characterized by low molecular weight and are present in trace amounts. They may also comprise several other compounds such as sulfur derivatives fatty, oxides, and fatty acids. These primary components, in general, determine the biological features of volatile oils. Terpenes are divided into two categories based on their structural and functional features (Aremu and Van Staden 2013). They are the most common molecules, accounting for 90% of volatile oils and allowing for a wide range of configurations. They are made up of isoprene, which is a compound made up of multiple 5-carbon-base (C5) units. Monoterpenes ($C_{10}H_{16}$) and sesquiterpenes ($C_{15}H_{24}$) are the most common terpenes, but diterpenes ($C_{20}H_{32}$), triterpenes ($C_{30}H_{40}$), and other longer chains occur as well (Maltarollo et al. 2015). Examples of terpene compounds include limonene, pinene, p-cymene, sabinene, and terpinene. The aromatic compounds are found in lesser proportions than the terpenes. Figure 18.1 represents the chemical structures of few volatile components. The design of target metabolites, as well as the mechanism of action of pharmacologically active compounds, can be determined through molecular docking studies (Ma et al. 2011b).

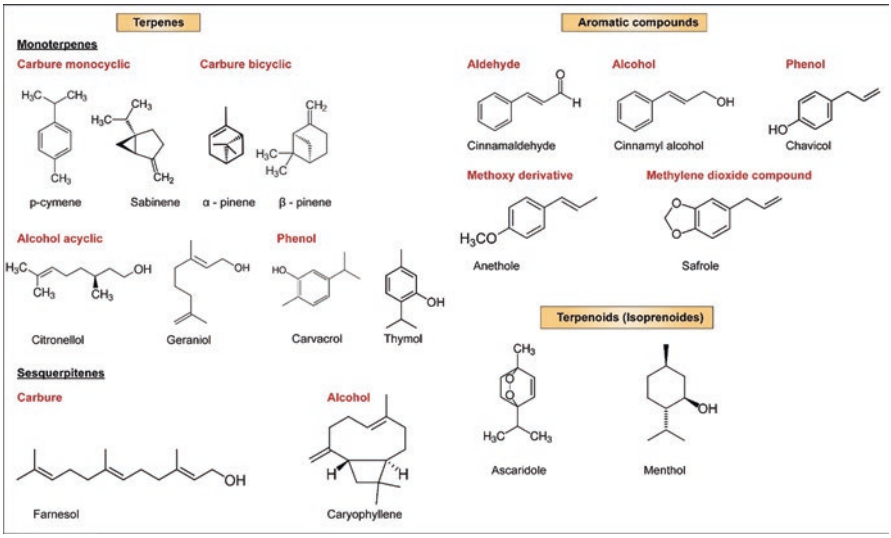

Fig. 18.1 The chemical structures of few volatile compounds

18.3.2 Molecular Modeling of Volatile Compounds with Antimicrobial Activity

Volatile compounds are secondary metabolites that are vital for plant defence because they often possess antibacterial capabilities (De Oliveira et al. 2019; Do Nascimento et al. 2020). De la Croix used volatile oil vapours to test the bactericidal activities of secondary metabolites for the first time in 1881. Since then, volatile oils and their components have been found to exhibit antibacterial effects across a wide range of bacteria. Volatile oils contain complex combinations of up to 45 distinct ingredients, making it difficult to identify the most active antibacterial molecules. The antibacterial effects of most volatile compounds are due to the disruption of bacterial membranes (Ooms 2012). Damage to membrane proteins (such as enzymes), motive proton force depletion, cell content leakage (leakage of cellular ions, Na^+, H^+, and K^+), and cytoplasm coagulation all seem to be common side effects. After treatment with volatile oils, disruption of plasma membrane integrity leads to efflux of DNA, RNA, and proteins, which has been identified as a key antimicrobial mode of action (Diao et al. 2014). Reduced membrane potentials, disruption of proton pumps, and ATP depletion are all linked to volatile compounds' antimicrobial properties as well (Carson et al. 2002). Nonetheless, inhibition of efflux pumps, which are responsible for antibiotic resistance, has been considered as a specific target for volatile compounds (Costa et al. 2019). This change in cell arrangement could trigger a cascade effect, affecting other cell organelles as well. These effects are almost certainly the outcome of the volatile compound's initial mode of bacterial membrane instability. Because of the effective hydroxyl group in

chemical structures of volatile compounds, phenolic content in them exhibits greater specificity for the inhibition of microbial growth that contributes in disruption of plasma membrane structure and hence disorganization of membrane permeability, particularly, by altering the activity of the enzymes involved in Krebs's cycle. However, the terpenoids in volatile oils have a significant impact on plasma membrane fatty acids, resulting in changes in membrane dynamicity, permeability, and cytoplasmic constituent leakage (Bouyahya et al. 2017; Antunes et al. 2021). The lipophilic characteristic of volatile oils is closely linked to their antibacterial activity. The major target of volatile oils and bioactive components is the cell wall and plasma membrane, which leads to interactions with cellular polysaccharides, fatty acids, and phospholipids (Burt 2004). Changes in antibacterial action between gram-positive bacteria and gram-negative are explained by differences in cell wall construction, with gram-positive strains being far more sensitive to volatile compounds. In various bacterial species, volatile compounds suppress cell-to-cell transmission and biofilm development (Calo et al. 2015). Moreover, an efficient breakdown in the sensory transmission is triggered by the impact of volatile compounds on biofilm formation inhibitions in bacterial species. The mechanism of quorum sensing modulation via volatile compounds involves complicated interactions of the compounds with bacterial cell wall receptors, which lowers signal molecule reception and impairs cell-to-cell signal transmission (Camele et al. 2019). The antibacterial activity of volatile oils is mainly attributed to the low proportion of terpenoids and phenolic compounds present in them, thereby exhibiting antibacterial activity in their pure form. The primary components of volatile oils from plants in the *Lamiaceae* family, carvacrol and thymol, have the most well-researched antibacterial action. 1,8-cineole, α-pinene, citral, perillaldehyde, eugenol, terpinen-4-ol, and geraniol are some of the other constituents with antibacterial activity (Singh et al. 2009). The anti-bacterial mechanism of action of volatile compounds is shown in Fig. 18.2.

Several volatile oils are currently being investigated as a potential treatment for viral infections. Clove and oregano volatile oils have potent antiviral properties against a variety of non-enveloped RNA and DNA viruses, including poliovirus, coxsackievirus B1, and adenovirus type 3 (Allahverdiyev et al. 2004) . Antiviral activity of some sesquiterpenes, triterpenes, and phenylpropanes has been confirmed against various herpesviruses and rhinoviruses (Hayashi et al. 1996). Volatile oils are thought to mask viral components or influence the viral envelope that is required for adsorption or entrance into host cells, according to most studies (Niedermeyer et al. 2005). They inhibit the virus replication by hindering cellular DNA polymerase and alter the phenylpropanoid pathways. Monoterpenes, in particular, increase the fluidity and permeability of the cytoplasmic membrane and disrupt the order of membrane-embedded proteins. Virion envelopes are found to be more sensitive to volatile oils than host-cell membranes (Benencia and Courrèges 1999). Because volatile oils are lipophilic, their antiviral activity is thought to disrupt or interfere with viral membrane proteins involved in host cell attachment. The schematic representation of the anti-viral mechanism of volatile compounds is shown in Fig. 18.3 (Schuhmacher et al. 2003).

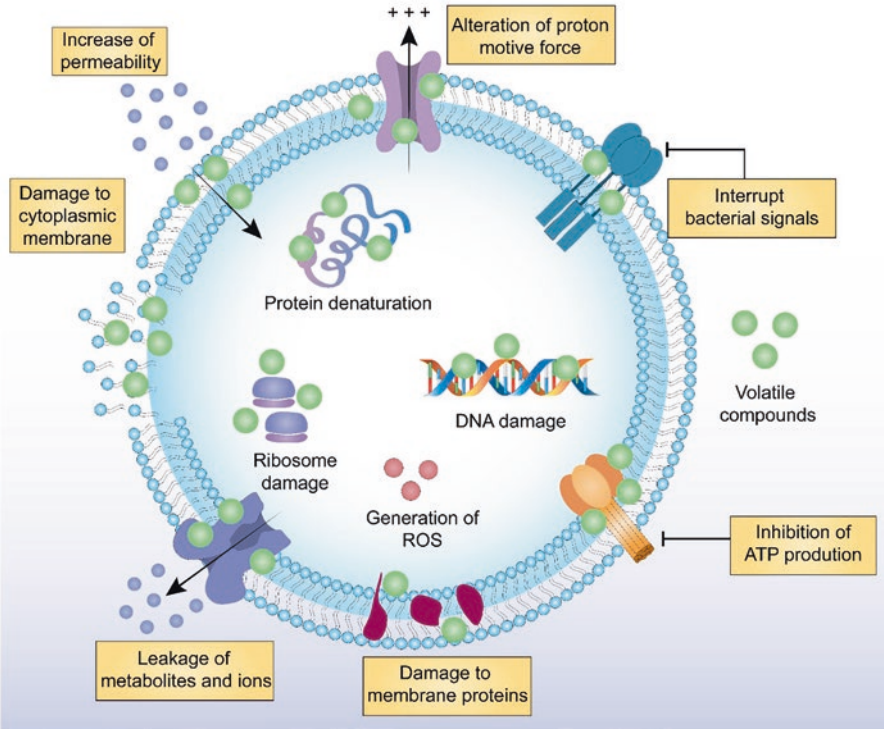

Fig. 18.2 The mechanism of action of volatile compounds against bacterial pathogens

Volatile oils have also been shown to have marked antifungal properties. Different species of fungus, including dermatophytes fungi, moulds, phytopathogenic fungi, and yeasts, have been reported to exhibit anti-fungal properties. The antifungal activity of volatile oils is governed by the existence of many active ingredients such as monoterpenes, sesquiterpenes, phenols, aldehyde, and ketones, all of which interact to produce synergistic, additive, and complementary effects (Soković et al. 2010). The majority of hypotheses about volatile compounds' antifungal effect have been postulated because of their hydrophobic character, which affects ergosterol synthesis in fungi's plasma membrane. Ergosterol is a sterol found only in the fungal plasma membrane, where it is responsible for maintaining membrane fluidity, viability, and integrity, as well as assisting in the biogenesis of certain membrane-bound enzymes (Hyldgaard et al. 2012).

The direct disruption of the plasma membrane is another important mechanism of anti-fungal action. When volatile compounds destabilize the plasma membrane, critical cellular ions like K^+, Ca^{2+}, and Mg^{2+} leak out. Volatile compounds have a significant impact on plasma membrane fluidity and permeability, causing damage to the structures of the membrane proteins. Furthermore, the cellular organelles such as the Golgi body, mitochondria, ribosome, and the endoplasmic reticulum are

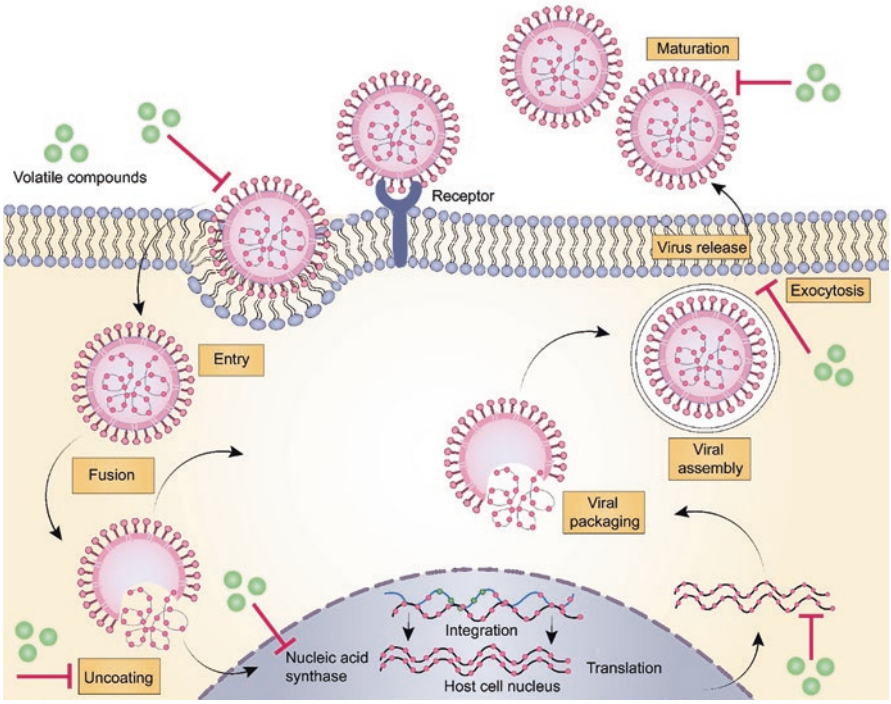

Fig. 18.3 A schematic representation of anti-viral mechanism of volatile compounds

also able to interact with the volatile compounds, resulting in reduced membrane potential (Ma et al. 2011a). This leads to proton pump disintegration, and eventually inhibition of the ATP generating enzyme, H^+ -ATPase, which helps to develop electrochemical gradients and maintain cell pH across the membrane. The normal growth and reproduction of fungal cells is also hampered by the volatile compounds due to damage to nuclear contents (Diniz et al. 2021). The mechanism of action of volatile compounds against fungi is shown in Fig. 18.4.

Nowadays, many researchers have carried out molecular docking of essential oil components to find out the possible mechanism of action for their observed antimicrobial activities (Sun et al. 2009). Depending on type of antimicrobial analysis, one can choose rightly protein database id (pdb id) for molecular docking analysis. The selection of appropriate pdb id is a crucial step while carrying out molecular docking and is based on the resolution of crystal structure of protein or enzyme. One should select the pdb id of the target with the lesser resolution based on previous literature analysis. Recently, Melaku et al., 2021 carried out a molecular docking analysis of essential oil components of plant *Ocimum cufodontii* ((Lanza) A.J. Paton) (Aliye et al. 2021). Their results suggested that essential oil components of this plant have strong interactions with bacterial DNA gyrase. The docking analysis was carried out with the help of AutoDock Vina (Chen et al. 2017). Further, elaboration of the use of molecular docking analysis has been summarized in Table 18.1.

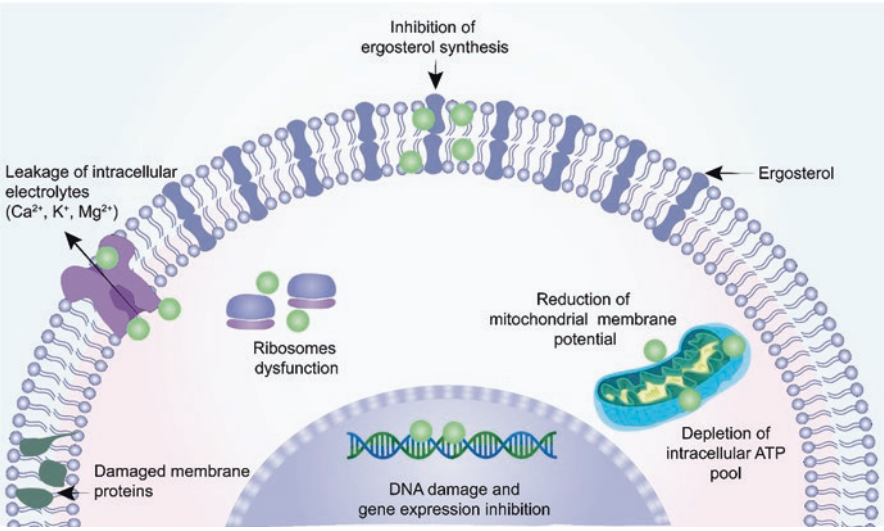

Fig. 18.4 A schematic representation of anti-fungal mechanism of volatile compounds

Table 18.1 Compounds present in essential oils used in molecular modeling

Plant name	Component used	Type of microorganism	Molecular modeling technique used	Ref.
Mentha species (Lamiaceae)	Carvone (55.71%), limonene (18.83%), trans-carveol (3.54%), cis-carveol (2.72%), beta-bourbonene (1.94%), and caryophyllene oxide (1.59%)	*Candida albicans* and *Candida parapsilosis; Salmonella enterica serotype Typhimurium (ATCC 14028), Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853), Shigella flexneri serotype 2b (ATCC 12022), Staphylococcus aureus (ATCC 25923)*	Molecular docking	Jianu et al. (2021)
Siparuna guianensis	Trans-β-Elemenone (11.78%) and Atractylone (18.65%), followed by δ-Elemene (5.38%), β-Elemene (3.13%), β- Yerangene (4.14%), γ-Elemene (7.04%), Germacrene D (7.61%), Curzerene (7.1%), and Germacrone (5.26%)	*Streptococcus mutans* (ATCC 3440), *Enterococcus faecalis* (ATCC 4083), *Escherichia coli* (ATCC 25922), and *Candida albicans* (ATCC 10231)	Molecular docking (Molegro Virtual Docker 6); Molecular Dynamics (MD) Simulation; and Free Energy Calculations	de Oliveira et al. (2020)

Table 18.1 (continued)

Plant name	Component used	Type of microorganism	Molecular modeling technique used	Ref.
Eryngium campestre	Essential Oils	*Staphylococcus aureus* (ATCC 6538), *S. epidermidis* (ATCC 12228), *Streptococcus pyogenes* (ATCC 19615), *Enterococcus faecalis* (ATCC 19433); *Escherichia coli* (ATCC 8739), *Pseudomonas aeruginosa* (ATCC 9027), *Proteus mirabilis* (ATCC 12453), *Klebsiella pneumoniae* (ATCC 10031)	Molecular docking (Molegro Virtual Docker 6)	Matejić et al. (2018)

18.3.3 Molecular Modeling of Volatile Compounds with Anticancer Activity

Cancer has recently emerged as one of the most pressing public health issues, as well as the second leading cause of death after heart disease (da Silva Júnior et al. 2021). Cancer is defined by uncontrolled cell proliferation that results in tumor formation. It develops as a result of somatic mutations in upstream cell signalling pathways or genetic abnormalities in any gene that encodes cell cycle proteins. Many standard therapeutic approaches have been unsuccessful against many malignant cancers due to cancer cell metastasis, recurrence, heterogeneity, and resistance to chemotherapy and radiotherapy (Siegel et al. 2016; de Oliveira et al. 2021). Another explanation for therapy failure has been linked to cancer cells' ability to evade immune responses. Natural products have recently become more popular as a therapy option for various types of cancers. The majority of volatile oils were first discovered and utilized to treat inflammatory and oxidative disorders. These volatile compounds demonstrate anticancer properties owing to the relationship between the production of ROS (reactive oxygen species) and the onset of inflammation and oxidation, both of which are known to cause cancer in humans (Sun 2015; Cascaes et al. 2021b). It is difficult to pinpoint a single mode of action for volatile compounds because of their highly varied compositions. A chemical may, in fact, affect one form of the tumor but not on others. Murata et al., for example, discovered that 1,8-cineole/eucalyptol causes apoptosis in human colon cancer cells (Jackson and Loeb 2001). This chemical, on the other hand, does not influence the survival of prostate cancer and glioblastoma cells. Furthermore, depending on the concentration of active chemicals, multiple processes, such as an effect on the cell cycle, cell proliferation, and/or death, may be observed (Murata et al. 2013; Silva et al. 2021).

Apoptosis is one of volatile oil's cancer-prevention methods which can be triggered by effects on genetic material, multiple signalling pathways, and other cellular events such as intracellular protein alterations by volatile compounds. In cancer cells, the cleavage of poly (ADP-ribose) polymerase-1 (PARP) by volatile oil components is an indication of both alteration of the DNA repair process and apoptosis (Cardile et al. 2009). The aberrant cells also undergo apoptosis as a result of elevated ROS levels. Cell death as a result of volatile oils treatment in cancer cells is characterized by reduced levels of cellular antioxidants like glutathione as well as increased production of ROS in the presence of the volatile oils (Santana de Oliveira et al. 2021). Increased ROS production damages DNA, which often leads the cancer cells towards cell death. This activity is particularly detrimental to cancer cells, whilst it does not affect normal cells (Itani et al. 2008). One of the unique aspects of volatile compounds is that, while they are cytotoxic to cancer cells, they promote normal cell proliferation. Downregulation of repair genes (DNA polymerases α, δ, and ε) volatile compounds may prove to be a viable approach for preventing DNA damage. The protein kinase B, often known as Akt, which regulates p53, is another target for volatile oils (Kelley et al. 2001). It has been demonstrated that upregulation of p21, which occurs from the deactivation of mdm2 as a result of the dephosphorylation of the Akt protein, causes the cell cycle to be interrupted in lung carcinoma cells. The G1-S phase transition was suppressed by increasing the binding of p21 to cyclins (Legault et al. 2003). A transcription factor (TF) called Nuclear factor, often known as NF- κB, is triggered in cancer cells. As a result, it is a promising target for developing anticancer therapeutics. Another TF called AP-1 (Activator protein-1) is involved in a variety of cell activities including differentiation, proliferation, transformation, and apoptosis. MAPK proteins, which are likewise impacted by volatile oils therapy in cancer cells, govern its activity. Furthermore, various MAPKs, such as p38 kinase, ERK, and JNK are the key signalling molecules in the MAPK pathway that are implicated in cancer cell apoptosis (Jaafari et al. 2007).

Volatile compounds are highly potent anticancer agents because they target several cell cycles phases in cancer cells. Volatile compounds such as thymol, carvacrol, and geraniol have shown to inhibit different phases of cell cycle (Frank et al. 2009). Monoterpenes exert their effects through modulating the expression of cell cycle regulators. Volatile oils have also shown to possess antimetastatic and antiangiogenic properties. They have shown to suppress tumor growth and metastasis (Mitoshi et al. 2012). The major sign of antiangiogenic behavior demonstrated by the volatile compounds is the suppression of vascular endothelial growth factor (VEGF), which is vital in the process of angiogenesis. In cell line models, certain volatile compounds function as inducers of several detoxifying enzymes (catalase, CAT; superoxide dismutase, SOD; glutathione reductase, GR; and glutathione peroxidase, GPx) preventing induced damage and even cancer (Suhail et al. 2011). A marked increase in these antioxidant enzymes after the treatment with volatile oils has been demonstrated as a chemo preventive activity (Seal et al. 2012). The cancer cell cycle can be seen in Fig. 18.5.

Natural essential oils are beneficial to human health. They are important to prevent as well as to treat varieties of cancers. A large number of essential oil

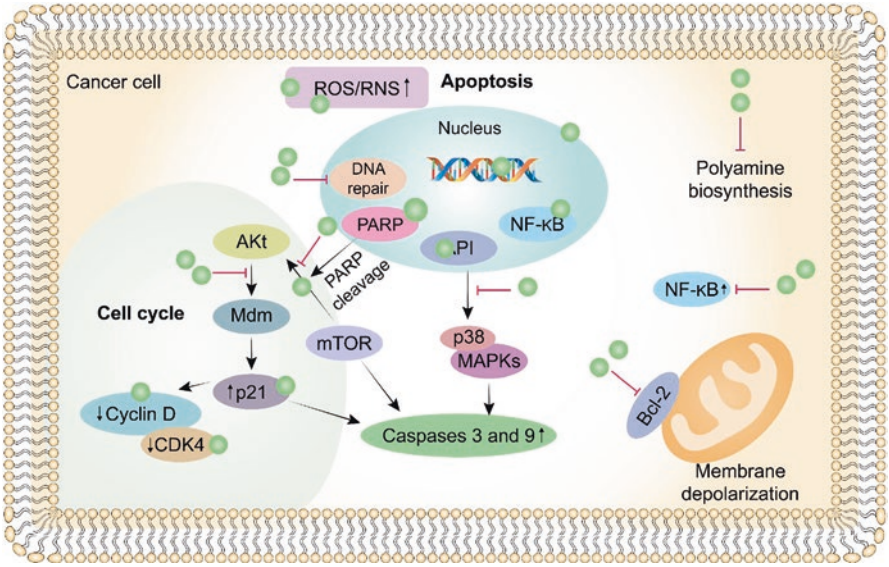

Fig. 18.5 Cancer cell cycle

components from varieties of aromatic herbs and dietary plants have been reported (Kim et al. 2000; Manjamalai and Grace 2012). These include oxygenated monoterpenes, oxygenated sesquiterpenes, phenolics, monoterpenes, sesquiterpenes, etc. (Chidambara Murthy et al. 2012). It is also known that various mechanisms such as antimutagenic, antiproliferative, enzyme induction, detoxification, modulation of drug resistance, antioxidant, etc. would be responsible for the chemoprotection properties of volatile oils (Cha et al. 2009). There are a large number of literatures reports available depicting the anticancer activity of volatile oils or essential oil components against various cancer types using molecular modeling techniques (Jaafari et al. 2012). Below are few examples showing implications of molecular modeling to predict the anticancer mechanism of volatile or essential oils from plants, Table 18.2.

18.3.4 Molecular Modeling of Volatile Compounds Against Neglected Diseases

A disease of poverty (DoP) is defined by the WHO (World Health Organization) Special Programme for Research and Training in Tropical Diseases (WHO-TDR) as a disease that mostly affects the poor in developing nations and is split into two classe. The "big three" DoPs are included in the first class: malaria, HIV/AIDS, and tuberculosis (Cascaes et al. 2021a). The community has paid close attention to these diseases and has invested much in their eradication. Around 70% of pharmaceutical

Table 18.2 Compounds present in essential oils used in potential cancer treatment and mechanism of action

Plant name	Component used	Type of cancer cell line	Molecular modeling technique used	Ref.
Ocimum viride Willd. (family: Lamiaceae)	Thymol (~50%) and γ-terpinene (~18%)	DU-145 (prostate), HEP-2 (liver), IMR-32 (neuroblastoma), HT-29 (colon), 502,713 (colon) and SW-620 (colon)	Molecular docking	Bhagat et al. (2020)
Ocimum basilicum (sweet basil) (family: Lamiaceae)	Essential Oil components	HeLa and FemX	Molecular docking	Zarlaha et al. (2014)
Mentha longifolia, M. spicata, and Origanum. majorana	Essential Oil components (Carvone (35.14%), limonene (27.11%), germacrene D (4.73%), β-caryophyllene (3.02%), γ-muurolene (2.75%), and α-bourbonene (2.27%))	Antioxidant and Anticancer	Molecular docking	Farouk et al. (2021)

development is devoted to these disorders. The other is a group of tropical diseases that are often overlooked, called Neglected Tropical Diseases (NTD) (Lenk et al. 2018). There are 17 NTDs, and they affect groups that have minimal visibility and political power. They create discrimination and stigma, as well as having a significant impact on morbidity and mortality; these diseases are mostly ignored by researchers, yet they can be prevented, controlled, and, in many cases, eliminated with the right solutions (Chen et al. 2017).

Leprosy, commonly known as Hansen's disease, is one of the neglected diseases which is caused by *Mycobacterium leprae*, an intracellular parasitic mycobacterium that causes skin lesions and nerve damage (Fotakis et al. 2020). Various plant-derived antileprotic agents have been found to be extremely effective in the management of leprosy. *Centella asiatica,* commonly known as Gotu kola or kodavan is a well-known and reputed herbal medicinal plant that constitutes saponin-containing triterpene acids along with sugar esters such as madecassic acid, asiatic acid, and asiaticosides (asiaticoside A, asiaticoside B, and asiaticoside) (Sharma et al. 2020). Asiaticosides have shown to accelerate wound healing and alleviate the symptoms of leprosy. Other volatile oils exhibiting antileprotic activity are Chaulmoogra oil (chaulmoogric acid and hydnocarpic acid), *Abutilon indicum* (β-sitosterol and α-amyrin), *Azadirachta indica* (azadirachtin), *Hemidesmus indicus* (hemidesmins and hemidesmosides A-C), Butea monosperma (Butin), etc. (Balasubramani et al. 2018).

Malaria kills one to three million people globally each year, the most portion involving pregnant women and children, but it remains a low priority for public health. Resistance to chloroquine, the first-line antimalarial treatment, has reached 90% in many parts of Africa, and resistance to sulfadoxine pyrimethamine is also on the rise (Vatandoost et al. 2018). Below are few examples showing the usefulness of molecular docking to predict the mechanism of volatile or essential oils from plants against two neglected diseases; malaria and dengue, the information is summarized in the Table 18.3.

Trypanosomiases are parasitic protozoan trypanosome illnesses caused by Trypanosoma genus parasites. The Chagas disease, Human African trypanosomiasis, and leishmaniases are all classified as neglected tropical illnesses by the WHO. There are roughly 20 Trypanosoma species, but only two species, *Trypanosoma brucei* (*T. brucei*) and *Trypanosoma cruzi* (*T. cruzi*) are the species that mainly infect humans. *T. cruzi* is the parasite that causes American trypanosomiasis, generally known as Chagas disease, which is found all over America. Triatominae insects, also known as "kissing bugs," spread it (de Morais et al. 2020). The parasite multiplies in the bloodstream and can spread to other organs such as the liver, spleen, and heart, where it can cause serious damage. African trypanosomiasis, sometimes known as sleeping sickness, is caused by *T. brucei*, which is most typically seen in equatorial Africa. If left untreated, both forms of trypanosomes infect the brain, causing mental degeneration, coma, and death. Several volatile oils from various species have found to be biologically active against trypanosomiasis (Bottieau and Clerinx 2019). Some volatile oils activity may be linked to the lipophilic properties of their constituents. Lipophilic substances can pass the cell membrane and interact with several proteins, inactivating enzymes and influencing cellular activity once within the cells (Yang and Hinner 2015). Depolarization of the mitochondrial membrane is linked to alterations in calcium channels and the production of ROS, both of which can lead to cell death via apoptosis and necrosis. Cell death through necrosis is characterized by a discontinuous plasma membrane, which indicates that the parasite has lost its integrity (Yoon et al. 2000). There are also changes to the mitochondria, ROS production, ATP depletion, and cytoplasm vacuolization in this kind of cell death. The essential oils of *Melaleuca alternifolia*, *Xylopia frutescens*, *Xylopia laevigata*, *Cymbopogon citratus*, exert this type of

Table 18.3 Molecular docking in neglected diseases

Plant name	Components of Oil Detected	neglected disease	Molecular modeling technique used	Ref.
Artemisia vulgaris	α-humulene (0.72%), βcaryophyllene (0.81%)	Dengue Fever	Molecular docking	Balasubramani et al. (2018)
Neem (Azadirachta indica)	Bitter principles of neem oil	Malaria	Molecular docking	Ghosh et al. (2021)
Eucalyptus globulus and Syzygium aromaticum	1,8-Cineol (78.20%), 2-methoxy-3-(2-propenyl) (77.04%)	Malaria	Molecular docking	Sheikh et al. (2021)

action (Giorgio et al. 2018). Loss of mitochondrial membrane potential, cytoplasmic blebbing, nuclear chromatin condensation, cell volume reduction, and DNA fragmentation are among the changes that occur during apoptosis. Such characteristics were also observed from the volatile oils of *Cinnamomum verum*, *Lippia dulcis*, *Achyrocline satureioides* (Menna-Barreto et al. 2005).

18.4 Conclusion and Future Perspectives

This chapter emphasizes the relevance of volatile oils investigations, particularly those involving pharmacology and bioinformatics/computational tools, which are now complementing and facilitating the identification of new compounds by steering and orienting studies toward specific molecular targets. The diversity of volatile compounds that make up volatile oils are becoming increasingly well characterized. Similarly, the range of biological activity of volatile oils and their constituents is beginning to be known and comprehended. Computational methods contribute to the selection of chemical structures with the highest probability of biological activity and the rationalization of natural volatile compounds. Moreover, these methods aid in the identification of chemical and structural descriptors thus providing insight into the active molecules' modes of action, and all of this information can be used to build novel structures that can be synthesized as small molecules. The discovery of new leads may thus provide an interesting platform for this research avenue in the future. Nonetheless, there is a broad scope for utilizing volatile oils not only as antimicrobial and anticancer agents but also in the treatment of neglected diseases in an array of settings, providing those critical issues such as effective delivery systems and potential toxicity the environment is addressed. Furthermore, pre-clinical studies are needed to ensure the security of the use of these compounds in humans. Likewise, administration strategies should be studied to enhance the effect of such compounds.

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