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# Review on the biosynthesis, regulation, multifaceted biological activities, and applications of volatile organic compounds

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ABSTRACT

The role of volatile organic compounds (VOCs) in food, medicine, and agriculture is gaining significant attention. This comprehensive review delves into the biosynthetic pathways, regulatory and bioactivity profiles, and prospects of VOCs, encompassing a spectrum from volatile terpenoids to phenolics, aldehydes, ketones, and acids. We commence with an exploration of the diverse biosynthetic routes of VOCs, focusing on the methylerythritol phosphate, mevalonate, and phenylpropanoid pathways and elucidating the key enzymes and intermediates. Subsequently, we examine the bioactivity of VOCs, highlighting their antibacterial, anticancer, anti-inflammatory, antioxidative, anthelmintic, and anti-mood disorder properties, and discuss their potential applications in the food, medicinal, and agricultural fields. This review highlights the need for future studies to focus on regulating the biosynthesis of VOCs, unraveling their bioactivity, and developing efficient synthetic and extraction methods to enable sustainable advancements in related fields.



## 1. Introduction

Volatile organic compounds (VOCs) are characterized by low boiling points and volatility and are found extensively in nature. They are integral to the life processes of various organisms, including plants and microorganisms, and play important roles in numerous biosynthetic pathways. Moreover, VOCs exhibit a broad spectrum of biological activities that significantly affect ecological systems and human health[1]. With the development of modern biotechnology, researchers have elucidated the diverse and complex biosynthetic pathways of VOCs. Different organisms synthesize VOCs with specific structures and functions through complex enzyme-catalyzed reactions within theirmetabolic networks[2]. These compounds contribute to the ecological balance by mediating communication, defense mechanisms, and attracting pollinators. In addition, they demonstrate potent biological activities, including antibacterial, antioxidant, and anticancer activities, showing vast potential for applications in medicine, food, and agriculture[3-4]. In-depth exploration of the bioactivity and mechanisms of VOCs holds promise for uncovering novel avenues for the development of innovative pharmaceuticals, biopesticides, and functional food additives[5].

In recent years, it has been discovered that organisms predominantly produce VOCs through fatty acid, amino acid, mevalonate (MVA), and methylerythritol phosphate (MEP) pathways[1,6-9]. Specifically, compounds such as citronellol, linalool, and perilla alcohol have been shown to inhibit the proliferation and metastasis of tumor cells[10-12]. Carvacrol, eugenol, and thymol are recognized for their antioxidant and antibacterial properties, which mitigate oxidative stress[1,13]. In addition, some VOCs have been shown to effectively modulate insect behavior, safeguard plants, and ameliorate mood disorders[14]. Despite these significant advancements, the VOC field has enigmas and hurdles. A comprehensive understanding of their biosynthetic pathways and regulation is still underway. Further in-depth investigations on the biological activities

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and mechanisms of action of VOCs are imperative. Moreover, the practical application of VOCs in food, medicine, and agriculture necessitates additional validation and optimization efforts to ensure their efficacy and safety.

Therefore, the objective of the article is to conduct a thorough review of the biosynthetic pathways, biological activities, and application prospects of VOCs. By addressing the current body of research findings, this review clarifies the research status and delineates the trajectory of future developments within VOCs. Overall, this review contributes to the theoretical foundation and practical guidance necessary for the applied research of VOCs.

## 2. Biosynthesis and regulation of VOCs

VOCs can be categorized as volatile terpenoids, phenolics, and volatile aldehydes/ketones/acids based on their chemical structure. These are diverse in type and function[1]. In recent years, researchers have increasingly come to appreciate the biological significance of VOCs, particularly in biodefense, signal transduction, and flavor modulation[5]. This growing recognition has spurred deeper investigations into their biosynthetic pathways and regulatory mechanisms[2] (Fig. 1). A thorough understanding and control of these processes can lead to innovative approaches and methodologies for applications in food preservation and pharmaceutical development.

### *2.1 Biosynthesis and regulation of volatile terpenoids*

Terpenoids are compounds derived from mevalonic acid, with their molecular framework based on the isoprene unit (C5) as the fundamental structural unit; their oxygen-containing derivatives can include alcohols, aldehydes, ketones, and esters[15]. They can be systematically classified based on the number of isoprene units. This classification includes monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), triterpenes (C30), and others[16]. Monoterpenes, which consist of exactly 2 isoprene units, are represented by linalool, limonene, geraniol, *α*-terpineol, and sabinene. These compounds possess simple structures, strong aromatic characteristics, and diverse biological activities[6]. Sesquiterpenes, which comprise 3 isoprene units and their derivatives, often exhibit linear, monocyclic, and bicyclic structures. Examples include farnesol, *β*-caryophyllene, germacrone, and curdione. These compounds have low boiling points and are known for their diverse biological activities including anti-inflammatory, antioxidant, and antibacterial effects[17]. Diterpenes and triterpenes, with 4 and 6 isoprene units respectively, along with their derivatives, are often complex, featuring bicyclic, tricyclic, and tetracyclic oxygenated structures[18-19]. These compounds have a broad spectrum of biological activities, including anti-inflammatory, antibacterial, and anticancer properties, and have extensive applications in medicinal and spice industries[3].

The biosynthesis of volatile terpenoids is primarily facilitated by 2 distinct metabolic pathways, MVA and MEP. Both pathways converge on the production of isopentenyl diphosphate (IPP), an important intermediate in terpenoid synthesis of terpenoids[20]. The biosynthetic pathways of volatile terpenoids can be divided into 3 primary stages: isopentenyl synthesis, synthesis of the core carbon skeleton of the terpenoid compounds, and subsequent tailoring modifications[18] (Fig. 1b).

In most eukaryotic organisms, the biosynthesis of 2 essential metabolites, IPP and dimethylallyl diphosphate (DMAPP), is initiated through the MVA pathway[21]. Acetyl-CoA, a key precursor in this process, is primarily sourced from central metabolic pathways, such as glycolysis, fatty acid oxidation, and amino acid degradation[21]. The MVA pathway begins with the condensation of three acetyl-CoA molecules to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), which is catalyzed by acetoacetyl-CoA thiolase[22]. This is followed by the reduction of HMG-CoA to MVA by the rate-limiting enzyme HMG-CoA reductase (HMGR). MVA then undergoes a series of phosphorylation, decarboxylation, and isomerization reactions, culminating in the production of IPP and DMAPP[22]. The MEP pathway is responsible for IPP biosynthesis. This pathway begins with pyruvate and *D*-glyceraldehyde 3-phosphate, which undergo oxidation, reduction, and rearrangement to yield 1-deoxy-*D*-xylulose-5-phosphate (DXP). DXP reductoisomerase converts DXP into 2-C-methyl-*D*-erythritol-4-phosphate, which is further processed through a series of enzymatic reactions to form IPP[23]. Once IPP and DMAPP are produced, they undergo a head-to-tail condensation reaction catalyzed by prenyltransferase to form geranyl diphosphate (GPP). GPP serves as a precursor for the synthesis of various monoterpenoids, which is facilitated by the action of monoterpene synthase. Further condensation of GPP results in the formation of farnesyl diphosphate (FPP), a precursor for sesquiterpene biosynthesis. During sesquiterpene synthase catalysis, FPP undergoes a series of complex chemical transformations, resulting in a diverse array of sesquiterpenoids[18] (Fig. 1b).

Beyond the natural MEP and MVA pathways, advancements in synthetic routes for IPP and DMAPP have led to innovative approaches for efficient terpenoid biosynthesis[18]. Clomburg et al.[24] developed a streamlined isoprenoid alcohol (IPA) pathway for terpenoid synthesis. This method efficiently converts isopentenol precursors into terpenoids in a minimal number of steps and reduces the ATP consumption. In addition, Chatzivasileiou et al.[25] introduced an isoprenoid utilization pathway (IUP) that effectively converts isoprenols, isoprenediols, and pentenols into IPP or DMAPP, further enhancing the flexibility and efficiency of terpenoid production. Acetyl-CoA is an important precursor at a critical juncture in terpenoid biosynthesis[19]. Lu et al.[26] have made significant strides by integrating protein engineering and pathway construction in *Escherichia coli*. They successfully used *E. coli* as a host organism to develop the most direct pathway for the biosynthesis of acetyl-CoA from formaldehyde, both *in vitro* and *in vivo*. This achievement simplifies the production process and underscores the potential of synthetic biology for optimizing terpenoid biosynthesis.

In recent years, there has been a significant push to harness *E. coli* and *Saccharomyces cerevisiae* as engineered microorganisms and transform them into efficient microbial cell factories for the sustainable and high-yield production of valuable terpenoid compounds[9,27-28]. Zhang et al.[9] developed genetic circuits that allow precise control over critical steps in the terpenoid biosynthetic pathway, thereby significantly boosting product yield and selectivity. Moreover, ongoing research on the post-modification enzymes of terpenoid compounds has led to enhancements in the efficiency of these post-synthetic modifications, which in turn has improved the quality and functionality of the end products[19]. The integration of engineered microorganisms, such as *E. coli* and *S. cerevisiae* with

advanced techniques such as metabolic engineering, gene editing, and synthetic biology is poised to play an important role in the future industrial production of terpenoids.

### 2.2 Biosynthesis and regulation of volatile phenolics

Volatile phenolics, known for their distinctive aromatic profiles and biological activities, occur in a variety of plants, microorganisms, and other life forms[4]. They play a significant role in plant defense mechanisms, signaling, and microbial interactions and have vast potential applications in the fields of food, fragrances, and pharmaceuticals[4]. The synthesis of volatile phenolic compounds is predominantly governed by 2 important biosynthetic pathways: the shikimic acid and phenylpropanoid pathways[29] (Fig. 1a).

The shikimate pathway, a cornerstone of the biosynthesis of aromatic amino acids and phenolic compounds, is initiated by the condensation of phosphoenolpyruvate (PEP) and erythrose-4-phosphate (E4P), both derived from glycolysis, to form 3-deoxy-*D*-arabinoheptulosonate-7-phosphate (DAHP)[30]. This initial step sets the stage for a series of enzymatic reactions that convert DAHP into shikimic acid (SA). This pathway includes through a dephosphorylation reaction catalyzed by 3-dehydroquinate synthase (DHQS), yielding 3-dehydroquinate (DHQ). DHQ is then subjected to aldol condensation followed by dehydration by 3-dehydroquinate dehydratase (DHQD) to produce 3-dehydroshikimate (DHS). The final step involves the conversion of DHS to SA by shikimate dehydrogenase (SDH), a critical precursor in the formation of chorismite. Chorismate, a key branch point in this pathway, undergoes transamination catalyzed by chorismate synthase (CS) to generate phenylalanine and tyrosine, which are central to phenylpropanoid metabolism[7,30-31]. These amino acids are further processed through non-oxidative deamination reactions catalyzed by phenylalanine

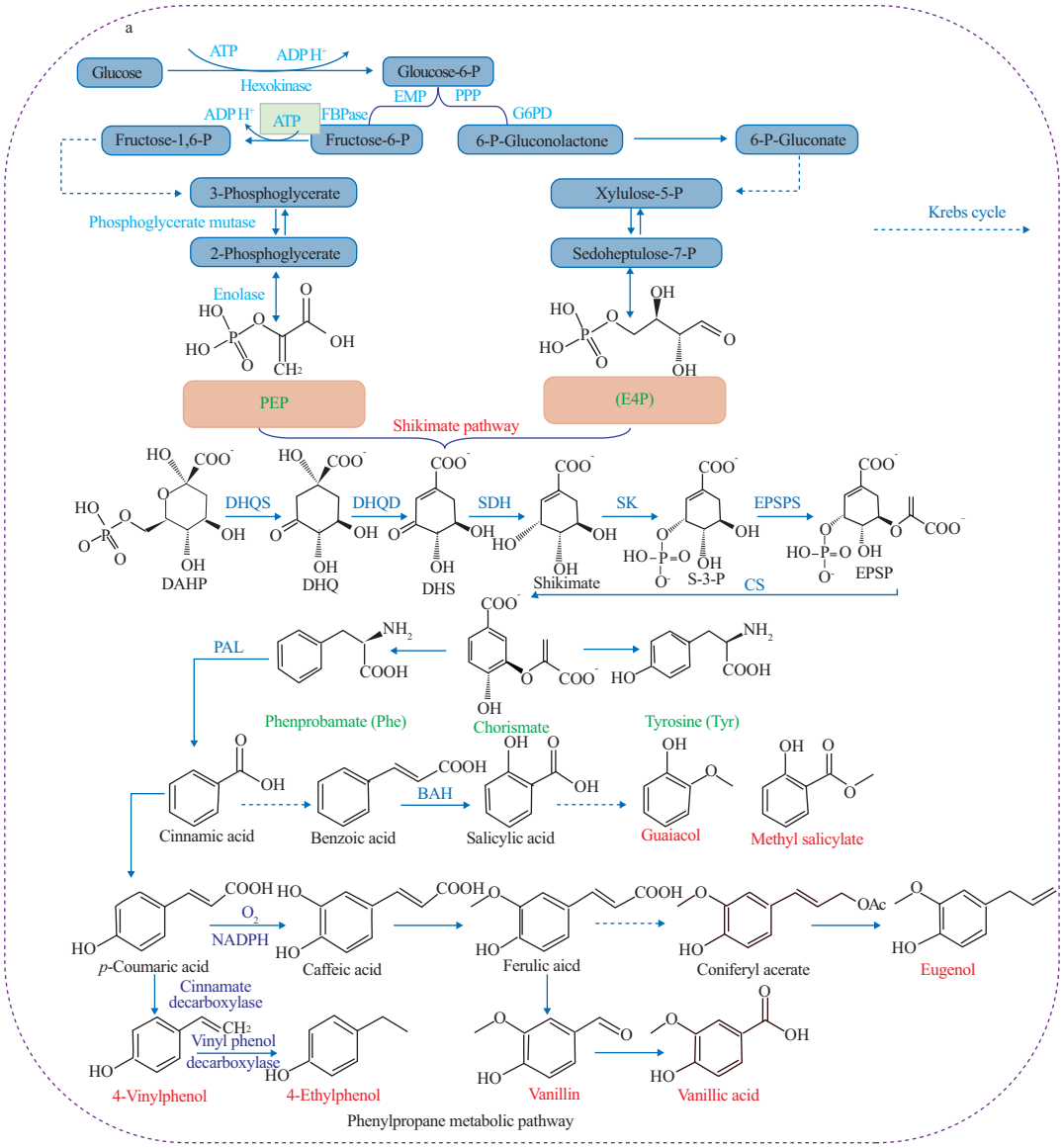


**Fig. 1** Biosynthetic pathways of (a) volatile phenolic compounds, (b) volatile terpenoids , and (c) volatile ketones/aldehydes/acids. Substances marked in red are representative chemical structures of the VOCs according to the structural classification. HMG-CoA-S: Acetoacetyl-CoA thiolase. HMGCS: 3-Hydroxy-3-methylglutaryl-coenzyme A synthase. HMG-CoA: 3-Hydroxy-3-methylglutaryl-coenzyme A. HMGR: 3-Hydroxy-3-methylglutaryl. MVK: Mevalonate kinase. PMK: Phosphomevalonate kinase. MVPD: 5-Diphosphomevalonate decarboxylase. IDI: Isopentenyl diphosphate isomerase. DXR: 1-Deoxy-D-xylulose-5-phosphate reductoisomerase. IDS: Isopentenyl diphosphate synthase. GPP: Geranyl pyrophosphate. FPP: Farnesyl pyrophosphate.

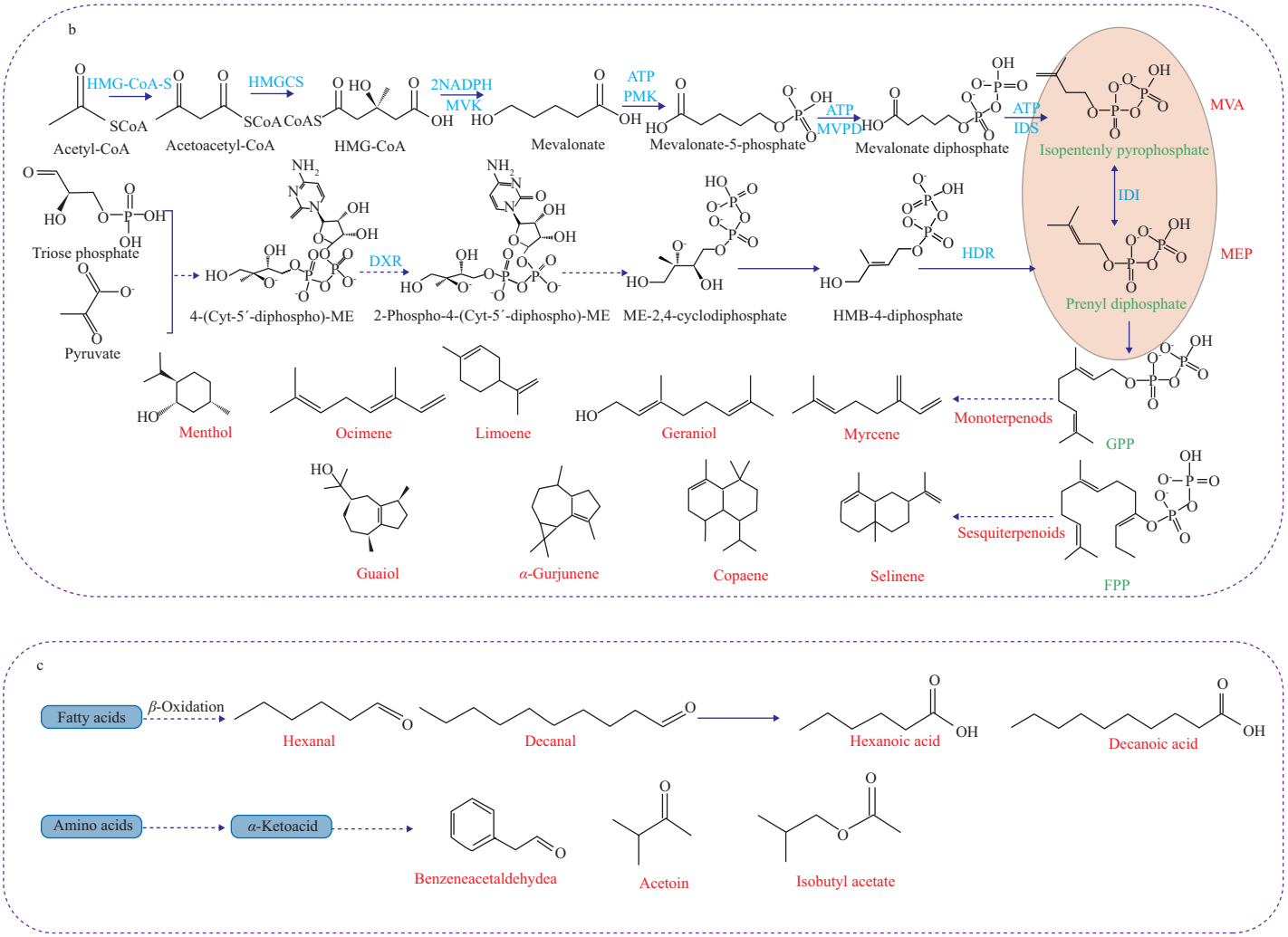


**Fig. 1** (*Continued*)

ammonia-lyase (PAL) and tyrosine ammonia-lyase (TAL), resulting in the formation of cinnamic acid and *p*-coumaric acid, respectively. The subsequent hydroxylation of cinnamic acid by cinnamic acid 4-hydroxylase (C4H) to *p*-coumaric acid marks the beginning of a cascade of enzymatic transformations that leads to the production of a variety of phenolic compounds, including caffeic acid, ferulic acid, and the volatile phenolics vanillin, eugenol, and isoeugenol[29,32-33].

The shikimate and phenylpropanoid pathways are the cornerstones of microbial synthesis of volatile phenolic compounds[33]. Strategies to enhance the metabolic flux through the shikimate pathway and fine-tune the structure and function of key enzymes in the phenylpropanoid pathway, such as PAL and C4H, have been shown to significantly boost the yield of these volatile phenolic compounds[34]. Advances in our understanding of plant hormone signaling have revealed that MeJA and SA can induce the expression of genes encoding key enzymes, such as PAL and C4H, thus stimulating the synthesis of volatile phenolic compounds[32]. Researchers have successfully manipulated enzymes such as benzoic acid methyltransferase (BAMT) to catalyze the formation of methylated volatile phenolic compounds[35]. Innovative approaches such as those described by Dell et al.[36] have increased the production of branched acids in recombinant *E. coli* strains. This was achieved by overexpressing the rate-limiting enzyme, DHQS, derepressing DAHP synthase, and knocking out the rate-limiting enzyme, CS, through the shikimate synthesis pathway. Similarly, An et al.[37] engineered *E.coli* strains capable of synthesizing various hydroxycinnamic acids by expressing combinations of enzymes, enabling the direct production of phenylpropanoid pathway intermediates, such as ferulic acid, caffeic acid, and cinnamic acid from glucose, thereby enhancing the overall content of volatile phenolic compounds. These discoveries highlight the impact of optimizing metabolic engineering and regulating key enzymes on the production of volatile phenolic compounds[38-40]. Ongoing advancements in molecular biology, metabolomics, and synthetic biology have enabled more precise control and optimization of the synthesis of volatile phenolic compounds. Techniques such as genetic tagging and metabolic engineering will unlock new possibilities for the application of these compounds in agriculture, medicine, and chemical engineering[18].

### *2.3 Biosynthesis and regulation of volatile ketones/aldehydes/acids (VKAAs)*

VKAAs are a class of low-molecular-weightthat significantly influence the secondary metabolism of plants, microorganisms, and animals[1]. VKAA biosynthesis is primarily channeled through two principal metabolic pathways: fatty acid and amino acid

metabolism[41] (Fig. 1c). In fatty acid metabolism, volatile ketones are predominantly derived from fatty acids, which are converted to acetyl-CoA through $\beta$-oxidation pathways. Notably, major ketones such as acetone emerge from the decarboxylation of acetoacetyl-CoA, an essential intermediate in fatty acid catabolism[42]. Volatile aldehydes are primarily generated from unsaturated fatty acids through the lipoxygenase pathway[43]. Volatile acids are predominantly formed through the catalytic action of aldehyde dehydrogenase[44]. Under the influence of enzymes such as transaminases and decarboxylases, amino acids are transformed into their corresponding VKAAs[45].

The intricate metabolic pathways of VKAAs are regulated by several factors, including gene expression, enzyme activity, substrate concentration, and environmental conditions[1]. In a pioneering study, Rodrigues et al.[46] used the heat shock protein promoters dnaK and ibpA to drive the expression of tyrosine ammonia-lyase. Through meticulous optimization of ribosome binding sites (RBS), they synthesized significant quantities of *p*-coumaric acid (2.5 mmol/L) and caffeic acid (370.0 mmol/L) in *E. coli*. Kunjapur et al.[47] advanced this field by constructing an engineered bacterial strain designed for the enhanced production of volatile aldehydes. This was achieved by knocking out the gene encoding the organic aldehyde reductase, thereby redirecting the metabolic flux towards the desired product. Building on genomic insights, Xu et al.[48] implemented metabolic engineering strategies to enhance acetyl-coenzyme A accumulation. They minimized carbon loss and significantly enhanced VKAA production by primarily upregulating glycolysis and downregulating the TCA cycle. The manipulation of the biosynthetic pathways of VKAAs through synthetic biology has significant potential.

## 3. Extraction techniques for VOCs

VOCs are integral to multiple industries, including food, pharmaceuticals, and cosmetics, where they significantly influence product quality and market competitiveness. Therefore, the extraction techniques used for these compounds are critical[1]. Traditional methods for extracting VOCs include steam distillation, maceration, and organic solvent extraction[6]. Steam distillation is a widely used technique owing to its simplicity, ease of operation, cost-effectiveness, and high yield. It capitalizes on the high solubility of VOCs in steam, where volatile compounds are co-distilled with steam and subsequently condensed and separated to yield pure volatile substances[34]. Maceration, another traditional approach, involves the immersion of plant materials in organic solvents to extract volatile components, which are then dissolved and evaporated[30]. Organic solvent extraction is particularly useful for capturing volatile substances from plants using solvents such as ethanol, methanol, and acetone. Fine-tuning of the solvent polarity, concentration, and extraction conditions enables the selective extraction of specific biologically active components. This method is efficient and adaptable, as well as economically advantageous, offering notable application value in VOC development[24,29]. However, the frontier of extraction technology is continuously expanding with the advent of sophisticated techniques aimed at enhancing efficiency and product quality. Supercritical fluid extraction is an advanced method, using carbon dioxide and other substances as solvents under high-pressure and low-temperature conditions. It is lauded for its efficiency, selectivity, and simplicity[17,20]. Microwave-assisted extraction leverages microwave radiation to expedite the release of intracellular substances, potentially modifying the sample morphology and structure to facilitate VOC extraction. Electrokinetic separation uses electric fields and ion-exchange membranes to effectively separate and purify volatile substances, making it ideal for the extraction of high-purity volatile components[14,22]. The evolution of VOC extraction technology is marked by a transition from traditional distillation methods to modern approaches, such as supercritical extraction and microwave-assisted extraction. The selection of the extraction technique depends on the specific properties and application requirements of the target VOCs. These technological strides augment the extraction efficiency and quality of compounds, and also broaden the horizon of VOC applications across diverse industries.

## 4. Bioactivity and applications of VOCs

Delving deeper into the biosynthetic pathways of VOCs, researchers have uncovered a rich tapestry of enzyme-catalyzed reactions and metabolic routes within organisms that facilitate VOC synthesis. This intricate network of pathways, modulated by environmental cues and gene expression patterns, lays the groundwork for the significant diversity and variability in VOC types and production levels. Although the biosynthetic mechanisms of VOCs have garnered considerable attention, unraveling the roles of these compounds both intracellularly and extracellularly, along with their potential biological activities, is important for discovering novel directions in ecological and medical applications. In recent years, extensive of research has highlighted an array of biological activities of VOCs, including antibacterial, antioxidant, anticancer, anti-inflammatory, and neuromodulatory effects[43,74] (Table 1). These properties highlight the significant potential of VOCs in a spectrum of fields, from medicine, where they may contribute to novel therapeutics, to agriculture and food industry, where they can enhance crop protection and food preservation.

### *4.1 Antibacterial*

Numerous VOCs emitted by plants and microorganisms have demonstrated potent antibacterial properties, making them viable candidates as natural antimicrobial agents[116]. The primary antibacterial mechanism of VOCs is the disruption of bacterial cell membrane structure and function, resulting in altered membrane permeability, leakage of cellular contents, and ultimately cell death[117] (Fig. 2). Using scanning electron microscopy (SEM), researchers have observed that certain compounds, such as $\alpha$-terpineol and eugenol, can swiftly neutralize pathogens such as *Staphylococcus aureus* and *Salmonella enterica*. This rapid action is largely attributed to the rupture of cell membranes and modifications in membrane ion channels ($Na^+$, $K^+$, $Ca^{2+}$, and $Cl^-$), which escalate membrane permeability and stimulate the release of crucial cellular constituents[118-119]. In addition, VOCs can inhibit key bacterial enzyme activities, thereby disrupting energy metabolism and biosynthetic pathways and impede bacterial growth and proliferation[1]. Compounds, such as thymol and eugenol, with their highly reactive hydroxyl groups, can form hydrogen bonds with the active sites of bacterial enzymes. This interaction leads to cell membrane dysfunction and inhibits the growth of Gram-positive and negative bacteria, including *Bacillus subtilis*, *E. coli*,

*Klebsiella pneumoniae*, and *S. aureus*, indicating the broad-spectrum antibacterial potency of VOCs[120-121]. Moreover, VOCs may perturb bacterial DNA replication and transcription, further reducing bacterial viability[122] (Fig. 2). Russo et al.[123] showed that limonene can trigger programmed cell death in the human neuroblastoma cell line SH-SY5Y by activating cytoplasmic Caspase-3 and binding to DNA, resulting in DNA fragmentation.

This emphasizes that the antimicrobial potency of VOCs is intrinsically linked to their chemical structure and properties, which endow different VOCs with distinct antibacterial mechanisms and efficacies[1]. Studies have shown that the antibacterial mechanisms of volatile terpenoids predominantly involve disruption of bacterial cell wall and membrane integrity, interference with metabolic pathways, and inhibition of bacterial biofilm formation[124]. Lopez-Romero et al.[125] showed that compounds, such as citronellol, citronellal, and citral, interact with phospholipid molecules in bacterial cell membranes. This interaction precipitates alterations in membrane structure, escalates permeability, and triggers the efflux of ions and metabolites, culminating in the death of bacteria such as *E. coli* and *S. aureus*. Gupta et al.[126] reported that *E. coli* cells underwent membrane rupture and leakage after limonene treatment. Moreover, the interaction between limonene and DNA impedes transcription and translation, thereby disrupting cellular metabolism and precipitating cell death. Thymol, another potent VOC, interfaces with the bacterial intracellular redox system and catalyzes the production of reactive oxygen species (ROS). An overabundance of ROS can inflict oxidative damage on bacterial cell structures and functions, impairing biological macromolecules such as DNA, proteins, and lipids, and ultimately leading to bacterial demise[70].

Volatile phenolic compounds significantly affect bacterial cell membranes by interacting with phospholipid molecules, thereby disrupting membrane integrity and precipitating cell death[30]. In addition to their impact on membrane structure, these compounds exert antimicrobial effects by inhibiting key enzymatic activities within bacteria, including those of DNA polymerase and proteins involved in synthesis processes, effectively stabilizing bacterial growth and reproduction[30,127]. When juxtaposed with conventional antibiotics, certain VOCs such as resorcinol and ferulic acid demonstrate superior efficacy in compromising the cell walls of *S. aureus*[127]. This leads to the leakage of cellular contents and highlights their potent activity against Gram-positive bacteria. Notably, the inhibitory effects were further amplified when these compounds were used in conjunction with antibiotics such as oxacillin[128]. Furthermore, compounds including phenol, thymol, and eugenol have been shown to impede bacterial DNA replication by targeting essential enzymes, such as DNA polymerase, ATP synthase, and proteases, in both Gram-negative and -positive bacteria. This targeted inhibition hampered the bacterial growth and division[129-130] (Fig. 2).

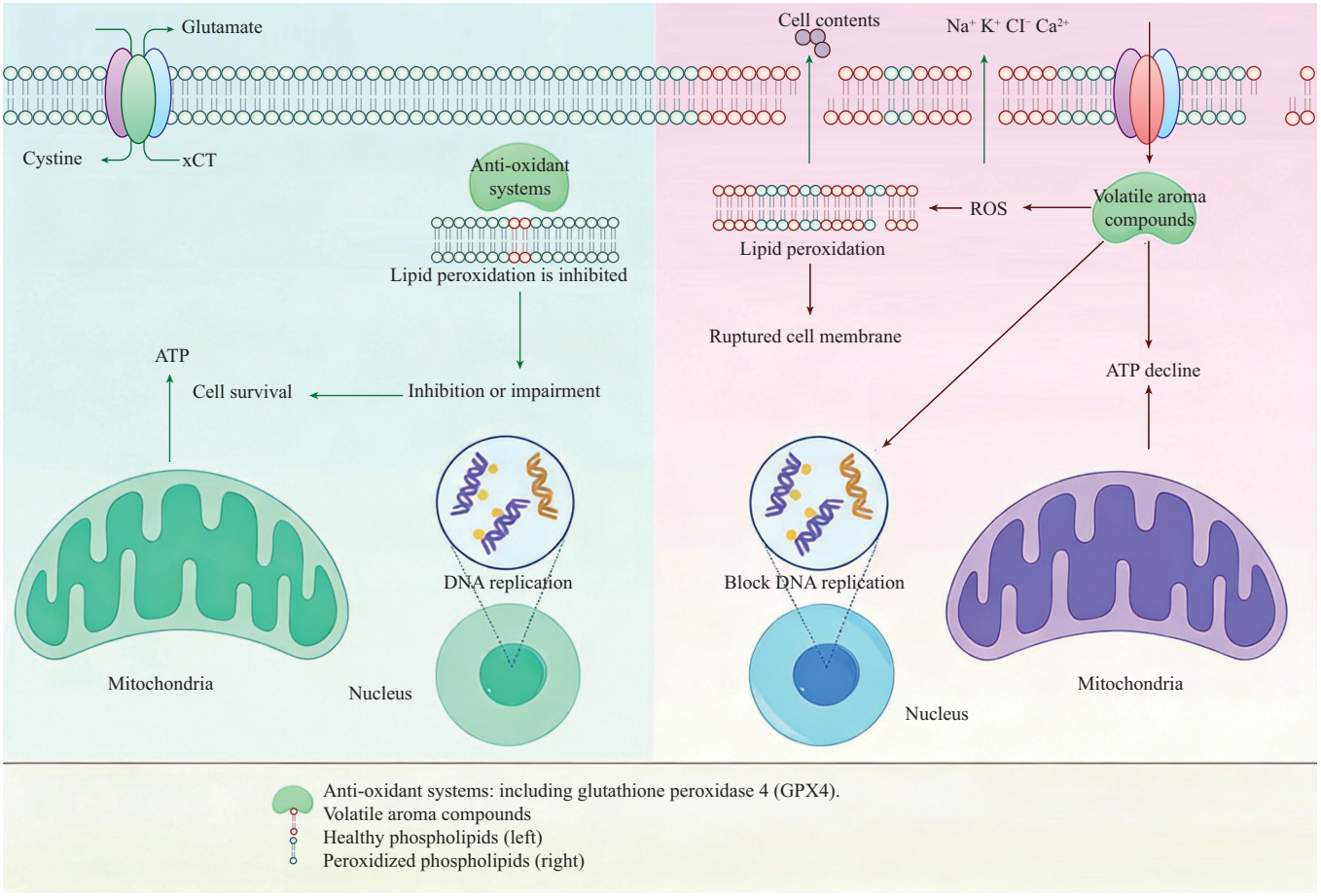


**Fig. 2** Antimicrobial mechanism of VOCs. On the left, are healthy phospholipids (protected by GSH maintaining cell membrane integrity). On the right, peroxidized phospholipids (volatile organic compounds disrupt the cell membrane, causing microbial cell morphological changes and leakage of cellular contents, VOCs disrupt the redox balance, increasing intracellular ROS levels, leading to lipid peroxidation, mitochondrial dysfunction, and decreased ATP levels).

VKAAs constitute a potent class of antimicrobial agents that interact with intracellular biomacromolecules such as proteins and nucleic acids within bacterial cells. These interactions disrupt the structural integrity of the biomolecules, thereby conferring antibacterial properties[1]. Decanoic and octanoic acids augment the intestinal epithelial immune barrier by inhibiting histone deacetylases, thereby playing a significant role in the production of antimicrobial peptides and defense mechanisms[131]. Nonanal has been shown to dramatically impede the growth of *Candida albicans* by severely compromising the integrity of fungal cell membranes. This results in the leakage of cellular constituents and potassium ions along with an increase in total lipid content, extracellular pH, and membrane permeability[132]. VOCs are produced through the disruption of bacterial cell membranes and inhibition of metabolic and biosynthetic processes in bacteria. However, the potency of these VOCs as antimicrobials depends on various factors, including their concentration, exposure duration, and environmental conditions. Optimizing these parameters is essential to maximize their antimicrobial effects. Moreover, advancements in VOC extraction are necessary to enhance its purity and stability, which, in turn, can augment its effectiveness. Continued research is vital for demystifying the full spectrum of antimicrobial mechanisms used by VOCs. Unraveling these mechanisms will deepen our understanding of their biological as well as refine their application strategies to improve their value in the food, medicine, and agriculture fields.

The continuous increase in multidrug-resistant microorganisms has become one of the greatest threats to public healthcare systems[133]. There is an acute demand for non-antibiotic therapeutic strategies to combat infections caused by resistant bacteria. Researchers have shown that numerous VOCs possess antimicrobial properties that target and disrupt bacterial cell membranes and walls to exert their effects[134]. Zhang et al.[70] demonstrated that a synergistic treatment involving carvacrol and blue light significantly reduced bacterial colony-forming units by up to 7.5 lg within 30 min in mice with burns infected with both Gram-negative (*Acinetobacter baumannii*) and Gram-positive (methicillin-resistant *S. aureus*) bacteria. This combined therapy exhibited minimal adverse effects on mammalian cell survival, wound healing, or host DNA integrity, and importantly, did not induce bacterial resistance even after 20 consecutive passages. Eugenol, whether used alone or in combination with carvacrol, has shown promising antibacterial activity against clinical strains of methicillin-resistant and methicillin-sensitive *S. aureus* biofilms, inhibiting biofilm formation and markedly reducing the expression of genes related to biofilm and enterotoxin production[130]. Cinnamaldehyde, a common preservative used in the food industry, inhibits the growth of multidrug-resistant bacteria, thereby ensuring food safety and hygiene[135]. The incorporation of linalool and $\alpha$-terpineol at a concentration of 0.4 mg/mL in toothpaste and mouthwash has been effective in controlling multidrug-resistant bacteria in the oral cavity, including periodontal pathogens and cariogenic bacteria, thus maintaining oral health[136]. VOCs have also been extensively used in medical disinfection and cleaning, extending the shelf life of food products in the food industry, and protecting crops from pathogen damage in agriculture, thereby enhancing crop yield and quality owing to their antimicrobial properties[1]. Therefore, VOCs hold significant promise for application in antimicrobial biological activities. However, our current understanding of the antimicrobial mechanisms of VOCs remains incomplete, necessitating further exploration. Future research should focus on the thorough elucidation of the antimicrobial mechanisms of VOCs to provide a robust theoretical foundation for their application in medicine, agriculture, and other sectors, optimizing the extraction and preparation methods of VOCs to enhance their purity and potency, and exploring the potential synergistic effects of VOCs with other antimicrobial agents to develop innovative antimicrobial formulations. In conclusion, as our understanding of the antimicrobial activity of VOCs deepens, we anticipate that more VOCs with efficient, low toxicity, and broad-spectrum antimicrobial properties will be discovered and harnessed. These discoveries are poised to make significant contributions to human health and overall quality of life.

### *4.2 Anticancer*

Cancer is a significant global health challenge that poses a threat to human life and well-being. Statistics from the World Health Organization (WHO) revealed that cancer is the second most common cause of death worldwide, accounting for nearly 10 million deaths annually. The rising incidence and mortality rates of cancer have a significant impact on the global public health infrastructure[137]. Currently, the primary treatment methods for cancer include surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy[10]. However, associated side effects (such as hair loss, nausea, and immune suppression) have propelled the pursuit of novel therapeutic strategies for cancer research[138]. In recent years, the spotlight has fallen increasingly on research concerning VOCs, a class of substances with distinctive biological activities in the context of cancer treatment. Certain VOCs, including menthol, geraniol, citronellal, and lauric acid, have shown potential for cancer therapy. They contribute to cancer treatment by inducing apoptosis in cancer cells, curbing their proliferation, and impeding tumor angiogenesis[10,51,58] (Fig. 3).

Researchers have shown that some VOCs can interfere with the growth cycle of cancer cells by inhibiting the activity of key enzymes, blocking signaling pathways, and inhibiting the proliferation of cancer cells[139] (Fig. 5). Yu et al.[10] conducted a study treating lung cancer in mice with citronellol, which induced the upregulation of TNF-α and RIP1/RIP3 activity while downregulating Caspase-3/Caspase-8 activity. This modulation ultimately leads to cell necrosis through the TNF-α pathway and ROS accumulation of ROS. Mariusz and team explored the impact of oxygenated *p*-menthane compounds, such as (–)-myrtenol, (–)-myrtanol, and (–)-myrtenal, on human colon tumor cells *in vitro*. Their findings revealed that these compounds exerted an inhibitory effect on human colon tumor cells by modulating mitochondrial enzyme activity, nitric oxide release, and membrane stability[140]. Myrtenal and $\beta$-elemene, among other compounds,have been shown to suppress carcinogenesis and induce apoptosis in cancer cells through signaling pathways involving TNF-α and the ROS-AMPK axis[75,141]. VOCs can also initiate apoptosis in cancer cells by activating apoptosis-associated genes or inhibiting the expression of anti-apoptotic factors, culminating in cancer cell death[139] (Fig. 3). Sheikh et al.[142] showed that citral induces p53- and ROS-mediated mitochondrial apoptosis in human colorectal cancer cells HCT116 and HT29. Carvacrol has been shown to induce apoptosis in human cervical cancer HeLa cells by inhibiting mitogen-activated protein kinase (MEK) and extracellular signal-regulated kinase (ERK) signaling pathways[143]. Furthermore, some VOCs can

impede the formation of blood vessels in cancer cells by disrupting the expression of angiogenic factors or blocking angiogenesis signaling pathways, effectively severing the blood supply necessary for cancer cell survival[144] (Fig. 3). Yang et al.[145] identified ferulic acid as a novel inhibitor of the fibroblast growth factor receptor 1 (FGFR1). It targets the PI3K-Akt signaling pathway mediated by FGFR1, thereby inhibiting melanoma growth and angiogenesis in both *in vivo* and *in vitro* vascular experiments. VOCs such as linalool, perillyl alcohol, and paeonol can directly interfere with the expression of key angiogenic factors, such as vascular endothelial growth factor (VEGF), in tumor cells, reducing their levels and inhibiting angiogenesis. In addition, they can interfere with signaling pathways, such as PI3K/AKT/mTOR, to disrupt the link between tumors and angiogenesis, thereby inducing tumor cell apoptosis[83,144,146] (Fig. 3).

Although considerable effort has been made to decipher the anti-cancer mechanisms of VOCs, their integration into cancer therapeutics remains nascent[83]. In early cancer detection, VOCs have emerged as promising non-invasive and expeditious quantitative tools, paving the way for timely cancer diagnosis[138]. As biotechnology and medical research continue to evolve, elucidation of the anticancer mechanisms of VOCs is expected to become increasingly precise. This will bolster the foundation for their application in cancer treatment and potentially transform these compounds into viable candidates for drug development. By refining their molecular structure and enhancing their purity, VOCs with anticancer bioactivities can be harnessed to create efficacious and minimally toxic anticancer medications. Furthermore, VOCs can be strategically used as adjunct therapies, complementing conventional treatments, such as chemotherapy and radiotherapy. This synergy can augment the efficacy of chemotherapeutic agents and increase the responsiveness of tumor cells to pharmacological interventions.

### 4.3 *Anti-inflammatory*

Inflammation is a critical physiological response to external stimuli or tissue injury, and serves as the innate defense mechanism of the body. However, excessive or chronic inflammation can precipitate a spectrum of diseases, including rheumatoid arthritis and inflammatory bowel disease[147]. The conventional arsenal against inflammation encompasses nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and acetaminophen, as well as corticosteroid medications such as prednisone[148]. Although these drugs have shown efficacy in managing inflammatory conditions, they have significant side effects and limitations, underscoring the need for alternative treatment strategies[147]. The quest for new anti-inflammatory therapies is driven by the need to enhance safety and tolerability profiles or target specific inflammatory pathways, thereby minimizing systemic adverse effects. In this context, VOCs have emerged as a promising avenue for anti-inflammatory interventions. They exhibit favorable biological activities and are associated with a reduced incidence of side effects, indicating their notable clinical significance[68] (Table 1).

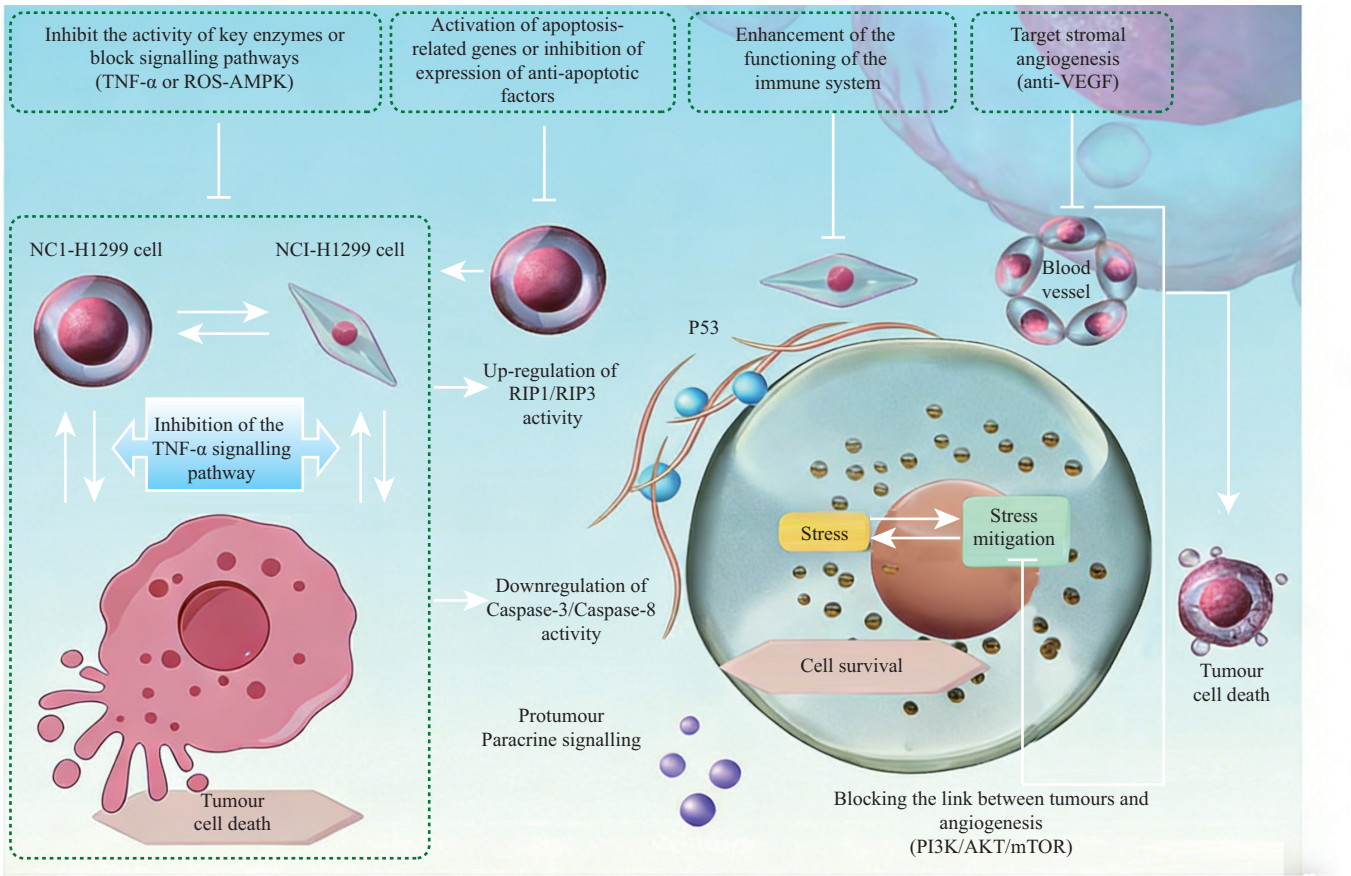


**Fig. 3** Anticancer mechanism of VOCs.

**Table 1**
Summary of bioactivity studies on commonVOCs.

| Compounds | Source | Odor properties | Concentration | Mechanism of actions | References |
|---|---|---|---|---|---|
| **Terpenoids** | | | | | |
| (–)-Menthol | *Perilla frutescens* (L.) Britt. | Peppermint scent | 0.8 mg/L | Antitumor by enhancing an antiproliferative activity of 1α,25(OH)2D3 in LNCaP prostatecancer cells | [49] |
| Sabinene | *Salvia japonica* Thunb. | Pine scent | 6.4 mg/kg | Anti-muscular atrophy by regulatingthe activation mechanism of ROS-mediated MAPK/MuRF-1 pathways in starved myotubes | [50] |
| Citronellol | *Rosa rugosa* Thunb. | Rose scent | 5.0 μg/mL | Antitumor by inducing necroptosis of NCI-H1299 cells *via* TNF-α pathwayand ROS accumulation | [10] |
| Geraniol | *R. rugosa* Thunb. | Rose scent | 0.25–1.00 mg/L | Antibacterial, antioxidant, improvement in diabetes, and antitumor-inhibiting cell proliferation and promoting apoptosis | [51] |
| *α*-Terpineol | *Amomum verum* Blackw. | Lilac scent | 4.0 μg/mL | Antibacterial by inhibiting periodontal and cariogenic bacteria, antifungal-leading to irreversible cellular disruption | [52] |
| Linalool | Burley tobacco | Citrus and rose scents | 1.0 mg/L | As a competitive antagonist of Nmethyl *d*-aspartate (NMDA) receptor, antitumor, anti-cardiotoxicity-regulating PPARα to reduce plasma thyroglobulin (TG) levels | [11,53] |
| *L*-Perillaldehyde | *P. frutescen*s (L.) Britt. | Peppermint scent | 0.965 mg/day | Antidepressants by regulating of the olfactory nervous system | [54] |
| Menthone | *Mentha canadensis* L. | Peppermint scent | 0–200 mg/kg | Antioxidation, anti-Inflammatory by inhibition of the secretion of the pro-inflammatory cytokine TNF-α and anti-inflammatory effects on LPS-stimulated lung mast cells | [55] |
| Myrcene | Cork fruit oil | Balsam scent | 0.015–1.500 mg/L | Anti-invasive action inhibits the cell cycle and leads to cancer cell apoptosis, anti-inflammation, and anti-inflammatory activity | [56] |
| (–)-Limonene | Citrus essential oils | Sweet orange and turpentine scents | 200 mg/L | Inducing a mild bronchoconstrictive effect, antioxidant and anti-inflammatory effect | [57] |
| *α*-Thujone | *Thuja occidentalis* L. | Cedar sidecar scent | 100–500 μg/mL | Antitumor: pro-apoptotic and anti-invasive effects on the spite of glioblastoma multiforme (GBM) cells, antinociceptive and anthelmintic | [58] |
| (–)-*α*-Pinene | Pinales | Pine scent | 25–100 mg/kg | Enhanced sleep through direct binding to GABAA-benzodiazepine receptors by acting as a partial modulator at the BZD binding site | [59] |
| Piperitone | *Piper nigrum* | Peppermint scent | | Antiappetent and Insecticidal activity | [60] |
| Perillyl alcohol | Lemon oil and perilla seed oil | Woody and floral scents | 0.25 mg/kg | Anti-cancer by inhibiting farnesylation of Ras upregulates the mannose-6-phosphate receptor and induces apoptosis | [61] |
| Myrtenal | Eucalyptus and myrtle oils | Peach and woody scents | 200 mg/kg | Antitumor by inhibiting liver cancer by preventing DEN-PB-induced upregulation of TNF-α protein expression | [62] |
| *γ*-Terpinene | Lemon oil | Citrus and lemon scents | 1.56–50.00 mg/kg | Antioxidant by generating hydroperoxyl (HOO•) radicals, antinociception | [63-64] |
| Umbellulone | Tamaricaceae link | Spicy mint scent | 7.46 mg/kg | Stimulating the TRPA1 channel in a subset of peptidergic, nociceptive neurons to activate the trigeminovascular system | [65] |
| *α*-Terpinyl acetate | Lavender oil | Lavender scent | | Inhibitory effect on cytochrome P450 2B6 enzymaticactivity | [66] |
| 3-Carene | Turpentine oil | Pine-like scent | | Inhibiting nociceptive stimulus-induced inflammatory infiltrates and COX-2 overexpression, and with antinociceptive effect | [67] |
| (*R*)-(–)-*α*-Phellandrene | Cinnamon oil | Pungencyscent | 50–200 mg/kg | Attenuating inflammatory response, and inducing DNA damage | [68-69] |
| Carvacrol | Thymus oil | Woody scent | 1–2 mg/mL | Inhibiting the growth of drug-resistant bacteria as a non-antibiotic substance | [70] |
| Eugenol | Clove oil | Clove and spice scents | 50 mg/kg | Antibacterial, anthelmintic, antioxidant activity, and inhibiting lipid peroxidation | [71] |
| Nerolidol | *Citrus* × *limon* (Linnaeus) Osbeck | Citrus and woody scents | 100 μg/mL | Antioxidant and antibacterial activities, potentiating the action of antibiotics | [72] |
| *β*-Caryophyllene | *Citrus* × *limon* (Linnaeus) Osbeck | Clove scent | 48 mg/kg | The anti-inflammatory effect involves CB2 receptor activation and the PPARγ pathway, anticancer and antimicrobial by inducing apoptosis *via* nuclear condensation and fragmentation pathways | [73-74] |
| *β*-Elemene | Rhizoma Wenyujin Concisum | Sweet scent | 0–200 μg/mL | Antitumor by enhancing cisplatin-induced apoptosis in bladder cancer cells through the ROS-AMPK signaling pathway | [75] |
| *β*-Farnesene | *Matricaria chamomilla* L. | Floral, green, and balsamic scents | 50 μg/mL | Antiviral and anticancer: inhibition of cell cycle protein-dependent kinase 2 (CDK2) and inducing apoptosis in HepG2 cells | [76] |
| Germacrone | *Ericaceae* Juss. | Pomegranate scent | | Inhibiting influenza virus infection through attenuating viral protein expression, RNA synthesis, and infectious progeny virus production in MDCK and A549 cells | [77] |
| *β*-Eudesmol | Eucalyptus oil | Camphorated sent | 50–100 mg/kg | Anti-inflammatory and antioxidant by activating NF-κB signaling | [78] |
| *α*-Bisabolol | Chamomile oil | Floral scent | 0–100 μmol/L | Anti-inflammatory and anticancer by inducing cell cycle arrest, mitochondrial apoptosis, and inhibition of PI3K/Akt signaling pathways | [79] |
| Santalol | *Santalum album* L. | Woody scent | | Anticancer: prevention of oral, breast, prostate, and skin cancers | [80] |

**Table 1** (*Continued*)

| Compounds | Source | Odor properties | Concentration | Mechanism of actions | References |
|---|---|---|---|---|---|
| *α*-Cedrene | Leaf tobacco | Woody scent | | Anti-leukemic, antimicrobial, and anti-obesity activities | [81] |
| Farnesol | Jasmine and neroli Oils | Floral scent | 10 μmol/L | Preventing neurodegeneration in Parkinson's disease: farnesol as an inhibitor of PARIS | [82] |
| **Phenols** | | | | | |
| Paeonol | *Paeonia* × *suffruticosa* Andrews | Green scent | 100–200 mg/kg | Inhibiting post-ischemic tissue damage, attenuating the inflammatory response, and inducing vasodilation | [83] |
| 4-Vinylsyringol | Natural decarboxylation of erucic acid | Animal leather scent | | Antioxidant by generating the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical and the superoxide anion radical | [84] |
| Apocynin | Vanilla bean | Sweet and vanilla scents | | Anti-aging by inhibiting NADPH oxidase and increases bone density and total bone mass | [85] |
| Vanillin | *Vanilla planifolia* Andrews | Vanilla bean and creamy scents | 5.0 mg/kg | Antagonist by regulating HIF-1α *via* inhibiting PGE2-cAMP signaling, antidepressant by elevating both serotonin and dopamine levels in brain tissue | [86-87] |
| 4-Methylum-belliferone | Vanilla bean | Vanilla scents | 0–2.0 mmol/L | Antiangiogenic by influencing endothelial cell proliferation, adhesion, tube formation, and extracellular matrix remodeling | [88] |
| Salicylic acid | Kiwi fruit | Nutty scent | 120 mg/kg | Inhibiting cyclo-oxygenase-2 (COX-2) activity independently of transcription factor (NF-κB) activation | [89] |
| Tyrosol | Compositae plants | Sweet floral and fruity scents | 100 μmol/L | Anti-oxidative and anti-inflammatory effects by attenuating pro-inflammatory cytokines from cultured astrocytes and NF-κB activation | [90-91] |
| Homovanillic acid | Aquifoliaceae Bercht. & J. Presl | Peppermint scent | | Treatment of Parkinson's disease | [92] |
| Guaiacol | Guaiacwood resin | Woody scent | | Anti-oxidative and anti-inflammatory activities by inhibiting COX-2 | [93] |
| Raspberry ketone | Raspberry juice | Sweet berry scent | 1–50 μmol/L | Inhibiting adipogenic and lipogenic gene expression in 3T3-L1 adipocytes | [94] |
| Methyl Paraben | Organic synthesis | Burning scent | 50 μg/kg | Increasing histamine release and cellular regulation of immunity, blocking sodium channels, and preventing ischemia-reperfusion injury | [95] |
| 4-Hydroxy-benzaldehyde | Organic synthesis | Almond and woody scents | 101.7 μmol/L | Withan antagonistic effect on the GABAA receptor of the α1β2γ2S subtype at high concentrations | [96] |
| 4-Vinylphenol | *Santalum album* L. | Phenolicscent | 100 μg/mL | Inducing apoptosis inhibiting blood vessel formation and suppressing invasive breast tumor growth *in vivo* | [97] |
| **Others (ketones, aldehydes, acids)** | | | | | |
| Nonanal | Rose and neroli oils | Fatty, rose and citrus scents | 6.23 g/kg | Antidiarrhoeal activity, antifungal by disrupting the integrity of the fungal cell membrane | [98-99] |
| Muscone | Moschus | Sweet musk scent | 50 mg/kg | Promoting myocardial glycolysis and inhibited NLRP3 pathway activation toimprove myocardial ischemia-reperfusion injury | [100-101] |
| Decanoic acid | Laurel and coconut oils | Fatty scent | 300 μmol/L | Treatment-resistant epilepsy through directAMPA receptor inhibition | [102] |
| Safranal | *Crocus sativus* L. | Tobacco and spicy scents | 500 mg/kg | Anti-inflammation by decreasing the productionand mRNA expression of IL-6 and TNF-α in the RAW264.7 cell line, etc. | [103] |
| Pentanoic acid | *Valeriana officinalis* L. | Cheesy scent | 2 mmol/L | Treatment of allergic skin diseases through activating ROCK signaling pathway | [104] |
| 1,3-Dihydroxy-acetone | Organic synthesis | Peppermint scent | | The main active ingredient in sunless tanning skin-care preparations | [105] |
| Maltol | Pine needles | Sweet caramel scent | 50–200 mg/kg | Attenuating diabeticperipheral neuropathy in streptozotocin-induced diabetic rats | [106] |
| Ethyl 3-methylthiop-ropionate | Organic synthesis | Metallic and pineapple scents | | Anticancer by promoting differentiation of colon cancer cells | [107] |
| 4-Ethylbenzaldehyde | Derivatives of benzaldehyde | Bitter almondscent | 11 mg/L | Ibuprofen degradation product with analgesic and anti-inflammatory properties | [108] |
| Nonanoic acid Octanoic acid | Organic synthesis | Cheese sent | | Anti-bacterial and defense peptide-induced roles by enhancing intestinal epithelial immunological barrier function viahistone deacetylase inhibition | [109] |
| Angelic Acid | *Angelica sinensis* (Oliv.) Diels | Pungent scent | 5–30 μmol/L | Angelic acid aids in wound healing and exhibits psychotropic properties | [110] |
| Cuminaldehyde | *Cuminum cyminum* L. | Spicy scent | | Anticancer with inhibitory effect on *a*-synuclein fibrillation and cytotoxicity | [111] |
| Octanal | Rose oil | Fruity scent | | Antioxidant and antimicrobial activities by showing cytotoxicity against Hela cells | [112] |
| Benzylacetone | Lignaloes | Floral scent | 7.4 μg/L | Appetite-enhancing and locomotor-reducing effects | [113] |
| 2-Amino-acetophenone | Organic synthesis | Grape sent | 381 mg/kg | As a potential breath biomarker for *Pseudomonas aeruginosa* in the cystic fibrosis lung | [114] |
| Sorbic acid | Fruits of plants | Fumes | | Inhibitor of most molds and yeasts and some bacteria | [115] |

VOCs have been shown to modulate inflammatory responses, offering a new frontier of anti-inflammatory therapy[148]. *β*-Patchoulene exerts a protective effect against lung injury in mice with LPS-induced acute lung injury by inhibiting the activation of the IκB-induced NF-κB pathway and its consequent gene expression, thus mitigating inflammation[149]. Xu et al.[150] discovered that *β*-eudesmol significantly mitigates the upregulation of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 while enhancing the levels of antioxidants such as superoxide dismutase (SOD) and glutathione (GSH), and reducing malondialdehyde (MDA) and myeloperoxidase (MPO) levels, thereby conferring protection against septic injury. (+/–)-Lavandulol has been shown to inhibit the activity of 5-lipoxygenase, impede the conversion of arachidonic acid to leukotrienes, and reduce associated inflammatory responses[151]. The anti-inflammatory effects of VOCs are achieved by regulating inflammatory signaling pathways, such as NF-κB and MAPK, and by inhibiting the synthesis and release of inflammatory mediators such as leukotrienes and prostaglandins[68,150] (Fig. 4). Moreover, VOCs, including menthone, tyrosol, octanoic acid, and nonanoic acid, can influence the activation, proliferation, and differentiation of immune cells, thereby fine-tuning the intensity and direction of immune responses[90-91] (Fig. 4). HSuan et al.[152] showed that the percutaneous absorption of menthone modulates the immune response by increasing serum OVA-specific IgG2a/IgG1 and IgG2a/IgE ratios and promoting splenic cell secretion of Th1-type cytokines, which alleviate allergic inflammatory responses in asthmatic mice. Luo et al.[91] reported that linalool regulates astrocyte inflammatory responses during ischemia by reducing the release of TNF-α and IL-6, suggesting its potential as an adjuvant therapy for stroke by modulating Janus N-terminal kinase (JNK).The antioxidant properties of VOCs contribute to their anti-inflammatory effects by neutralizing free radicals and curbing oxidative stress pathways[147] (Fig. 4). For example, metabolites of tyrosol produced in the intestines and liver can prevent the escalation of ROS, protect against the depletion of GSH, and downregulate key antioxidant enzymes, demonstrating their therapeutic potential in modulating inflammatory responses[90]. VOCs exert anti-inflammatory effects through various pathways, including scavenging free radicals, inhibiting oxidative stress, and regulating the synthesis and release of inflammatory mediators, which give them unique advantages in alleviating inflammatory symptoms such as redness, pain, and itching[68,131].

VOCs have a versatile array of anti-inflammatory applications. Their integration into cosmetics and skincare formulations ameliorates skin inflammation and promotes skin repair[18]. Moreover, VOCs are instrumental in the development of functional foods and pharmaceuticals designed to prevent and treat diseases with inflammatory components[18]. Plant-derived VOCs, such as menthol, and nerolidol have been used in aromatherapy and steam inhalation therapies to effectively address inflammatory conditions, such as arthritis and asthma[152-153]. These systems leverage the natural propensity of VOCs to evaporate or penetrate tissues and deliver therapeutic agents directly to the inflamed areas. This targeted approach amplifies the local efficacy of drugs as well as minimizes systemic side effects[80]. As a class of bioactive compounds with anti-inflammatory properties, VOCs have broad applications across the fields of medicine, cosmetics, and food. Future research should focus on uncovering the intricate anti-inflammatory mechanisms of VOCs, broadening their application spectrum, and conducting rigorous safety evaluations. Such

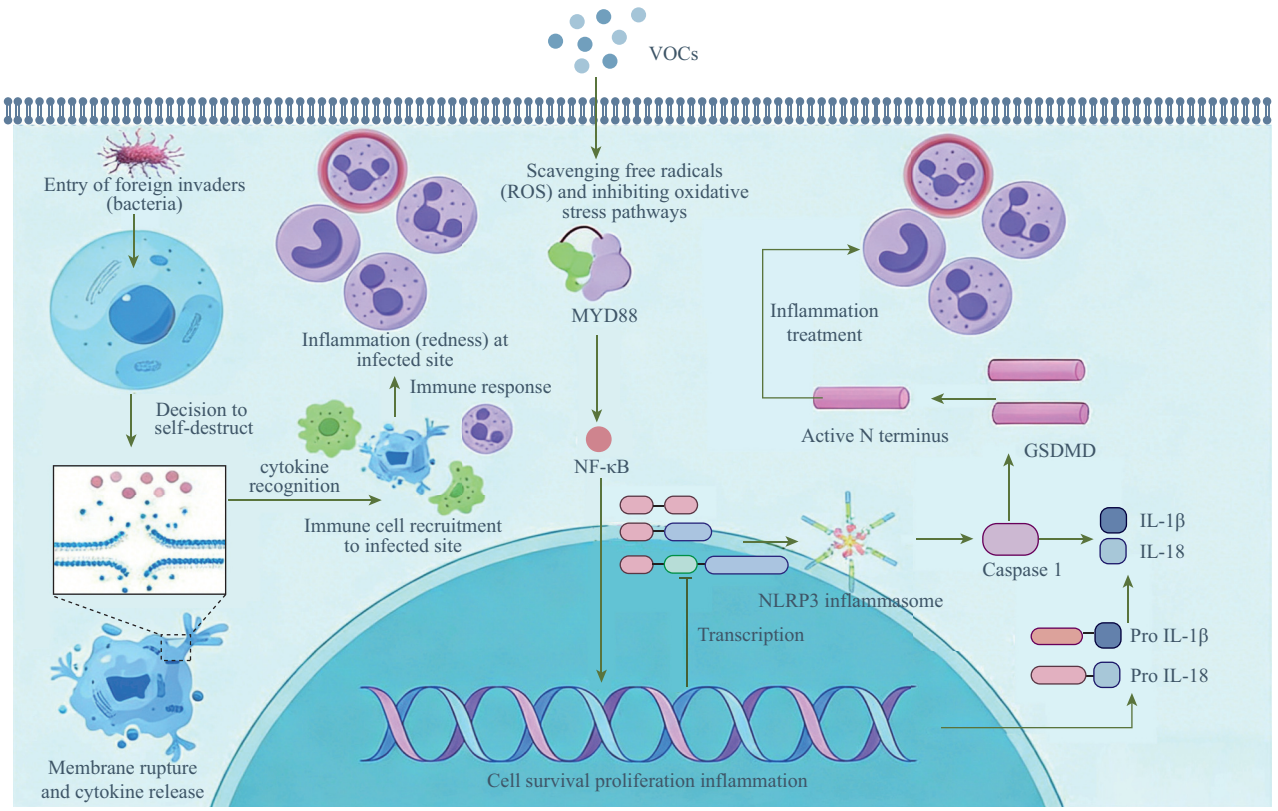


**Fig. 4** Anti-inflammatory mechanism of VOCs. On the left side, infections such as bacteria trigger inflammatory reactions such as redness and swelling. On the right side, VOCs treat inflammation by modulating signaling pathways such as TNF-α, scavenging free radicals, and inhibiting oxidative stress pathways.

investigations are pivotal for fortifying the foundation for the development of innovative anti-inflammatory medications and functional products.

### 4.4 Anti-oxidative

VOCs demonstrate potent antioxidant activity primarily through structurally active groups that engage with and neutralize free radicals, thereby mitigating oxidative stress in biological systems[154]. The antioxidant mechanisms of VOCs include free radical scavenging, inhibition of oxidative stress reactions, and modulation of the redox balance[133,155]. For instance, styrene, with its ethenyl group, can chemically interact with free radicals to neutralize their harmful effects. In biological organisms, styrene can undergo addition or substitution reactions with ROS such as superoxide anion radicals and hydroxyl radicals, converting them into stable compounds and safeguarding cells and tissues from oxidative damage[156]. Volatile phenolic compounds (such as phenol and cresol), which are characterized by their hydroxyl groups, also exhibit robust antioxidant properties. These groups can undergo hydrogen atom transfer reactions with free radicals, directly scavenging them and supporting cellular redox balance and antioxidant defenses by modulating redox enzyme activity or promoting endogenous antioxidant prouction[157-158]. Focusing on commercial sunflower oil, Mollica et al.[64] showed that $\gamma$-terpinene can extend the induction period of endogenous tocopherol, highlighting its potential as a natural antioxidant in high-temperature food applications. Dahham et al.[74] reported that $\beta$-caryophyllene can induce apoptosis in colon cancer cells through various pathways, including mitochondrial membrane potential disruption, showing its multifaceted potential as an anticancer, antioxidant, and antibacterial agent suitable for colorectal malignancy chemotherapy drugs. These findings highlight the capacity of certain VOCs to bolster cellular antioxidant defenses by modulating intracellular redox signaling pathways, influencing the activity of redox enzymes, and enhancing antioxidant generation[158]. Farag et al.[159] showed that some VOCs, such as cinnamaldehyde, can modulate oxidative stress responses by affecting intracellular signaling pathways such as NF-κB and MAPK, protecting cells from oxidative damage induced by agents such as cyadox. Currently, biomedical applications of VOCs are centered on their antioxidant, anticancer, and antimicrobial properties. VOCs (such as styrene) show promise for alleviating oxidative stress and may be instrumental in the prevention and treatment of cardiovascular diseases and cancer[156]. Phenolic compounds (such as eugenol), can reduce oxidative stress and inhibit low-density lipoprotein (LDL) oxidation, contributing to the management of cardiovascular diseases and prevention of atherosclerosis[160-161]. In addition, VOCs (such as coumarin and vanillin), contribute to the antioxidative and anti-inflammatory benefits of cosmetics for skin health[162]. Owing to their antioxidative properties, butylated hydroxyanisole and butylated hydroxytoluene extend the shelf life of food products by preventing oxidative deterioration during storage and transportation[163]. However, the application of VOCs in biomedicine faces several challenges, including elucidating their antioxidant mechanisms, dosage optimization, long-term safety assessments, and addressing potential toxicity concerns. Future research must delve into the mechanisms of action, optimal application strategies, and safety guidelines to harness the full spectrum of biological activities of VOCs while ensuring their safety and efficacy.

### 4.5 Anthelmintic

Plants have evolved the ability to disrupt insect behavior, including feeding, mating, and oviposition, by releasing VOCs[164]. Some VOCs (such as isoprene and linalool), exert direct effects on the insect nervous system by inducing aberrant behavior and impeding the ability of insects to locate their hosts, thus manifesting insecticidal properties[165]. Moreover, volatile phenolic compounds found in plants can interact with key enzymes or receptors in insects, impairing their physiological functions and directly inhibiting their growth and reproduction[164]. For instance, $\alpha$-pinene, a component of pine oil, can modulate insect juvenile hormone levels, disrupting the molting process and potentially leading to developmental abnormalities that reduce insect mortality or reproductive capacity[166]. In addition, VOCs can diminish insect feeding by emitting specific odors. Jasmone is known to inhibit feeding behavior in aphids and other pests[167]. In agriculture, the application of VOCs is primarily focused on plant protection and pest management. The cultivation of plants emitting insecticidal VOCs is an effective strategy to reduce pest populations, mitigate reliance on chemical pesticides, and foster sustainable agricultural practices[164]. Future research should explore the intricate interaction mechanisms between VOCs and insects, as well as the potential synergistic effects among different VOCs. Such studies are essential to provide a theoretical foundation for the development of more efficient and environmentally benign pest control strategies.

### 4.6 Anti-mood disorders

Mood disorders, which encompass conditions such as depression, bipolar disorder, anxiety, mood-related sleep disturbances, and binge eating disorders, represent a spectrum of mental illnesses that significantly affect emotional well-being and related functions. The current therapeutic landscape for mood disorders primarily comprises pharmacotherapy, psychotherapy, and physical therapy[14]. However, the financial burden associated with these treatments can be significant, affecting the patients and their families. Aromatherapy has emerged as an alternative and complementary approach that uses essential oils or VOCs to achieve therapeutic objectives[168]. Researchers have shown that some VOCs can directly influence the emotional and behavioral centers of the brain, such as the amygdala and hippocampus, through the olfactory system[168]. By interacting with specific olfactory receptors, these compounds can activate or inhibit associated neural pathways, thus modulating emotions and behaviors[14]. In addition, VOCs can indirectly modify the emotional state and behavioral responses of an individual through their effects on hormonal levels and metabolic processes, including the synthesis and release of neurotransmitters, such as serotonin and dopamine[169]. VOCs (such as linalool and linalyl acetate) can act as cholinergic inhibitors by altering the function of ion channels in neuromuscular junctions and interacting with gamma-aminobutyric (GABA) acid neurotransmitters and dopaminergic systems to serve as central nervous system (CNS) inhibitors[146,168]. Studies have shown that inhalation of perillaldehyde in a mouse model of depression exhibits antidepressant-like activity through olfactory nerve function[170]. Sánchez-Vidaña et al.[171] demonstrated that treating depressive model mice with lavender oil increases the complexity of immature neuronal

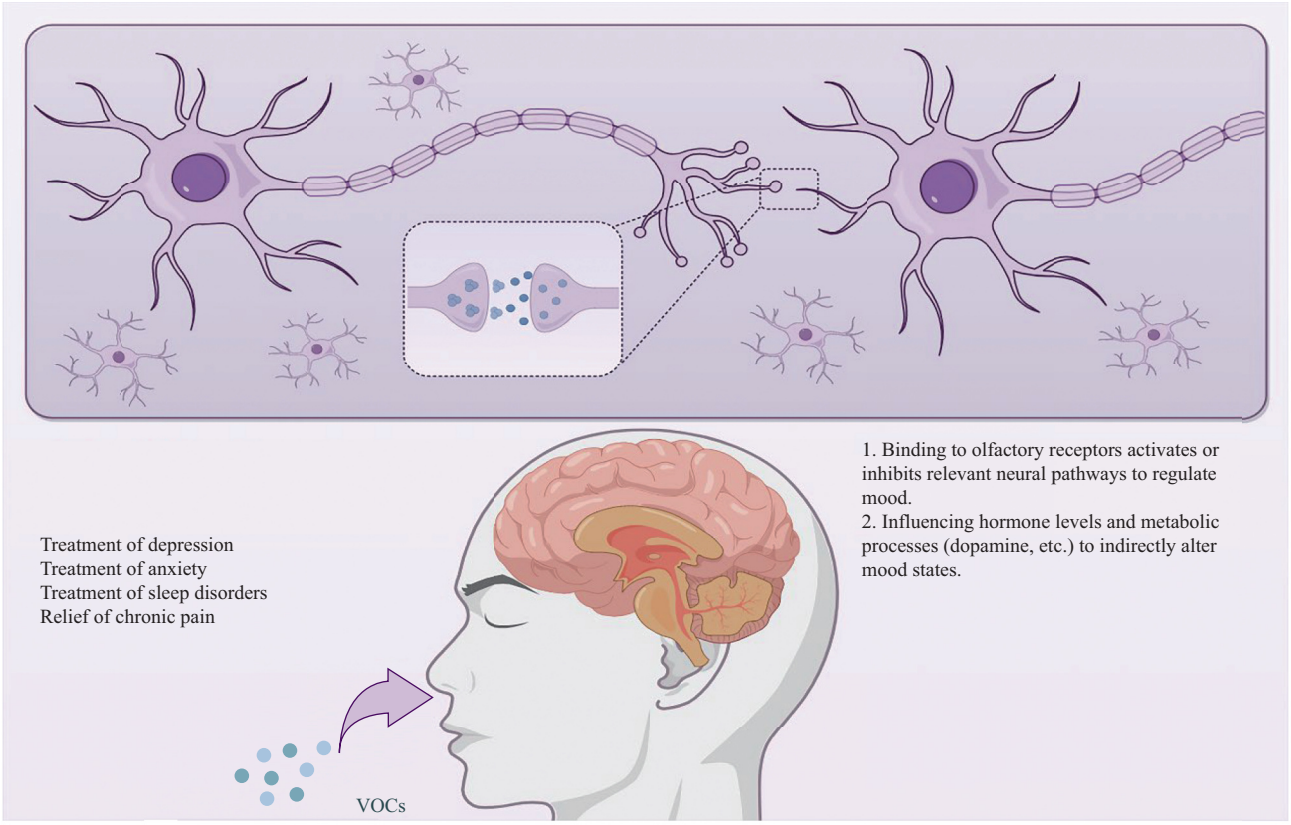


**Fig. 5** Mechanism of anti-mood disorder bioactivity of VOCs map.

dendrites and reduces the occurrence of depressive behaviors in mice. Once in the brain, they can influence the cerebral cortex, thalamus, and limbic system, potentially improving the symptoms of anxiety and depression and enhancing sleep quality[168] (Fig. 5).

Aromatherapy has achieved significant therapeutic success[170]. VOCs with sedative and antidepressant properties are increasingly recognized as valuable adjuncts in the treatment of emotional disorders such as anxiety and depression[4]. Through inhalation or topical application of these compounds, patients often report marked improvements in mood and symptom alleviation. Moreover, VOCs are used to enhance sleep quality and mitigate chronic pain, thereby offering patients a more comfortable and efficacious therapeutic alternatives[168,172]. Animal studies have demonstrated that lavender oil inhalation can ameliorate anxiety-like behaviors in rats, with a decrease in peripheral activity and open-field defecation observed after a 30-min exposure[173]. Pause et al.[174] showed that environments scented with citral were more attractive and pleasurable for people feeling sad. Studies have shown that sniffing aromatic molecules has little to no adverse effects, making aromatherapy a good option for treating mood disorders[175]. Both animal and clinical experimental data suggest that inhalation of aromatic molecules may offer higher efficiency than conventional treatments because the blood-brain barrier does not impede their effects[174]. This characteristic renders aromatherapy a simpler, more economical, and lower-risk complementary strategy for mood disorder management[171]. In conclusion, VOCs exhibit distinctive biologically active mechanisms and are valuable in the modulation of emotions and behavior. Further investigations into their mechanisms of action and regulatory modalities will enable us to harness these compounds more effectively to enhance emotional well-being and quality of life.

### *4.7 Other bioactivities*

VOCs have various physiological and ecological functions within biology. In addition to their established roles in antimicrobial, anticancer, anti-inflammatory, antioxidative, anthelmintic, and mood disorder mitigation activities, VOCs demonstrate neuroprotective and antiviral properties, regulate plant growth, and function as signaling molecules[3,8,29]. Recent studies have shown that specific VOCs, particularly terpenes, can mitigate neurodegenerative processes. This was achieved by modulating neurotransmitter levels and shielding neuronal cells from oxidative stress and apoptosis, unveiling promising avenues for the treatment of diseases such as Alzheimer's and Parkinson's diseases[3]. In addition, some VOCs, such as carvacrol, have shown promising results in accelerating wound healing by regulating local cytokine levels and promoting reepithelialization[176]. Pazyar et al.[177] showed that $\alpha$-terpinene can inhibit the activity of influenza viruses, herpes simplex virus, and other viruses. Volatile phenolic compounds have been shown to promote the growth of neighboring plants and enhance their stress resistance, which has significant implications for agricultural productivity and the development of innovative and eco-friendly plant growth regulators[4]. VOCs play a crucial role in communication between animals and plants[8]. Animals use specific VOCs to mark territories, attract mates, and alert conspecifics to threats. In the plant kingdom, VOCs attract pollinating insects and convey signals of

herbivore attack within plant communities[178]. The diverse biological activities of VOCs have garnered increasing interest because of their applications in food, medicine, and agriculture. As our understanding of the biological roles of VOCs deepens and as technological advancements progress, it is anticipated that an expanding array of VOC-based products will be developed and integrated into practical applications.

## 5. Conclusion and prospects

This review summarizes the latest advancements in understanding VOC biosynthesis, regulatory pathways, biological functions, and practical applications. The biosynthetic pathways of VOCs are intricately woven and are primarily categorized into volatile phenolics, terpenoids, and ketones/aldehydes/acids. The MVA and MEP pathways are central to these processes, and key enzymes and regulatory elements are crucial in VOC production. VOCs exert their biological effects through a broad spectrum of mechanisms. They can inhibit key enzymatic activities, disrupt energy metabolism and biosynthetic routes, modulate the expression of genes involved in apoptosis, neutralize free radicals, mitigate oxidative stress, and influence the CNS by engaging specific neural pathways. These multifaceted actions endow VOCs with antibacterial, anticancer, and anti-inflammatory properties, underpinning their potential for use in food preservation, medicinal applications, and agricultural disease prevention. In practical terms, VOCs have demonstrated considerable promise in controlling foodborne pathogens, managing agricultural diseases, and serving the medical and cosmetic industries. Technological advancements in the extraction and preparation of VOCs encompassing both traditional methods and cutting-edge synthetic biology techniques have provided robust support for the large-scale production and application of these versatile compounds.

The rapid evolution of nanotechnology and biotechnology has driven continuous innovations in the extraction, synthesis, and application of VOCs. Through precise engineering and redesign of key enzymes and regulatory elements within VOC biosynthetic pathways, efficient and targeted synthesis of these compounds can be realized. Through gene editing technologies, such as CRISPR-Cas9, the expression of genes pivotal to VOC synthesis can be finely tuned to optimize the performance of production strains. Moreover, the construction of artificial synthetic pathways opens the door to the *de novo* synthesis of novel VOC molecules, offering innovative avenues for drug development and the flavor and fragrance industries. Advancements in nanotechnology and bioengineering are anticipated to enhance the extraction and purification of VOCs and improve their yield and purity. Amidst the global focus on environmental protection and sustainable development, VOCs, as natural and biodegradable compounds, are poised to replace traditional chemicals in various sectors. In the food industry, VOCs can be used as natural preservatives and flavoring agents to enhance food safety and quality. In agriculture, they can act as biological pesticides and fertilizers, potentially reducing the reliance on chemical pesticides. In the medical field, some VOCs endowed with antibacterial, anti-inflammatory, and antioxidant properties offer therapeutic benefits against skin infections and inflammatory diseases. Despite the diverse biological activities and significant application potential of VOCs, VOC extraction and purification face significant economic challenges. Traditional extraction methods, such as distillation and solvent extraction, are hampered by their high energy consumption and suboptimal efficiency. Although innovative technologies (supercritical fluid extraction and microwave-assisted extraction) offer greater efficiency, their high equipment costs represent a barrier to their wider adoption. Therefore, reducing VOC extraction and purification costs is a critical priority in the field. In addition, a thorough investigation of the safety and toxicological profiles of VOCs is imperative to guarantee their secure application in sensitive sectors, such as medicine and food. Looking ahead, the ongoing evolution of emerging technologies, coupled with in-depth interdisciplinary research, is set to unlock broader development prospects for the study and application of VOCs.

## Conflict of interest

The authors declare no conflict of interest.

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### Reference

[1] Q. Ma, Y.Q. Xu, H. Xiao, et al., Rethinking of botanical volatile organic compounds applied in food preservation: challenges in acquisition, application, microbial inhibition, and stimulation, Trends Food Sci. Technol. 125 (2022) 166-184. https://doi.org/10.1016/j.tifs.2022.05.007.

[2] Z. Qiao, H. Hu, S. Shi, et al., An update on the function, biosynthesis, and regulation of floral volatile terpenoids, Horticulturae 7(11) (2018) 451. https://doi.org/10.3390/horticulturae7110451.

[3] A. Masyita, R.M. Sari, A.D. Astuti, et al., Terpenes and terpenoids as main bioactive compounds of essential oils, their roles in human health and potential application as natural food preservatives, Food Chem.: X 13 (2022) 100217. https://doi.org/10.1016/j.phyplu.2024.100549.

[4] J. Dai, R.J. Mumper, Plant phenolics: extraction, analysis and their antioxidant and anticancer properties, Molecules 15 (2010) 7313-7352. https://doi.org/10.1016/j.plaphy.2013.05.009.

[5] X. Zhao, J. Zhou, R. Tian, et al., Microbial volatile organic compounds: antifungal mechanisms, applications, and challenges, Front. Microbiol. 13 (2022) 922450. https://doi.org/10.3389/fmicb.2022.922450.

[6] A. Farhat, Y. Ke, Y. Rangcai, et al., Volatile terpenoids: multiple functions, biosynthesis, modulation and manipulation by genetic engineering, Planta 246(5) (2022) 803-816. https://doi.org/10.1007/s00425-017-2749-x.

[7] L.M. Babenko, O. Smirno, K. Romanenko, et al., Phenolic compounds in plants: biogenesis and functions, Ukr. Biokhim. Zh. 91 (2019) 5-18. https://doi.org/10.15407/ubj91.03.005.

[8] R. Li, K. Wang, D. Wang, et al., Production of plant volatile terpenoids (rose oil) by yeast cell factories, Green Chem. 23(14) (2021) 5088-5096. https://doi.org/10.1039/D1GC00917F.

[9] C. Zhang, K. Hong., Production of terpenoids by synthetic biology approaches, Front. Bioeng. Biotechnol. 8 (2020) 347. https://doi.org/10.3389/fbioe.2020.00347.

[10] W. Yu, Y. Lai, J. Ma, et al., Citronellol induces necroptosis of human lung cancer cells *via* TNF-α pathway and reactive oxygen species accumulation, *In Vivo* 33 (4) (2019) 1193-1201.https://doi.org/ 10.21873/invivo.11590.

[11] I. Pereira, P. Severino, A.C. Santos, et al., Linalool bioactive properties and potential applicability in drug delivery systems, Colloids Surf. B. Biointerfaces 1(17) (2018) 566-578. https://doi.org/10.1194/ jlr.M045807.

[12] J. Ma, J. Li, K. Wang, et al., Perillyl alcohol efficiently scavenges activity of cellular ROS and inhibits the translational expression of hypoxia-inducible

factor-1 α *via* mTOR/4E-BP1 signaling pathways, Int. Immunopharmacol. 39 (2016) 1-9. https://doi.org/10.1016/j.intimp.2016.06.034.

[13] T.A.N. Ribeiro, G.A. dos Santos, C.T. dos Santos, et al., Eugenol as a promising antibiofilm and anti-quorum sensing agent: a systematic review, Microbial Pathogenesis 196 (2015) 106937. https://doi.org/10.1371/journal.pone.0119564.

[14] X. Chen, C. Wang, Q. He, et al., Chemical composition and potential properties in mental illness (anxiety, depression, and insomnia) of agarwood essential oil: areview, Molecules 27(14) (2022) 4528. https://doi.org/10.3390/molecules27144528.

[15] M. Fan, S. Yuan, L. Li, et al., Application of terpenoid compounds in food and pharmaceutical products, Fermentation 9(2) (2023) 119. https://doi.org/10.3390/fermentation9020119.

[16] P. Jeandet, Y. Vasserot, T. Chastang, et al., Engineering microbial cells for the biosynthesis of natural compounds of pharmaceutical significance, Biomed. Res. Int. 9 (2013) 780145. https://doi.org/10.1155/2013/780145.

[17] J.L. Bicas, A.P. Dionisio, G.M. Pastore, et al., Bio-oxidation of terpenes: an approach for the flavor industry, Chem. Rev. 109(9) (2009) 4518-4531. https://doi.org/10.1021/cr800190y.

[18] J. Hui, J.W. Xi, Biosynthesis of monoterpenoid and sesquiterpenoid as natural flavors and fragrances, Biotechnol. Adv. 65 (2023) 108151-108151. https://doi.org/10.1016/j.biotechadv.2023.108151.

[19] Z. Zhang, Q. Wu, Y. Ge, et al., Hydroxylases involved in terpenoid biosynthesis: a review, Bioresour. Bioprocess. 10(1) (2023) 39. https://doi.org/10.1186/s40643-023-00656-1.

[20] Q. Wang, R. Cao, Y. Zhang, et al., Biosynthesis and regulation of terpenoids from basidiomycetes: exploration of new research, Amb. Express. 11(1) (2011) 150. https://doi.org/10.1186/s13568-021-01304-7.

[21] P.K. Ajikumar, K. Tyo, S. Carlsen, et al. Terpenoids: opportunities for biosynthesis of natural product drugs using engineered microorganisms, Mol. Pharm. 5(2) (2008) 167-190. https://doi.org/10.1021/mp700151b.

[22] X. Chen, C. Zhang, N. D. Lindley, Metabolic engineering strategies for sustainable terpenoid flavor and fragrance synthesis, J. Agric. Food Chem. 68(38) (2020) 10252-10264. https://doi.org/10.1021/acs.jafc.9b06203.

[23] L. Daviet, M. Schalk, Biotechnology in plant essential oil production: progress and perspective in metabolic engineering of the terpene pathway, Flavour Fragr. J. 25(3) (2010) 123-127. https://doi.org/10.1002/ffj.1981.

[24] J.M. Clomburg, S. Qian, Z. Tan, et al., The isoprenoid alcohol pathway, a synthetic route for isoprenoid biosynthesis, PNAS 116(26) (2019) 12810-12815. https://doi.org/10.1073/pnas.1821004116.

[25] A.O. Chatzivasileiou, V. Ward, S.M. Edgar, et al., Two-step pathway for isoprenoid synthesis, PNAS 116(2) (2019) 506-511. https://doi.org/10.1073/pnas.1812935116.

[26] X. Lu, Y. Liu, Y. Yang, et al., Constructing a synthetic pathway for acetyl-coenzyme A from one-carbon through enzyme design, Nat. Commun. 10(1) (2019) 1378. https://doi.org/10.1038/s41467-019-09095-z.

[27] F.M. Carrau, K. Medina, E. Boido, et al., *De novo* synthesis of monoterpenes by *Saccharomyces cerevisiae* wine yeasts, FEMS Microbiol. Lett. 243(1) (2005) 107-115. https://doi.org/10.1016/j.femsle.2004.11.050.

[28] C. Wang, L. Mudanguli, J.B. Park, et al., Microbial platform for terpenoid production: *Escherichia coli* and yeast, Front. Microbiol. 9 (2018) 2460. https://doi.org/10.3389/fmicb.2018.02460.

[29] R. Marchiosi, W.D. Dos Santos, R.P. Constantin, et al., Biosynthesis and metabolic actions of simple phenolic acids in plants, Phytochem. Rev. 19(4) (2020) 865-906. https://doi.org/10.1007/s11101-020-09689-2.

[30] A. Schieber, M. Wuest, Volatile phenols-important contributors to the aroma of plant-derived foods, Molecules 25(19) (2020) 4529. https://doi.org/10.3390/molecules25194529.

[31] N. Santos Sánchez, R. Salas-Coronado, B. Hernandez-Carlos, Shikimic acid pathway in biosynthesis of phenolic compounds, in: M. Soto-Hemández, R. Garcia-Mateos, M. Palma-Tenango (eds), Plant physiological aspects of phenolic compounds. 2019. https://doi.org/10.5772/intechopen.83815.

[32] N.J. Gallage, B.L. Moeller, Vanillin-bioconversion and bioengineering of the most popular plant flavour and its *de novo* biosynthesis in the vanilla orchid, Mol. Plant. 8(1) (2014) 40-57. https://doi.org/10.1016/j.molp.2014.11.008.

[33] G. Fuchs, M. Boll, J. Heider, et al., Microbial degradation of aromatic compounds-from one strategy to four, Nat. Rev. Microbiol. 9(11) (2011) 803-816. https://doi.org/10.1038/nrmicro2652.

[34] D. Huccetogullari, Z. Luo, S.Y. Lee, Metabolic engineering of microorganisms for production of aromatic compounds, Microb. Cell Fact. 18(1) (2019) 41. https://doi.org/10.1186/s12934-019-1090-4.

[35] M. Suastegui, Z. Shao, Yeast factories for the production of aromatic compounds: from building blocks to plant secondary metabolites, J. Ind. Microbiol. Biotechnol. 43(11) (2016) 1611-1624. https://doi.org/10.1007/s10295-016-1824-9.

[36] K. Dell, J.W. Frost, Identification and removal of impediments to biocatalytic synthesis of aromatics from *D*-glucose: rate-limiting enzymes in the common pathway of aromatic amino acid biosynthesis, J. Am. Chem. Soc. 115 (1993) 11581-11589. https://doi.org/10.1021/JA00077A065.

[37] D.G. An, M.N. Cha, S.P. Nadarajan, et al., Bacterial synthesis of four hydroxycinnamic acids, Appl. Biol. Chem. 59(2) (2016) 173-179. https://doi.org/10.1007/s13765-015-0137-4.

[38] J. Ahn, B.K.S. Chung, D.Y. Lee, et al., NADPH-dependent *pgi*-gene knockout *Escherichia coli* metabolism producing shikimate on different carbon sources, FEMS Microbiol. Lett. 324(1) (2011)10-16. https://doi.org/10.1111/j.1574-6968.2011.02378.x.

[39] K. Gottlieb, C. Albermann, G.A. Sprenger, Improvement of *L*-phenylalanine production from glycerol by recombinant *Escherichia coli* strains: the role of extra copies of *glpK*, *glpX*, and *tktA* genes, Microb. Cell Fact. 13(1) (2014) 96. https://doi.org/10.1186/s12934-014-0096-1.

[40] P. Gu, X. Fan, Q. Liang Q, et al., Novel technologies combined with traditional metabolic engineering strategies facilitate the construction of shikimate-producing *Escherichia coli*, Microb. Cell Fact. 16(1) (2017) 167. https://doi.org/10.1186/s12934-017-0773-y.

[41] A.R. Awan, W.M. Shaw, T. Ellis., Biosynthesis of therapeutic natural products using synthetic biology, Adv. Drug Deliv. Rev. 105 (2016) 96-106. https://doi.org/10.1016/j.addr.2016.04.010.

[42] J.S. Dickschat, H.B. Bode, S.C. Wenzel, et al., Biosynthesis and identification of volatiles released by the myxobacterium *Stigmatella aurantiaca*, ChemDioChem 6(11) (2005) 2023-2033. https://doi.org/10.1002/cbic.200500174.

[43] M.S. Wright, D.M. Greene-McDowelle, H.J. Zeringue Jr, et al., Effects of volatile aldehydes from *Aspergillus*-resistant varieties of corn on *Aspergillus parasiticus* growth and aflatoxin biosynthesis, Toxicon 38(9) (2000) 1215-1223. https://doi.org/10.1016/s0041-0101(99)00221-4.

[44] N. Dudareva, A. Klempien, J.K. Muhlemann, et al., Biosynthesis, function and metabolic engineering of plant volatile organic compounds, New Phytol. 198(1) (2013) 16-32. https://doi.org/10.1111/nph.12145.

[45] I. Maoz, E. Lewinsohn, I. Gonda, Amino acids metabolism as a source for aroma volatiles biosynthesis, Curr. Opin. Plant Biol. 67 (2022) 102221. https://doi.org/10.1016/j.pbi.2022.102221.

[46] J.L. Rodrigues, M.R. Couto, R.G. Araujo, et al., Hydroxycinnamic acids and curcumin production in engineered *Escherichia coli* using heat shock promoters, Biochem. Eng. J. 125 (2017) 41-49. https://doi.org/10.1016/j.bej.2017.05.015.

[47] A.M. Kunjapur, Y. Tarasova, K.L.J. Prather, Synthesis and accumulation of aromatic aldehydes in an engineered strain of *Escherichia coli*, J. Am. Chem. Soc. 136(33) (2014) 11644-11654. https://doi.org/10.1021/ja506664a.

[48] P. Xu, S. Ranganathan, Z.L. Fowler, et al., Genome-scale metabolic network modeling results in minimal interventions that cooperatively force carbon flux towards malonyl-CoA, Metab. Eng. 13(5) (2011) 578-587. https://doi.org/10.1016/j.ymben.2011.06.008.

[49] E.J. Park, S.H. Kim, B.J. Kim, et al., Menthol enhances an antiproliferative activity of 1a, 25-dihydroxyvitamin $D_3$ in LNCaP cells, J. Clin. Biochem. Nutr. 44(2) (2009) 125-130. https://doi.org/10.3164/jcbn.08-201.

[50] Y. Ryu, D. Lee, S.H. Jung, et al., Sabinene prevents skeletal muscle atrophy by inhibiting the MAPK-MuRF-1 pathway in rats, Int. J. Mol. Sci. 20(19) (2019) 4955. https://doi.org/10.3390/ijms20194955.

[51] S. Babukumar, V. Vinothkumar, C. Sankaranarayanan, et al., a natural monoterpene, ameliorates hyperglycemia by attenuating the key enzymes of carbohydrate metabolism in streptozotocin-induced diabetic rats, Pharm. Biol. 55(1) (2017) 1442-1449. https://doi.org/10.1080/13880209.2017.1301494.

[52] L. Li, C. Shi, Z. Yin, et al., Antibacterial activity of *α*-terpineol may induce morphostructural alterations in *Escherichia coli*, Braz. J. Microbiol. 45(4) (2015) 1409 -1413. https://doi.org/10.1590/s1517-83822014000400035.

[53] E. Altinoz, Z. Oner, H. Elbe, et al., The protective and therapeutic effects of linalool against doxorubicin-induced cardiotoxicity in Wistar albino rats, Hum. Exp. Toxicol. 38(7) (2019) 803-813. https://doi.org/10.1177/0960327119842634.

[54] H. Xue, R. Dong, R. Zhang, et al., The structural properties, biological activities, and applications of perillaldehyde: an updated overview, Evid. J. Agric. Food Res. 28(2026) 102910. https://doi.org/10.1093/ecam/nen045.

[55] Y. Su, J. Lin. Menthone supplementation protects from allergic inflammation in the lungs of asthmatic mice, Eur. J. Pharmacol. 931(2022) 175222. https://doi.org/10.1016/j.ejphar.2022.175222.

[56] E. Hwang, H.T.T. Ngo, B. Park, et al., Myrcene, an aromatic volatile compound, ameliorates human skin extrinsic aging *via* regulation of MMPs production, Am. J. Chin. Med. 45(5) (2017) 1113-1124. https://doi.org/10.1142/s0192415x17500604.

[57] S.T. Larsen, K.S. Hougaard, M. Hammer, et al., Effects of *R*-(+)-and *S*-(–)-limonene on the respiratory tract in mice, Hum. Exp. Toxicol. 19 (2009) 457-466. https://doi.org/10.1164/rccm.202110-2360LE.

[58] M. Pudełek, J. Catapano, P. Kochanowski, et al., Therapeutic potential of monoterpene *α*-thujone, the main compound of *Thuja occidentalis* L. essential oil, against malignant glioblastoma multiforme cells *in vitro*, Fitoterapia 134 (2019) 172-181. https://doi.org/10.1016/j.fitote.2019.02.020.

[59] H. Yang, J. Woo, A.N. Pae, et al., *α*-Pinene, a major constituent of pine tree oils, enhances non-rapid eye movement sleep in mice through GABA *α*-benzodiazepine receptors, Mol. Pharmacol. 90(5) (2016) 530-539. https://doi.org/10.1124/mol.116.105080.

[60] G.K. Ketoh, A.I. Glitho, J. Huignard, et al., Comparative effects of *Cymbopogon schoenanthus* essential oil and piperitone on *Callosobruchus maculates* development, Fitoterapia 77(7-8) (2006) 506-510. https://doi.org/10.1016/j.fitote.2006.05.031.

[61] B.W. Liston, R.Nines, P.S. Carlton, et al., Perillyl alcohol as a chemopreventive agent in *N*-nitrosomethylbenzylamine-induced rat esophageal tumorigenesis, Cancer Res. 63(10) (2003) 2399-2403. https://doi.org/10.1016/j.fitote.12750258.

[62] L.H. Babu, S. Perumal, M.P. Balasubramanian, Myrtenal attenuates diethylnitrosamine-induced hepatocellular carcinoma in rats by stabilizing intrinsic antioxidants and modulating apoptotic and anti-apoptotic cascades, Cell Oncol. 35(4) (2012) 269-83. https://doi.org/10.1007/s11010-012-1381-0.

[63] F.F. de Brito Passos, E.M. Lopes, J.M. de Araujo, et al., Involvement of cholinergic and opioid system in *γ*-terpinene-mediated antinociception, Evid. Based Complement. Alternat. Med. 2015(2015) 829414. https://doi.org/10.1155/2015/829414.

[64] F. Mollica, I. Gelabert, R. Amorati, Synergic antioxidant effects of the essential oil component *γ*-terpinene on high temperature oil oxidation, ACS Food Sci. Technol. 2(6) (2022) 1050. https://doi.org/10.1021/acsfoodscitech.2c00156.

[65] R. Nassini, S. Materazzi, J. Vriens, et al., The 'headache tree' *via* umbellulone and TRPA1 activates the trigeminovascular system, Brain 135 (2012) 376-390. https://doi.org/10.1093/brain/awr272.

[66] Y. Lee, H.G. Park, V. Kim, et al., Inhibitory effect of *α*-terpinyl acetate on cytochrome P450 2B6 enzymatic activity, Chem. Biol. Interact. 289 (2018) 90-97. https://doi.org/10.1016/j.cbi.2018.04.029.

[67] X. Huang, X. Li, Q. Qin, et al., Anti-inflammatory and antinociceptive effects of active ingredients in the essential oils from *Gynura procumbens*, a traditional medicine and a new and popular food material, J. Ethnopharmacol. 239 (2019) 111916. https://doi.org/10.1016/j.jep.2019.111916.

[68] H. Siqueira, B.S. Neto, D.P. Sousa, et al., *α*-Phellandrene, a cyclic monoterpene, attenuates inflammatory response through neutrophil migration inhibition and mast cell degranulation, Life Sci. 160 (2016) 27-33. https://doi.org/10.1016/j.lfs.2016.07.008.

[69] J.J. Lin, C.C. Yu, K.W. Lu, et al., *α*-Phellandrene alters expression of genes associated with DNA damage, cell cycle, and apoptosis in murine leukemia WEHI-3 cells. Anticancer Res. 34(8) (2014) 4161-80.

[70] K. Zhang, Y. Xu, Y. Zheng, et al., Bifidobacterium pseudolongum-derived bile acid from dietary carvacrol and thymol supplementation attenuates colitis *via* cGMP-PKG-mTORC1 pathway, Adv. Sci. 11(43) (2024) e2406917. https://doi.org/10.1002/advs.202406917.

[71] D. Garabadu, A. Shah, S. Singh, et al., Protective effect of eugenol against restraint stress-induced gastrointestinal dysfunction: potential use in irritable bowel syndrome, Pharm. Biol. 53(7) (2015) 968-974. https://doi.org/10.3109/13880209.2014.950674.

[72] R. Carvalho, A. Almeida, N. Campelo, et al., Nerolidol and its pharmacological application in treating neurodegenerative diseases: a review, Recent Pat. Biotechnol. 12(3) (2018) 158-168. https://doi.org/10.2174/1872208312666171206123805.

[73] Y. Cheng, Z. Dong, S. Liu, *β*-Caryophyllene ameliorates the Alzheimer-like phenotype in APP/PS1 mice through CB2 receptor activation and the PPAR *γ* pathway, Pharmacology 94(1-2) (2014) 1-12. https://doi.org/10.1159/000362689.

[74] S.S. Dahham, Y.M. Tabana, M.A. Iqbal, et al. The anticancer, antioxidant and antimicrobial properties of the sesquiterpene *β*-caryophyllene from the essential oil of *Aquilaria crassna*, Molecules 20(7) (2015) 11808-11829. https://doi.org/10.3390/molecules200711808.

[75] D. Gan, W. He, H. Yin, et al., *β*-Elemene enhances cisplatin-induced apoptosis in bladder cancer cells through the ROS-AMPK signaling pathway, Oncol. Lett. 19(1) (2020) 291-300. https://doi.org/10.3892/ol.2019.11103.

[76] U.K. Torky, O.A. Eldahshan, E.A. Abdelghffar, et al., Chemical profiling, antiviral and antiproliferative activities of the essential oil of *Phlomis aurea Decne* grown in Egypt, Food Funct. 12(10) (2021) 4630-4643. https://doi.org/10.1039/d0fo03417g.

[77] Q. Liao, Z. Qian, R. Liu, et al., Germacrone inhibits early stages of influenza virus infection, Antiviral Res. 100(3) (2013) 578-588. https://doi.org/10.1016/j.antiviral.2013.09.021.

[78] G.Y. Deniz, F. Geyikoglu, Amelioration of diethylnitrosamine-induced acute brain injury by α-eudesmol and *β*-eudesmol, Toxicon. 226 (2025) 108550. https://doi.org/10.1016/j.toxicon.2025.108550.

[79] S. Wu, L. Peng, H. Sang, et al., Anticancer effects of *α*-bisabolol in human non-small cell lung carcinoma cells are mediated *via* apoptosis induction, cell cycle arrest, inhibition of cell migration and invasion and upregulation of P13K/AKT signalling pathway, J. Buon. 23(5) (2018) 1407-1412. https://doi.org/10.1016/j.fitote.12750258.

[80] A. Bommareddy, S. Brozena, J. Steigerwalt, et al., Medicinal properties of alpha-santalol, a naturally occurring constituent of sandalwood oil: review, Nat. Prod. Res. 33(4) (2019) 527-543. https://doi.org/10.1080/14786419.2017.1399387.

[81] T.H. Kim, S.D. Yoo, H.S. Lee, et al., *In vivo* absorption and disposition of *α*-cedrene, a sesquiterpene constituent of cedarwood oil, in female and male rats, Drug Metab. Pharmacokinet. 30(2) (2015) 168-173. https://doi.org/10.1016/j.dmpk.2014.12.003.

[82] A. Jo, Y. Lee, T.I. Kam, et al., PARIS farnesylation prevents neurodegeneration in models of Parkinson's disease, Sci. Transl. Med. 13(604) (2021) eaax8891. https://doi.org/10.1126/scitranslmed.aax8891.

[83] L. Ma, C.C. Chuang, W. Weng, et al., Paeonol protects rat heart by improving regional blood perfusion during no-reflow, Front. Physiol. 7 (2016) 298. https://doi.org/10.3389/fphys.2016.00298.

[84] P. Terpinc, A. Polak, N.P. Ulrih, et al., Antioxidant properties of 4-vinyl derivatives of hydroxycinnamic acids, Food Chem. 128(1) (2011) 62-69. https://doi.org/10.1016/j.foodchem.2011.02.077.

[85] J. Sun, F. Shang, L. Shen, et al., Apocynin suppression of NADPH oxidase reverses the aging process in mesenchymal stem cells to promote osteogenesis and increase bone mass, Sci. Rep. 5(1) (2015) 18572. https://doi.org/10.1038/srep18572.

[86] S.Y. Lee, S.H. Park, M.O. Kim, et al., Vanillin attenuates negative effects of ultraviolet A on the stemness of human adipose tissue-derived mesenchymal stem cells, Food Chem. Toxicol. 96 (2016) 62-69. https://doi.org/10.1016/j.fct.2016.07.023.

[87] J. Xu, H. Xu, Y.Liu, et al., Vanillin-induced amelioration of depression-like behaviors in rats by modulating monoamine neurotransmitters in the brain, Psychiatry Res. 225(3) (2015) 509-514. https://doi.org/10.1016/j.psychres.2014.11.056.

[88] J.A. Garcia-Vilas, A.R. Quesada, M. Angel Medina, 4-Methylumbelliferone inhibits angiogenesis *in vitro* and *in vivo*, J. Agric. Food Chem. 61(17) (2013) 4063-4071. https://doi.org/10.1021/jf303062h.

[89] M. Nixon, D.J. Wake, D.E. Livingstone, et al., Salicylate downregulates 11 *β*-HSD1 expression in adipose tissue in obese mice and in humans, mediating insulin sensitization, Diabetes 61(4) (2012) 790-796. https://doi.org/10.2337/db11-0931.

[90] F.J.G. Muriana, S. Montserrat-De La Paz, R. Lucas, et al., Tyrosol and its metabolites as antioxidative and anti-inflammatory molecules in human endothelial cells, Food Funct. 8(8) (2017) 2905-2914. https://doi.org/10.1039/c7fo00641a.

[91] G. Luo, Y. Huang, D. Mo, et al., Tyrosol attenuates pro-inflammatory cytokines from cultured astrocytes and NF-κB activation in *in vitro* oxygen glucose deprivation, Neurochem. Int. 121 (2018) 140-145. https://doi.org/10.1016/j.neuint.2018.10.006.

[92] P. Lewitt, M. Lu., CSF xanthine, homovanillic acid, and their ratio as biomarkers of Parkinson's disease, Brain Res. 1408 (2011) 88-97. https://doi.org/10.1016/j.brainres.2011.06.057.

[93] Y. Murakami, A. Hirata, S. Ito, et al., Re-evaluation of cyclooxygenase-2-inhibiting activity of vanillin and guaiacol in macrophages stimulated with lipopolysaccharide, Anticancer Res. 27(2) (2007) 801-807. https://doi.org/10.1016/j.fitote.17465205.

[94] P.K. Sik, Raspberry ketone, a naturally occurring phenolic compound, inhibits adipogenic and lipogenic gene expression in 3T3-L1 adipocytes, Pharm. Biol. 53(6) (2015) 870-875. https://doi.org/10.3109/13880209.2014.946059.

[95] S.R. Kopalli, S.J. Noh, S. Koppula, et al., Methylparaben protects 6-hydroxydopamine-induced neurotoxicity in SH-SY5Y cells and improved behavioral impairments in mouse model of Parkinson's disease, Neurotoxicol. 34 (2013) 25-32. https://doi.org/10.1016/j.neuro.2012.10.003.

[96] J. Zhang, H. Mohamad, J.H. Wong, et al., The effect of 4-hydroxybenzaldehyde on the gamma-aminobutyric acid type areceptor, Malays. J. Med. Sci. 24(2) (2017) 94-99. https://doi.org/10.21315/mjms2017.24.2.12.

[97] H.W. Leung, C.H. Ko, G. Yue, et al., The natural agent 4-vinylphenol targets metastasis and stemness features in breast cancer stem-like cells, Cancer Chemother. Pharmacol. 82(2) (2018) 185-197. https://doi.org/10.1007/s00280-018-3601-0.

[98] M.A. Zavala-Sánchez, Antidiarrhoeal activity of nonanal, an aldehyde isolated from *Artemisia ludoviciana*, Pharm. Biol. 40(4) (2002) 263-268. https://doi.org/10.1076/phbi.40.4.263.8465.

[99] S.A. Chougule, T.C. Gavandi, S.B. Patil, et al., Nonanal inhibits growth and virulence factors in *Candida albicans*, Pharmacological Research-Natural Products 7 (2025) 100256. https://doi.org/10.1016/j.prenap.2025.100256.

[100] Y. Du, X. Gu, H. Meng, et al., Muscone improves cardiac function in mice after myocardial infarction by alleviating cardiac macrophage-mediated chronic inflammation through inhibition of NF-κB and NLRP3 inflammasome, Am. J. Transl. Res. 10(12) (2018) 4235-4246. https://doi.org/10.1186/s40529-017-0168-8.

[101] X. Gu, N. Bao, J. Zhang, et al., Muscone ameliorates myocardial ischemia-reperfusion injury by promoting myocardial glycolysis, Heliyon 9(11) (2023) e22154. https://doi.org/ 10.1016/j.heliyon.2023.e22154.

[102] P. Chang, K. Augustin, K. Boddum, et al., Seizure control by decanoic acid through direct AMPA receptor inhibition, Brain 139 (2016) 431-443. https://doi.org/10.1093/brain/awv325.

[103] P. Lertnimitphun, Y. Jiang, N. Kim, et al., Safranal alleviates dextran sulfate sodium-induced colitis and suppresses macrophage-mediated inflammation, Front. Pharmacol. 10 (2019) 1281. https://doi.org/10.3389/fphar.2019.01281.

[104] N. Mizuno, K. Abe, Y. Morishita, et al., Pentanoic acid induces thymic stromal lymphopoietin production through Gq/11 and Rho-associated protein kinase signaling pathway in keratinocytes, Int. Immunopharmacol. 50 (2017) 216-223. https://doi.org/10.1016/j.intimp.2017.06.024.

[105] Z.C. Hu, Y.G. Zheng, A highthroughput screening method for 1,3-dihydroxyacetone-producing bacterium by cultivation in a 96-well microtiter plate, J. Rapid Methods Autom. Microbiol. 17(2) (2009) 233-241. https://doi.org/10.1111/j.1745-4581.2009.00173.x.

[106] G. Nan, L. Caina, L. Quan, et al., Maltol, a food flavor enhancer, attenuates diabetic peripheral neuropathy in streptozotocin-induced diabetic rats, Food Funct. 9(12) (2018) 6287-6297. https://doi.org/10.1039/c8fo01964a.

[107] Y. Nakamura, Y. Nakayama, H. Ando, et al., 3-Methylthiopropionic acid ethyl ester, isolated from Katsura-uri (Japanese pickling melon, *Cucumis melo* var. conomon), enhanced differentiation in human colon cancer cells, J. Agric. Food Chem. 56(9) (2008) 2977-2984. https://doi.org/10.1021/jf072898i.

[108] D. Bencsik, G. Gazsi, B. Urbanyi, et al., Assessment of subacute genotoxic and histopataological effects of a food flacour ingredient, 4-ethylbenzaldehyde (EBA) on zebrafish (*Danio rerio*) model, Acta Aliment. 47(2) (2018) 245-251. https://doi.org/10.1556/066.2018.47.2.14.

[109] Y. Li, The application of caprylic acid in downstream processing of monoclonal antibodies, Protein Express. Purif. 153 (2019) 92-96. https://doi.org/10.1016/j.pep.2018.09.003.

[110] J. E. Ku, Photodamage attenuation effect by angelic acid in UVA irradiation-induced damages in normal human dermal fibroblast, Biomed. Dermatol. 2(1) (2018) 8. https://doi.org/10.1186/s41702-017-0013-4.

[111] D. Morshedi, F. Pan-Montojo, Cuminaldehyde as the major component of cuminum cyminum, a natural aldehyde with inhibitory effect on alpha-synuclein fibrillation and cytotoxicity, J. Food Sci. 80(10) (2015) H2336-45. https://doi.org/10.1111/1750-3841.13016.

[112] H. Liu, Q. Chen, Y. Liu, et al., Isolation and biological activities of decanal, linalool, valencene, and octanal from sweet orange oil, J. Food Sci. 77(11) (2012) C1156-61.https://doi.org/10.1111/j.1750-3841.2012.02924.x.

[113] K. Ogawa, M. Ito, Appetite-enhancing effects: the influence of concentrations of benzylacetone and *trans*-cinnamaldehyde and their inhalation time, as well as the effect of aroma, on body weight in mice, Biol. Pharm. Bull. 39(5) (2016) 794-748. https://doi.org/10.1248/bpb.b15-00937.

[114] A. J. Scott-Thomas, M. Syhre, P. K. Pattemore, et al., 2-Aminoacetophenone as a potential breath biomarker for *Pseudomonas aeruginosa* in the cystic fibrosis lung, BMC Pulm. Med. 10 (2010) 56. https://doi.org/10.1186/1471-2466-10-56.

[115] Y. Qiannan, Antiseptic effect of microencapsulated sorbic acid on bakery products, Chin. Food Addit. 33(5) (2022) 16-22. https://doi.org/10.19804/j.issn1006-2513.2022.05.003.

[116] F.J. Alvarez-Martinez, E. Barrajon-Catalan, M. Herranz-Lopez, Antibacterial plant compounds, extracts and essential oils: an updated review on their effects and putative mechanisms of action, Phytomedicine 90 (2020) 153626. https://doi.org/10.1016/j.phymed.2021.153626.

[117] N.R. Sardar, S.H. Akbari, R.B. Modi, et al., Application of essential oils in food packaging: a concise review, Eur. J. Nutr. Food Saf. 16(3) (2024) 60-67. https://doi.org/10.9734/ejnfs/2024/v16i31399.

[118] M. Meenu, B. Padhan, M. Patel., Antibacterial activity of essential oils from different parts of plants against *Salmonella* and *Listeria* spp., Food Chem. 404 (2023) 134723. https://doi.org/10.1016/j.foodchem.2022.134723.

[119] M. Oz, Y. Lozon, A. Sultan, Effects of monoterpenes on ion channels of excitable cells, Pharmacol. Ther. 152 (2015) 83-97. https://doi.org/10.1016/j.pharmthera.2015.05.006.

[120] K. Jeongmok, M.R. Marshall, I.W. Cheng, Antibacterial activity of some essential oil components against five foodborne pathogens, J. Agric. Food Chem. 43(11) (1995) 2839-2845. https://doi.org/10.1021/jf00059a013.

[121] A. Wattanasatcha, S. Rengpipat, S. Wanichwecharungruang, Thymol nanospheres as an effective anti-bacterial agent, Int. J. Pharm. 434(1-2) (2012) 360-365. https://doi.org/10.1016/j.ijpharm.2012.06.017.

[122] J.J. Lin, C.C. Wu, S.C. Hsu, et al., Alpha-phellandrene-induced DNA damage and affect DNA repair protein expression in WEHI-3 murine leukemia cells *in vitro*, Environ. Toxicol. 30(11) (2015) 1322-1330. https://doi.org/10.1002/tox.22003.

[123] R. Russo, A. Ciociaro, L. Berliocchi, et al., Implication of limonene and linalyl acetate in cytotoxicity induced by bergamot essential oil in human neuroblastoma cells, Fitoterapia 89 (2013) 48-57. https://doi.org/10.1016/j.fitote.2013.05.014.

[124] A.C. Guimaraes, L.M. Meireles, M.F. Lemos, et al., Antibacterial activity of terpenes and terpenoids present in essential Oils, Molecules 24(13) (2019) 2471. https://doi.org/10.3390/molecules24132471.

[125] J.C. Lopez-Romero, H. Gonzalez-Ros, A. Borges, et al., Antibacterial effects and mode of action of selected essential oils components against *Escherichia coli* and *Staphylococcus aureus*, Evid. Based Complement. Alternat. Med. 1 (2015) 795435. https://doi.org/10.1155/2015/795435.

[126] A. Gupta, E. Jeyakumar, R. Lawrence, Strategic approach of multifaceted antibacterial mechanism of limonene traced in *Escherichia coli*, Sci. Rep. 11(1) (2021) 13816. https://doi.org/10.1038/s41598-021-92843-3.

[127] V. Cheynier, G. Comte, K.M. Davies, et al., Plant phenolics: recent advances on their biosynthesis, genetics, and ecophysiology,

Plant Physiol. Biochem. 72 (2013) 1-20. https://doi.org/10.1016/j.plaphy.2013.05.009.

[128] O.A. Aldulaimi, General overview of phenolics from plant to laboratory, good antibacterials or not, Pharmacogn. Rev. 11(22) (2017) 123-127. https://doi.org/10.4103/phrev.phrev_43_16.

[129] G. Sandra, R. Anabela, Inhibitory properties of phenolic compounds against enzymes linked with human diseases, IntechOpen. (2017) p Ch. 6. http://doi.org/10.5772/66844.

[130] M.K. Yadav, S.W. Chae, Eugenol: a phyto-compound effective against methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* clinical strain biofilms, Plos One 10(3) (2015) e0119564. https://doi.org/10.1371/journal.pone.0119564.

[131] J. Wang, N. Huang, J. Xiong, et al., Caprylic acid and nonanoic acid upregulate endogenous host defense peptides to enhance intestinal epithelial immunological barrier function *via* histone deacetylase inhibition, Int. Immunopharmacol. 65 (2018) 303-311. https://doi.org/10.1016/j.intimp.2018.10.022.

[132] J.H. Zhang, H.L. Sun, S.Y. Chen, et al., Anti-fungal activity, mechanism studies on *α*-phellandrene and nonanal against *Penicillium cyclopium*, Bot. Stud. 58(1) (2018) 13. https://doi.org/10.1186/s40529-017-0168-8.

[133] T.U. Berendonk, C.M. Manaia, C. Merlin, et al., Tackling antibiotic resistance: the environmental framework, Nat. Rev. Microbiol. 13(5) (2015) 310-317. https://doi.org/10.1038/nrmicro3439.

[134] M. Lu, T. Dai, C.K.K. Murray, et al., Bactericidal property of oregano oil against multidrug-resistant clinical isolates, Front. Microbiol. 12 (2021) 2329. https://doi.org/10.3389/fmicb.2021.713573.

[135] A.A. Doyle, J.C. Stephens, A review of cinnamaldehyde and its derivatives as antibacterial agents, Fitoterapia 139 (2019) 104415. https://doi.org/10.1016/j.fitote.2019.104405.

[136] S.N. Park, Y.K. Lim, M.O. Freire, et al., Antimicrobial effect of linalool and *α*-terpineol against periodontopathic and cariogenic bacteria, Anaerobe 18(3) (2012) 369-372. https://doi.org/10.1016/j.anaerobe.2012.04.001.

[137] D.T. Debela, S.G.Y. Muzazu, K.D. Heraro, et al., New approaches and procedures for cancer treatment: current perspectives, Sage Open Med. 9 (2021). https://doi.org/10.1177/20503121211034366.

[138] J. Zugazagoitia, C. Guedes, S. Ponce, et al., Current challenges in cancer treatment, Clin. Ther. 38(7) (2016) 1551-1566. https://doi.org/10.1016/j.clinthera.2016.03.026.

[139] Z. D. Stevanovic, E. Sieniawska, K. Glowniak, et al., Natural macromolecules as carriers for essential oils: from extraction to biomedical application, Front. Bioeng. Biotechnol. 8 (2020) 563. https://doi.org/10.3389/fbioe.2020.00563.

[140] M. Trytek, R. Paduch, M. Piet, et al., Biological activity of oxygenated pinene derivatives on human colon normal and carcinoma cells. Flavour. Frag. J. 33(6) (2018) 428-437. https://doi.org/10.1002/ffj.3471.

[141] L.H. Babu, S. Perumal, M.P. Balasubramanian, Myrtenal, a natural monoterpene, down-regulates TNF-α expression and suppresses carcinogen-induced hepatocellular carcinoma in rats, Mol. Cell. Biochem. 369(1-2) (2012) 183-193. https://doi.org/10.1002/ffj.3471.

[142] B.Y. Sheikh, M.M.R. Sarker, M.N.A. Kamarudin, Antiproliferative and apoptosis inducing effects of citral *via* p53 and ROS-induced mitochondrial-mediated apoptosis in human colorectal HCT116 and HT29 cell lines, Biomed. Pharmacother. 96 (2017) 834-846. https://doi.org/10.1016/j.biopha.2017.10.038.

[143] I. Potocnjak, I. Gobin, R. Domitrovic, Carvacrol induces cytotoxicity in human cervical cancer cells but causes cisplatin resistance: involvement of MEK-ERK activation, Phytother. Res. 32(6) (2018) 1090-1097. https://doi.org/10.1002/ptr.6048.

[144] B.I.M. Silva, E.A. Nascimento, C.J. Silva, et al., Anticancer activity of monoterpenes: a systematic review, Mol. Biol. Rep. 48(7) (2021) 5775-5785. https://doi.org/10.1007/s11033-021-06578-5.

[145] T. Yang, J.S. Jiang, W.Q. Lu, et al., Ferulic acid exerts anti-angiogenic and anti-tumor activity by targeting fibroblast growth factor receptor 1-mediated angiogenesis, Int. J. Mol. Sci. 16(10) (2015) 24011-24031. https://doi.org/10.3390/ijms161024011.

[146] H.J. Jun, J.H. Lee, J.Y. Kim, et al., Linalool is a PPARalpha ligand that reduces plasma TG levels and rewires the hepatic transcriptome and plasma metabolome, J. Lipid Res. 55(6) (2014) 1098-1110. https://doi.org/ 10.1194/jlr.M045807.

[147] Z. Cai, S. Wang, J. Li., Treatment of inflammatory bowel disease: acomprehensive review, Front. Med. 8 (2021) 765474. https://doi.org/10.3389/fmed.2021.765474.

[148] K. Dhama, S.K. Latheef, A.K. Munjal, et al., Probiotics in curing allergic and inflammatory conditions-research progress and futuristic vision, Rec. Pat. Inflamm. Allergy Drug Discov. 10(2) (2017) 105-118. https://doi.org/10.2174/1872213x10666161226162229.

[149] X.Y. Chen, Y.X. Dou, D.D. Luo, et al., *β*-Patchoulene from patchouli oil protects against LPS-induced acute lung injury *via* suppressing NF-κB and activating Nrf2 pathways, Int. Immunopharmacol. 50 (2017) 270-278. https://doi.org/10.1016/j.intimp.2017.07.001.

[150] Q. Xu, J. Li, Z. Chen, et al., Protective effects of *β*-eudesmol against septic liver injury *via* inhibition of NF-KB signaling, Trop. J. Pharm. Res. 21(6) (2022) 1183-1188. https://doi.org/10.4314/tjpr.v21i6.7.

[151] T.Q. Wang, X. Fu, Q. Chen, et al., Arachidonic acid metabolism and kidney inflammation, Int. J. Mol. Sci. 20(15) (2019) 3683. https://doi.org/10.3390/ijms20153683.

[152] S.Y. Hsuan, L. J. Yuarn, Menthone inhalation alleviates local and systemic allergic inflammation in ovalbumin-sensitized and challenged asthmatic mice, Int. J. Mol. Sci. 23(7) (2022) 4011-4011. https://doi.org/10.3390/ijms23074011.

[153] W.K. Chan, L. Tan, K.G. Chan, Nerolidol: asesquiterpene alcohol with multi-faceted pharmacological and biological activities, Molecules 21(5) (2016) 529. https://doi.org/10.3390/molecules21050529.

[154] C. Wang, Y. Chen, C. Hou, Antioxidant and antibacterial activity of seven predominant terpenoids, Int. J. Food Prop. 22(1) (2019) 230-238. https://doi.org/10.1080/10942912.2019.1582541.

[155] T. Kim, B. Song, K.S. Cho, et al., Therapeutic potential of volatile terpenes and terpenoids from forests for inflammatory diseases, Int. J. Mol. Sci. 21(6) (2020) 2187. https://doi.org/10.3390/ijms21062187.

[156] L.R.C. Barclay, C.E. Edwards, M.R. Vinqvist, Media effects on antioxidant activities of phenols and catechols, J. Am. Chem. Soc. 121(26) (1999) 6226-6231. https://doi.org/10.1556/066.2018.47.2.14.

[157] N. Martins, L. Barros, I. Ferreira, *In vivo* antioxidant activity of phenolic compounds: facts and gaps, Trends Food Sci. Technol. 48 (2016) 1-12. https://doi.org/10.1016/j.tifs.2015.11.008.

[158] M.M. Vuolo, V.S. Lima, Chapter 2-phenolic compounds: structure, classification, and antioxidant power, Woodhead Publishing. (2019) 33-50.

[159] M.R. Farag, M. Alagawany, V. Tufarelli, *In vitro* antioxidant activities of resveratrol, cinnamaldehyde and their synergistic effect against cyadox-induced cytotoxicity in rabbit erythrocytes, Drug Chem. Toxicol. 40(2) (2017) 196-205. https://doi.org/10.1080/01480545.2016.1193866.

[160] Q. Li, L.L. Zhang, J.G. Xu, Antioxidant, DNA damage protective, antibacterial activities and nitrite scavenging ability of essential oil of *Amomum kravanh* from China, Nat. Prod. Res. 35 (2020) 5415-5419. https://doi.org/10.1080/14786419.2020.1775225.

[161] L.L. Zhang, L.F. Zhang, J.G. Xu, et al., Comparison study on antioxidant, DNA damage protective and antibacterial activities of eugenol and isoeugenol against several foodborne pathogens, Food Nutr. Res. 61(1) (2017) 1353356. https://doi.org/10.1080/16546628.2017.1353356.

[162] Q. Ren, C. Gao, Z. Xu, et al., Bis-coumarin derivatives and their biological activities, Curr. Top. Med. Chem.18(2) (2018) 101-113. https://doi.org/10.2174/1568026618666180221114515.

[163] W.Y. Wang, P. Xiong, H. Zhang, et al., Analysis, occurrence, toxicity and environmental health risks of synthetic phenolic antioxidants: areview, Environ. Res. 201 (2021) 111531. https://doi.org/10.1016/j.envres.2021.111531.

[164] P.U. Rani, Plant volatile chemicals and insect responses, Function and Improvement (2015) 671-695. http://doi.org/10.5772/66844.

[165] A. Reinecke, M. Hilker, Plant semiochemicals-perception and behavioural responses by insects, Annual Plant Reviews (2014) 115-153.

[166] C.C. Chiu, J. Bohlmann, Mountain pine beetle epidemic: an interplay of terpenoids in host defense and insect pheromones, Annu. Rev. Plant Biol. 73(2022) 475-494. https://doi.org/10.1146/annurev-arplant-070921-103617.

[167] A. Tonğa, S. Çakmak, K. Şeker. et al., *Cis*-jasmone treatments affect multiple sucking insect pests and associated predators in cotton, Entomol. Gen. 40 (2020) 49-61. https://doi.org/10.1127/entomologia/2019/0771.

[168] S.E. Brennan, S. Mcdonald, M. Murano, et al., Effectiveness of aromatherapy for prevention or treatment of disease, medical or preclinical conditions, and injury: protocol for a systematic review and meta-analysis, Syst. Rev. 11(1) (2022) 148. https://doi.org/10.1186/s13643-022-02015-1.

[169] J. Cui, M. Li, Y. Wei, et al., Inhalation aromatherapy *via* brain-targeted nasal delivery: natural volatiles or essential oils on mood disorders, Front. Pharmacol. 13 (2022) 860043. https://doi.org/10.3389/fphar.2022.860043.

[170] N. Ito, T. Nagai, T. Oikawa, et al., Antidepressant-like effect of l-perillaldehyde in stress-induced depression-like model mice through regulation of the olfactory nervous system, Evid. Based Complement Alternat. Med. (2011) 512697. https://doi.org/10.1093/ecam/nen045.

[171] D.I. Sánchez-Vidaña, K. Po, T. Fung, et al., Lavender essential oil ameliorates depression-like behavior and increases neurogenesis and dendritic complexity in rats, Neurosci. Lett. 701 (2019) 180-192. https://doi.org/10.1016/j.neulet.2019.02.042.

[172] D. Reis, T. Jones, Aromatherapy using essential oils as a supportive therapy, Clin. J. Oncol. Nurs. 21(1) (2017) 16-19. https://doi.org/10.1188/17.Cjon.16-19.

[173] D. Shaw, J.M. Annett, B. Doherty, et al., Anxiolytic effects of lavender oil inhalation on open-field behaviour in rats, Phytomedicine 14(9) (2007) 613-620. https://doi.org/10.1016/j.phymed.2007.03.007.

[174] B.M. Pause, A. Miranda, R. Göder, et al., Reduced olfactory performance in patients with major depression, J. Psychiatr. Res. 35(5) (2001) 271-277. https://doi.org/10.1016/s0022-3956(01)00029-2.

[175] X.N. Lv, Z.J. Liu, H.J. Zhang, et al., Aromatherapy and the central nerve system (CNS): therapeutic mechanism and its associated genes, Curr. Drug Targets. 14(8) (2013) 872-879. https://doi.org/10.2174/13894501113140800007.

[176] M. Lu, S. Wang, T. Wang, et al., Bacteria-specific phototoxic reactions triggered by blue light and phytochemical carvacrol, Sci. Transl. Med. 13(575) (2021) eaba3571. https://doi.org/10.1126/scitranslmed.aba3571.

[177] N. Pazyar, R. Yaghoobi, N. Bagherani, et al., A review of applications of tea tree oil in dermatology, Int. J. Dermatol. 52(7) (2013) 784-790. https://doi.org/10.1111/j.1365-4632.2012.05654.x.

[178] A. Rani, A. Rana, R.K. Dhaka, et al., Bacterial volatile organic compounds as biopesticides, growth promoters, and plant-defense elicitors: current understanding and future scope, Biotechnol. Adv. 63 (2023) 108078. https://doi.org/10.1016/j.biotechadv.2022.108078.