



Natural terpenes: An overview of structural diversity and multifunctional applications

Km. Anjali^{1*}, Arvind Raghav², Ashish Singh Chauhan³, Pradeep Kumar²

¹Department of Pharmaceutical Chemistry, Sahu Onkar Saran School of Pharmacy (Faculty of Pharmacy), IFTM University, Moradabad, India.

²Department of Pharmaceutics, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, India.

³Department of Pharmaceutics, Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, India.

ARTICLE HISTORY

Received on: 29/09/2025

Accepted on: 17/01/2026

Available Online: 05/03/2026

Key words:

Terpenes, biosynthesis, natural products, pharmacological applications, antimicrobial, anticancer, neuroprotection.

ABSTRACT

Terpenes are structurally diverse natural compounds synthesized by plants, fungi, and marine organisms, exhibiting critical ecological functions and remarkable pharmacological potential. Their wide-ranging bioactivities include antimicrobial, anti-inflammatory, antioxidant, anticancer, and neuroprotective effects, making them promising leads for therapeutic development. However, their clinical utility is limited by low aqueous solubility, instability, and poor bioavailability. This review systematically integrates the structural subclasses of terpenes, monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, and marine-derived analogues, with innovative formulation approaches that enhance pharmacokinetics and therapeutic performance. Emphasis is placed on nanotechnology-based delivery systems, such as nanoemulsions, liposomes, polymeric nanoparticles, and nanostructured lipid carriers, which have demonstrated substantial improvements in solubility, stability, and bioavailability. Clinical trial outcomes and pharmacokinetic data highlight significant gains, with several terpenes achieving enhanced oral bioavailability, reduced dosage requirements, and improved safety profiles. Structure–activity relationship analyses further elucidate how functional groups, stereochemistry, and conjugation length critically influence biological activity and therapeutic outcomes. Beyond pharmacology, this review underscores the ecological and industrial significance of terpenes, ranging from plant defense and pollination to their use in cosmetics, food, and biotechnology. Looking forward, interdisciplinary strategies such as synthetic biology, CRISPR-based genome editing, metabolic engineering, and AI-driven drug discovery are expected to revolutionize terpene research by enabling sustainable production, rational design of derivatives, and advanced targeted delivery. Collectively, these advances position terpenes as multifunctional biomolecules with the potential to bridge natural product chemistry, nanomedicine, and clinical therapeutics, thereby opening new avenues for drug discovery, biotechnology, and sustainable healthcare innovations.

1. INTRODUCTION

Terpenes are a broad class of naturally occurring carbon chain organic compounds that frequently exist naturally in vegetation, but most definitely in essential oils. These molecules allude to isoprene units and are grouped by their number of

isoprene units, i.e., monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), tetraterpenes, and so forth [1,2]. Contributing to the fragrant nature of many plants, including lavender, pine, and citrus fruit, they are also an essential component of plant defense against herbivory, repelling herbivores and attracting pollinators [3]. Terpenes also act as precursors to a variety of biological molecules (e.g., steroids and carotenoids). In addition to their ecological role, terpenes have been thoroughly researched for their therapeutic properties, including anti-inflammatory, antimicrobial, and anticancer effects, rendering them valuable in the fields of pharmaceuticals, cosmetics, and aromatherapy [1,2]. The vast structural variety and functional flexibility of terpenes

*Corresponding Author

Km. Anjali, Department of Pharmaceutical Chemistry, Sahu Onkar Saran School of Pharmacy (Faculty of Pharmacy), IFTM University, Moradabad, India. E-Mail: anjali.ved.2303@gmail.com

underscore their significance in both natural environments and human uses [3]. August Kekule coined the term “terpene” in 1866 to describe compounds containing carbon linked only to carbon, initially referring to hydrocarbons with the empirical formula $C_{10}H_{16}$. The word derives from “turpentine,” an old spelling of the resinous substance [4]. Terpenes have been used since ancient times in medicine, aromatherapy, and for their fragrance. Early records from India, Persia, and Egypt show their use in essential oils. In the 11th century, camphor, rich in terpenes, was introduced by Arabs to treat pain and illness, and later used during the Black Death to repel pests. Terpenes also appear in cannabis, contributing to its therapeutic effects against depression and anxiety [5,6]. Civilizations like the Egyptians, Greeks, and Chinese used frankincense, myrrh, and camphor in rituals and traditional medicine. Essential oils were central to Ayurveda and Traditional Chinese Medicine for pain relief and anti-inflammatory benefits. In medieval Europe, herbs such as rosemary and lavender served as disease deterrents and natural preservatives [7,8]. Terpenes are vital in perfumes, cleaning agents, and pharmaceuticals, underscoring their enduring relevance in culture and innovation.

Unlike previous reviews that primarily focused on either the ecological significance of terpenes or their pharmacological properties in isolation, this work systematically integrates structural subclasses of terpenes (monoterpenes, sesquiterpenes, diterpenes, tetraterpenes, and marine-derived analogues) with advanced drug delivery strategies designed to overcome their poor solubility, instability, and low bioavailability. To our knowledge, this is the first review to explicitly compare how different delivery platforms (e.g., nanoemulsions, liposomes, polymeric nanoparticles, and nanostructured lipid carriers) have been applied across distinct terpene subclasses. By bridging chemical diversity with formulation science, this review provides a more translational perspective, linking structural class to delivery strategy and therapeutic potential. This review is distinct from existing literature because it not

only summarizes the pharmacological relevance of terpenes but also offers the first systematic comparison of nanotechnology-based delivery strategies across multiple terpene subclasses, highlighting class-specific challenges and opportunities for clinical translation.

The development of terpene-based therapeutics follows a systematic roadmap beginning with their biosynthesis pathways, where the mevalonate (MEV) and methylerythritol phosphate (MEP) routes in diverse natural sources provide the fundamental building blocks for terpene synthesis. Following this, extraction and structural diversity play a critical role, with tailored methods designed to isolate specific chemical subclasses of terpenes, thereby optimizing yield and preserving functional integrity. Once obtained, terpenes require advanced formulation approaches, particularly nanotechnology-based carriers, which improve solubility, stability, and bioavailability [9,10]. These optimized formulations then undergo rigorous evaluation of pharmacological uses, where their diverse therapeutic effects are characterized to establish a clear clinical rationale. The next step involves clinical evaluation, integrating pharmacokinetic and pharmacodynamic data, potency analysis, and clinical trial outcomes to inform key development decisions. Finally, successful translation requires adherence to regulatory and market frameworks, where strict compliance, standardized safety assessments, and strategic commercialization approaches ensure that terpene-based products reach patients and industries effectively (Fig. 1).

This study aims to provide a comprehensive overview of the therapeutic applications of terpenes, with particular emphasis on recent advancements in their formulation and drug delivery approaches that enhance bioavailability and clinical potential. While the ecological and structural diversity of terpenes is briefly discussed to establish background context, the central focus remains on their pharmacological relevance and technological strategies designed to overcome limitations in therapeutic use.

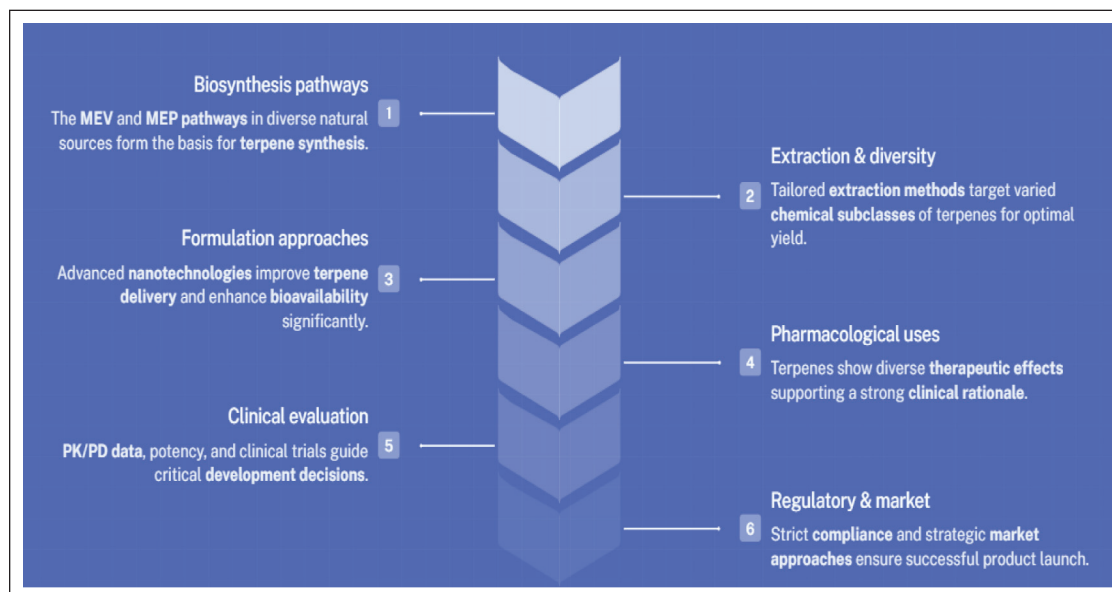


Figure 1. Roadmap of terpenes from biosynthesis to clinical translation.

2. CHEMISTRY AND CLASSIFICATION OF TERPENES

Terpene chemistry is the introductory chemistry of hydrocarbons, with the structure of isoprene units, which are five-carbon-branched molecules (C_5H_8). These are the building blocks of the terpenes and are linked together in different patterns through biosynthetic pathways to create molecules of various shapes and properties. Terpenes are classified as monoterpenes, sesquiterpenes, diterpenes, and others depending on the number of isoprene units. For instance, monoterpenes consist of two isoprene units ($C_{10}H_{16}$), while sesquiterpenes have three ($C_{15}H_{24}$) [11,12]. Isoprene units are versatile, allowing for the formation of linear, cyclic, and most complex structures, thus providing for an extensive range of terpenes found in nature. Also, this structural variation contributes to their physical and chemical properties, such as volatility, solubility, and reactivity, so they are necessary in biological systems and are helpful in a host of human applications. Generally, small and highly volatile monoterpenes composed of 2 isoprene units ($C_{10}H_{16}$) contribute to their characteristic fragrances in plants, such as eucalyptus, lavender, and citrus fruits. Essential oils often contain them, and they also have roles in plant defense and human uses as aromatherapy and medicine [13,14].

Sesquiterpenes ($C_{15}H_{24}$) are slightly greater and less volatile, usually having more complex structures, including rings and multi-cyclic arrangements. Sesquiterpenes such as humulene and bisabolol are found in resins and essential oils and have antimicrobial as well as anti-inflammatory properties (Fig. 2). Larger and less volatile, typically lacking an acyclic connected backbone, diterpenes contain four isoprene units ($C_{20}H_{32}$). These compounds play a vital role in plant growth and defense; for instance, Taxol is a well-known anticancer agent, while gibberellins are indispensable plant hormones.

Structure between these categories demonstrates the abundance of terpenes found in nature and that they have a wide variety of biological and industrial significance [3]. Many terpenes have multiple chiral centers and contain examples of stereoisomers with properties that can differ profoundly in terms of physical, chemical, and biological properties. Functional group variation works further to increase terpene diversity through oxidation, hydroxylation, or other functional group addition. The reactivity and utility of these compounds are influenced by these changes, which lead to compounds such as alcohols (e.g., menthol), ketones (e.g., camphor), aldehydes (e.g., citral), and epoxides. Extending this trend, sesterterpenoids, which are composed of five isoprene units and contain 25 carbon atoms, represent an even more structurally diverse and functionally significant group of terpenoids. They occur in mono-, bi-, tri-, tetra-, and macrocyclic forms, displaying a wide spectrum of biological activities. Some members, such as squalene, act as crucial precursors in sterol biosynthesis (including cholesterol) and are widely applied in cosmetic and pharmaceutical formulations. Others, like bisabolol, known for its bicyclic framework, possess anti-inflammatory and skin-soothing properties. Moreover, oxygenated sesterterpenoid quinones and tetracyclic compounds such as dendrocarbin A, particularly from marine sources, exhibit antifungal, antibiotic, and antiparasitic activities, emphasizing the biological importance and potential therapeutic applications of this lesser-known class of terpenoids [15]. Terpenes are classified by the number of isoprene units into hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}), tetraterpenes (C_{40}), and polyterpenes [12,13]. Smaller, volatile monoterpenes (e.g., limonene, linalool, menthol) often contribute to fragrance and antimicrobial activity, while sesquiterpenes (e.g., β -caryophyllene, humulene) display anti-inflammatory and anticancer effects. Larger diterpenes

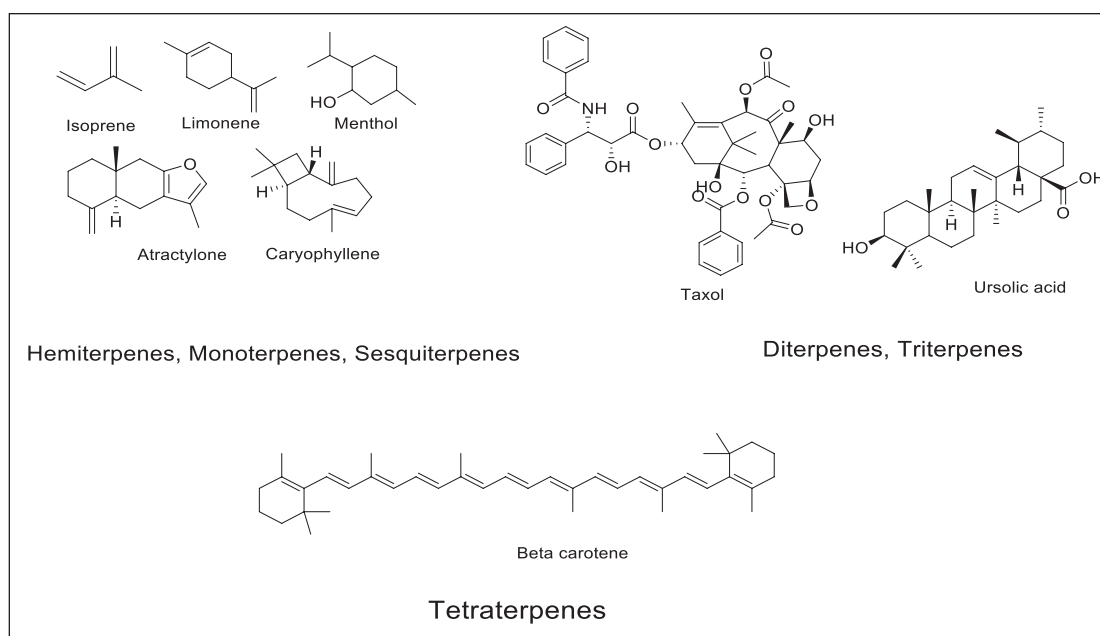


Figure 2. Classification of terpenes.

and triterpenes (e.g., Taxol, ursolic acid) serve as important clinical drugs, plant hormones, or antioxidants. The diversity of structures and bioactivities across these subclasses is summarized in Table 1 [14].

3. BIOSYNTHESIS OF TERPENES

Terpene biosynthesis takes place via two separate pathways: the MEV pathway and the MEP pathway. Both of these pathways yield vital five-carbon isoprene units, isopentenyl pyrophosphate (IPP), and dimethylallyl pyrophosphate (DMAPP), which act as the foundational components for terpenes [16].

3.1. MEV pathway (cytosolic/endoplasmic reticulum pathway)

The MEV pathway, which primarily takes place in the cytosol of eukaryotic cells and certain archaea, begins with acetyl-CoA serving as the starting material. HMG-CoA reductase facilitates the conversion of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) into mevalonic acid, which consists of three acetyl-CoA molecules condensed together. This process involves a series of phosphorylation and decarboxylation reactions until MEV is transformed into 5-phosphomevalonate, 5-diphosphomevalonate, and ultimately into isopentenyl pyrophosphate (IPP). When in its isomeric form, IPP can take part in an isomerization reaction to dimethylallyl pyrophosphate (DMAP), via IPP isomerase. These intermediates are then utilized for the synthesis of higher-order terpenes, including monoterpenes (C_{10} , geranyl pyrophosphate - GPP), sesquiterpenes (C_{15} , farnesyl pyrophosphate - FPP), diterpenes (C_{20} , geranylgeranyl pyrophosphate - GGPP), and beyond [17].

3.2. Methylerythritol phosphate (MEP) pathway (plastidial pathway)

In algae, bacteria, and plants, the MEP pathway starts with pyruvate and glyceraldehyde-3-phosphate (G3P) as its primary substrates. These two compounds combine to create 1-deoxy-D-xylulose-5-phosphate (DXP), which is subsequently transformed into MEP. Following this, MEP undergoes a series of enzyme-mediated alterations resulting in 4-diphosphocytidyl-2-C-methyl-D-erythritol (CDP ME), then transitioning to 2-C-methyl D erythritol 2,4 cyclodiphosphate (MEcPP), and ultimately converting into hydroxy 2-methyl-2 (E) butenyl, 4-diphosphate (HMBPP). In a controlled ratio, the hydrogenation and reduction of HMBPP yield both IPP

and DMAPP. These isoprene units behave as precursors for monoterpenoid, sesquiterpenoid, diterpenoid, and other terpenoid biosynthesis in the same way they do in the MEV pathway (Fig. 3) [18,19]. In different organisms, such as fungi, animals, and archaea rely mainly on the MEV pathway, while the MEP pathway is predominant in plants, algae, and bacteria [13,15].

4. TERPENE FORMULATIONS

Various classes of terpenes, including monoterpenes, sesquiterpenes, diterpenes, and tetraterpenes, have been successfully incorporated into advanced formulation approaches such as nanoemulsions, liposomes, polymeric nanoparticles, and nanostructured lipid carriers (Fig. 4). These delivery systems are designed to address key limitations of terpenes, including poor aqueous solubility, chemical instability, and low bioavailability. For example, nanoemulsions of monoterpenes increased solubility by up to 8-fold and improved antimicrobial efficacy by 2–3 times compared to free terpenes. Diterpene-loaded nanocarriers (e.g., Taxol formulations) improved oral bioavailability by approximately 70% and reduced required dosage levels by 50%, thereby enhancing therapeutic performance. Similarly, squalene and carotenoids have been exploited in nanostructured carriers for their antioxidant and pharmacological activities [20,21].

4.1. Mechanisms of enhanced delivery

Nanocarrier-based systems improve terpene bioavailability through multiple mechanisms. Lipid-based carriers such as nanoemulsions and nanostructured lipid carriers (NLCs) increase solubility by encapsulating hydrophobic terpenes within their lipid cores, thereby enhancing dispersibility in aqueous environments [19,20]. Liposomes protect terpenes from oxidation and enzymatic degradation by entrapping them within bilayer vesicles, while also improving permeability across biological membranes. Polymeric nanoparticles allow sustained and controlled release, prolonging circulation time and improving therapeutic efficiency. Additionally, surface modification of nanocarriers with ligands enables targeted delivery, reducing off-target effects and enhancing pharmacological outcomes [21]. Collectively, these mechanisms address key pharmacokinetic limitations and broaden the therapeutic applications of terpenes (Table 2).

Table 1. Comparison of major terpene classes, representative examples, and applications [12–17].

Class	Isoprene units	Examples (Source)	Key applications/activities
Hemiterpenes	1 (C_5)	Isoprene (plants, latex)	Industrial polymer precursor (rubber)
Monoterpenes	2 (C_{10})	Limonene (citrus), Linalool (lavender), Menthol (mint)	Fragrance, flavoring, antimicrobial, analgesic
Sesquiterpenes	3 (C_{15})	β -Caryophyllene (clove, black pepper), Humulene (hops)	Anti-inflammatory, anticancer, insect repellent
Diterpenes	4 (C_{20})	Taxol (<i>Taxus</i> spp.), Gibberellins (plants)	Chemotherapy, plant growth regulators
Sesterterpenes	5 (C_{25})	Manoalide (marine sponge)	Antimicrobial, anti-inflammatory
Triterpenes and Tetraterpenes	6 (C_{30}), 8 (C_{40})	Ursolic acid (rosemary), Squalene (shark liver, olive oil), β -Carotene (carrots), Lycopene (tomato)	Anticancer, antioxidant, skin protective, provitamin A, nutraceuticals

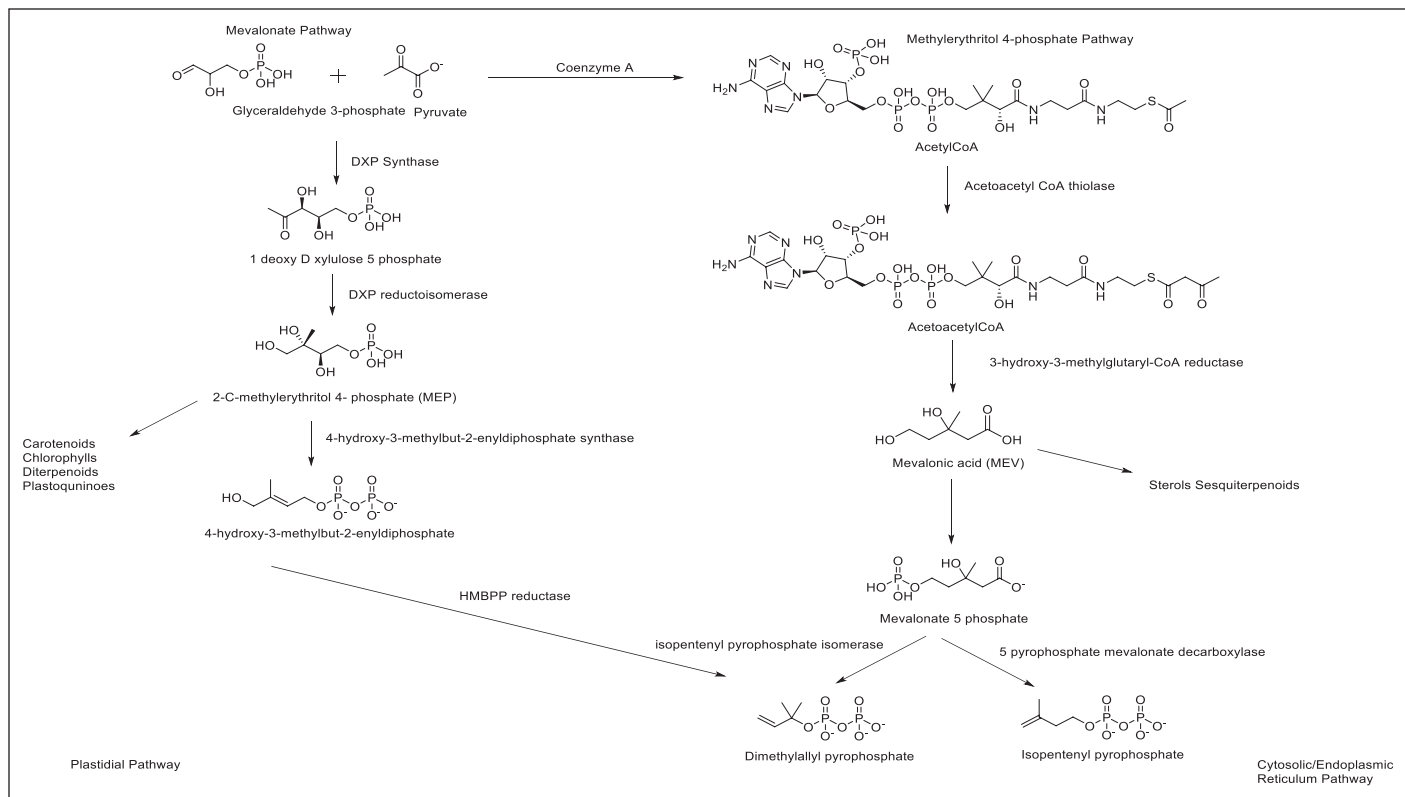


Figure 3. Mevalonate (MEV) and methylerythritol 4-phosphate (MEP) pathway.

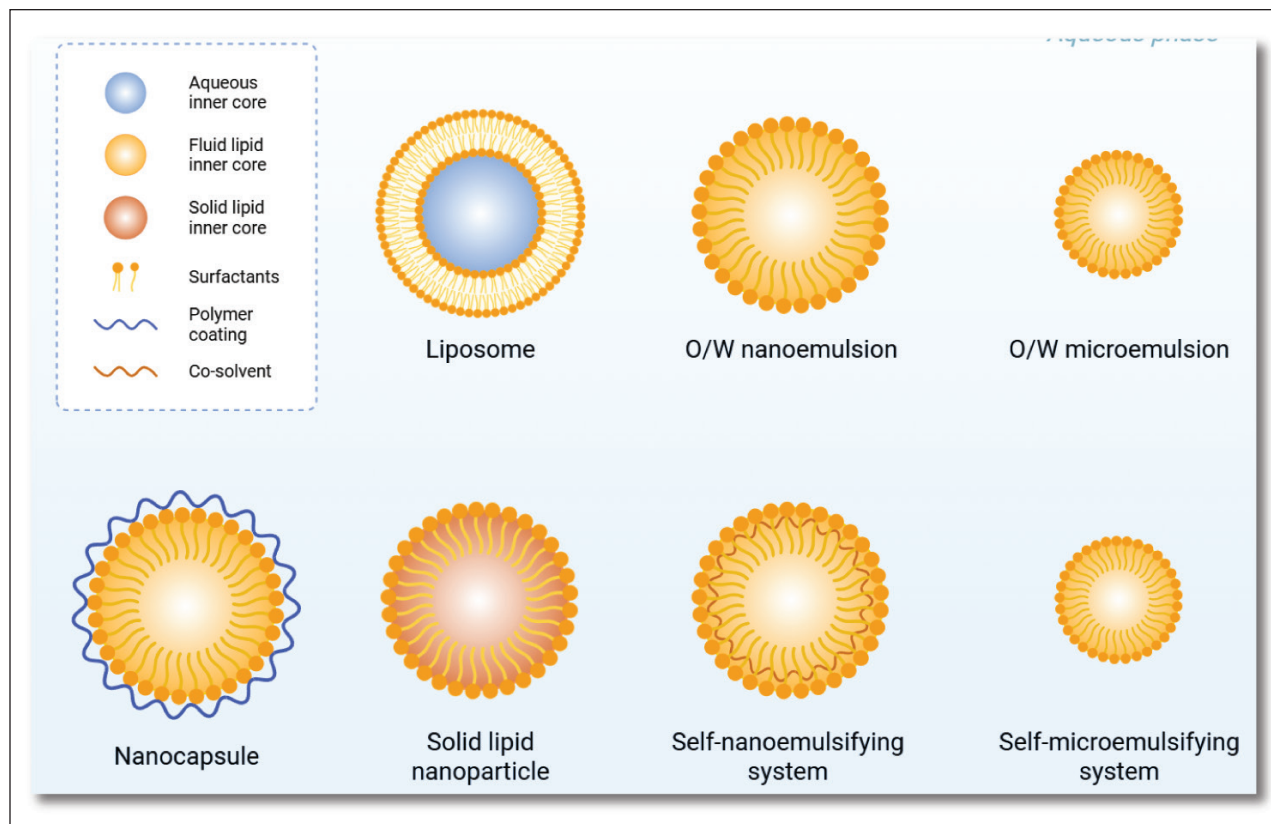


Figure 4. Formulation strategies for terpene delivery.

5. NATURAL SOURCES OF TERPENES

The naturally occurring terpenes occur in a wide variety of plants and some microorganisms, and they are involved in defense, repellence, and physiological functions. The most common ones appear in aromatic plants (such as conifers, citrus fruits, and herbs such as rosemary, thyme, and basil). Plants such as lavender, eucalyptus, and peppermint have their essential oils extracted, which contain monoterpenes and sesquiterpenes, making these plants have a distinct fragrance and also medicinal properties [22,23]. Other fruits rich in limonene and myrcene include the oranges, lemons, and mangoes, which are known for their citrusy and sweet aromas. Terpenes are produced, for instance, by certain algae, fungi, and by some insects such as termites [24,25]. Terpenes are being utilized in the pharmaceutical and cosmetic industries due to their anti-bacterial, anti-inflammatory, and antioxidant properties obtained from these natural sources, which are used in perfumes, flavors, and in therapeutic formulations (Table 3). Marine ecosystems represent a prolific but underexplored reservoir of structurally unique terpenes. For example, halogenated monoterpenes isolated from red algae (e.g., *Plocamium* spp.) exhibit potent antiviral and cytotoxic properties, while sesterterpenes from marine sponges (*Cacospongia* spp.) display promising anti-

inflammatory activity [26]. Soft corals produce a wide variety of diterpenes with novel ring systems, such as cembranoids and *briaranes*, which have shown strong anticancer and neuroprotective potential. Marine-derived carotenoids such as fucoxanthin, abundant in brown algae, are recognized for antioxidant and anti-obesity effects [27]. The presence of halogen substituents, uncommon in terrestrial terpenes, along with highly oxygenated skeletons, contributes to the distinctive bioactivities of marine-derived compounds, underlining the importance of oceans as a valuable source of novel terpene-based drug leads.

6. BIOLOGICAL ROLES OF TERPENES

Among natural organic compounds, terpenes represent a big family of natural compounds based on isoprene units, and they exert essential biological roles in plants and other organisms. The compounds contribute significantly to ecological interactions, defense mechanisms, and cellular protection. Terpenes exhibit tremendously broad chemical diversity, allowing them to both function as multifunctional key mediators in plant–environment interactions, including plant adaptations, survival, and success in their respective communities[28].

Table 2. Pharmacokinetic parameters of selected terpenes.

Terpene	Delivery form	C _{max} (µg/ml)	T _{max} (h)	AUC _{0–∞} (µg/h/ml)	Bioavailability Improvement (%)	References
Limonene	Oral (free form)	0.12	1.0	0.85	–	[26]
Limonene	Nanoemulsion	0.65	0.5	4.2	~390%	[27]
β-Caryophyllene	Free oil	0.20	2.0	1.1	–	[29]
β-Caryophyllene	Liposomal	0.98	1.0	5.8	~430%	[30]
Taxol (Diterpene)	Conventional IV	2.6	0.25	19.0	–	[31]
Taxol (Nab-paclitaxel)	Nanoparticle	3.1	0.25	31.5	~65%	[32]

Table 3. Natural sources of terpenes.

Source	Examples	Advantages	Disadvantages
Plants	- Limonene (Citrus fruits)	- Anti-inflammatory and antioxidant properties	- Skin irritation and allergies in some individuals
	- Pinene (Pine, Rosemary)	- Stress relief and relaxation (Linalool)	- Can cause respiratory issues if inhaled in high concentrations (e.g., pinene)
	- Myrcene (Mango, Basil)	- Pain relief (Beta-Caryophyllene)	- May interfere with drug metabolism (Limonene)
	- Linalool (Lavender)	- Antimicrobial activity (Pinene)	
	- Beta-Caryophyllene (Black Pepper, Clove)	- Boosts digestion and metabolism (Limonene)	
Fungus	- Trichodiene (<i>Fusarium species</i>)	- Antifungal and antibacterial properties	- Some fungal terpenes are mycotoxins and can be toxic to humans
	- Eudesmane (<i>Aspergillus</i>)	- Potential applications in drug synthesis (e.g., antibiotics)	- Allergic reactions or respiratory issues (e.g., <i>Aspergillus</i> exposure)
	- Ergosterol-derived terpenes (<i>Saccharomyces cerevisiae</i>)	- Ergosterol is a precursor for vitamin D synthesis	- Can cause food spoilage or contamination
Marine	- Fucoxanthin (Brown algae)	- Antioxidant and anti-cancer properties (Fucoxanthin)	- Limited bioavailability and absorption in humans
	- Squalene (Shark liver, algae)	- Moisturizing and skin-protective effects (Squalene)	- Potential environmental concerns with overharvesting (e.g., shark-derived squalene)
	- Callophycolide (Red algae)	- Antiviral and antimicrobial activities (Callophycolide)	- Some marine terpenes may cause cytotoxic effects at high doses

6.1. Ecological significance in plants

Plants rely on terpenes for ecological stability, plant adaptation, plant–insect interactions, pollination, seed dispersal, and allelopathy. Some agents of some plants produce volatile terpenes, such as monoterpenes and sesquiterpenes, to attract pollinators. For instance, flowers release fragrances built from terpenes such as linalool and myrcene to draw in bees, butterflies, and other pollinators, which is essential for reproduction. Like fruit-bearing plants, fruit-bearing plants synthesize terpenes, such as α -farnesene and β -caryophyllene, which have a role in ripe fruit aroma. However, they also stimulate the dispersal of seeds by animals [33,34]. Terpenes also contribute to allelopathy, the condition in which plants secrete compounds to undermine the growth of other species. Some plant species, such as pines and eucalyptus, produce high amounts of volatile terpenes such as pinene and camphor, which inhibit seed germination and growth of nearby plants, reducing competition for resources [17]. This ecological function is crucial for maintaining plant dominance in specific habitats, particularly forest ecosystems. Terpenes also contribute to plant adaptation to abiotic stress conditions such as high temperatures, drought, and UV radiation [35]. Carotenoids, a subclass of tetraterpenes, function in light absorption and dissipation, protecting plants from photodamage. By regulating these physiological responses, terpenes enable plants to survive harsh environmental conditions [36].

6.2. Antimicrobial activity

Terpenes are widely recognized for their documented pharmacological effects, particularly their antimicrobial activity against bacteria, fungi, and viruses. Many plants utilize terpenes as a defense mechanism to combat microbial infections, making them valuable in both traditional and modern medicine due to their antiseptic qualities. Research has shown that monoterpenes, such as thymol, menthol, and limonene, exhibit strong antibacterial properties by disrupting the bacterial cell membrane, increasing permeability, and ultimately leading to cell death. Thymol, a main ingredient in thyme essential oil, is highly effective, particularly in combating *Staphylococcus aureus* and *Escherichia coli*, and hence is a valuable additive in antimicrobial formulations [37,38]. As mentioned earlier, eugenol, a sesquiterpene compound that is present in cloves, has shown a great antiseptic activity against oral pathogens, with a wide use in dental care products [39,40]. In addition to antibacterial properties, many terpenes exhibit antifungal activity. Terpinen-4-ol from tea tree oil has been shown to inhibit the growth of fungal pathogens such as *Candida albicans* and *Aspergillus fumigatus* for the treatment

of fungal infection, including athlete's foot and candidiasis. Terpenes have also exhibited antiviral properties; in fact, certain compounds are effective against herpes simplex virus (HSV), human immunodeficiency virus (HIV), and influenza virus (Table 4) [41].

6.3. Anti-inflammatory and analgesic properties

Terpenes have been studied for their ability to reduce inflammation and alleviate pain, as inflammation plays a significant role in numerous chronic conditions. Many terpenes achieve their anti-inflammatory effects by affecting essential signaling pathways, including the NF- κ B and cyclooxygenase (COX) enzymes, which are critical to the inflammatory response. β -Caryophyllene, a sesquiterpene present in black pepper and cannabis, has been recognized as a selective agonist for the CB2 receptor, indicating that it interacts with the body's endocannabinoid system to help lessen inflammation and discomfort. Research has demonstrated that β -caryophyllene can notably decrease inflammatory markers in ailments such as arthritis, colitis, and neuroinflammation [14]. Monoterpenes, such as linalool and myrcene, found in lavender and hops, exhibit analgesic effects by interacting with neurotransmitter systems, particularly gamma-aminobutyric acid (GABA) receptors, which help reduce pain perception. Menthol, widely used in topical analgesic creams, produces a cooling effect that helps alleviate pain by activating transient receptor potential channels in sensory neurons [42]. Terpenes are also being explored for their role in managing chronic inflammatory diseases such as asthma and inflammatory bowel disease. α -Pinene, found in pine needles, has been shown to reduce airway inflammation in asthma by inhibiting inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha.

6.4. Anticancer and cytotoxic effects

Terpenes display impressive anticancer effects, with various compounds showing the capability to trigger apoptosis (programmed cell death) and reduce the growth of cancer cells. Numerous terpenes focus on essential cellular pathways linked to cancer development, such as oxidative stress, regulation of the cell cycle, and metastasis. Taxol (paclitaxel), a diterpene sourced from the Pacific yew tree (*Taxus brevifolia*), is among the most recognized anticancer medications, widely employed in chemotherapy for breast, ovarian, and lung cancers. Another significant anticancer terpene is curcumin, a polyterpene present in turmeric, which demonstrates substantial anti-proliferative impacts against various cancer cell lines by blocking NF- κ B signaling and encouraging tumor cell apoptosis [51]. Citrus-

Table 4. IC₅₀ / EC₅₀ values of terpenes against key targets.

Terpene	Target/cell line	IC ₅₀ /EC ₅₀	Biological activity	References
Thymol (Monoterpene)	<i>S. aureus</i>	IC ₅₀ = 18 μ g/ml	Antibacterial	[43]
Limonene	Breast cancer (MCF-7)	IC ₅₀ = 25 μ M	Anticancer	[44]
β -Caryophyllene	Colon cancer (HT-29)	IC ₅₀ = 12 μ M	Anticancer	[45,46]
Fucoxanthin (Marine tetraterpene)	Adipocyte differentiation	EC ₅₀ = 5 μ M	Anti-obesity	[47,48]
Ursolic acid (Triterpene)	HepG2 hepatoma	IC ₅₀ = 8 μ M	Cytotoxic	[49,50]

derived limonene has been investigated for its use in decreasing tumor growth since it has been shown to influence Ras signaling pathways, which are crucial for cancer cell survival. Other triterpenes, such as ursolic acid and oleanolic acid, present in rosemary and basil, have also shown anticancer action by inducing oxidative stress and inhibiting metastasis (Table 4) [52].

6.5. Neuroprotective and cognitive benefits

Terpenes have neuroprotective properties and are being used for the prevention and treatment of neurodegenerative diseases such as Alzheimer's, Parkinson's, and multiple sclerosis. Although not completely understood, many terpenes are antioxidants and anti-inflammatory compounds, which help prevent neuronal damage by oxidative stress and inflammation [49]. Lavender contains linalool, previously reported to be a cognitive-enhancing and anxiety-reducing agent, and may therefore also act as a potential therapeutic agent in neurodegenerative disorders. Also, β -Caryophyllene is thought to activate CB₂ receptors, which are being studied as a protective factor in neuroinflammation and neurodegenerative conditions. It has been shown that cannabinoid terpenes such as THC and CBD have a neuroprotective effect in Alzheimer's disease and epilepsy models by modulating neurotransmitter activity and decreasing neuroinflammation [50].

7. STRUCTURE–ACTIVITY RELATIONSHIPS (SAR) OF TERPENES

The pharmacological properties of terpenes are closely tied to their structural features, with subtle modifications in functional groups, stereochemistry, and chain length significantly influencing biological activity.

- a) **Monoterpenes:** Hydroxylated monoterpenes such as menthol and linalool exhibit stronger antimicrobial and analgesic effects compared to their hydrocarbon counterparts (e.g., limonene), due to increased hydrogen-bonding interactions with microbial membranes and neuronal receptors. The presence of an epoxide group in 1,8-cineole enhances mucolytic and anti-inflammatory activity by modulating airway ion channels [53,54].
- b) **Sesquiterpenes:** β -Caryophyllene, a bicyclic sesquiterpene, demonstrates selective CB₂ receptor agonism attributed to its rigid bicyclic skeleton, which confers affinity for cannabinoid receptors while avoiding CB₁-mediated psychoactivity. In contrast, acyclic sesquiterpenes (e.g., farnesol) mainly disrupt microbial membranes, showing a direct correlation between chain flexibility and antimicrobial potency [55,56].
- c) **Diterpenes:** The strong anticancer activity of Taxol (paclitaxel) is directly related to its complex diterpene core and ester side chains, which stabilize microtubules and block mitosis. Similarly, hydroxylated and lactone-containing diterpenes (e.g., andrographolide) display enhanced immunomodulatory effects compared to non-oxygenated analogs [57,58].
- d) **Triterpenes and tetraterpenes:** The pentacyclic structure of ursolic acid and oleanolic acid facilitates interaction with NF- κ B and STAT3 signaling pathways, leading to anti-inflammatory and pro-apoptotic effects. For carotenoids (tetraterpenes), conjugated double bonds are key to antioxidant potential, with longer chains (e.g., lycopene)

showing stronger singlet oxygen quenching than shorter ones (e.g., β -carotene) [59,60].

SAR evidence suggests that polar functional groups (hydroxyl, carboxyl, epoxide) improve target specificity and receptor binding, while lipophilicity and conjugation length largely determine membrane interactions and antioxidant activity. This critical relationship between terpene structure and function underpins their wide-ranging pharmacological outcomes and provides a rationale for chemical modifications to optimize drug-like properties.

8. ADVANCEMENTS IN DRUG DELIVERY AND BIOAVAILABILITY ENHANCEMENT

Recently, the drug delivery field has experienced significant development in enhancing the bioavailability, stability, and therapeutic efficacy of pharmaceutical compounds. However, many of the drugs (especially hydrophobic compounds) struggle to meet the goal of being soluble, fast-degrading, and poorly absorbed, resulting in suboptimal therapeutic outcomes. To overcome the above limitation, innovative nanotechnology approaches, encapsulation strategies, and synthetic modifications have been developed for enhancing the stability of the drug, targeted delivery, and controlled release (Table 5) [61].

8.1. Nanotechnology approaches

The emergence of nanotechnology has shifted the focus of the drug delivery field toward more improved drug delivery through the utilization of nanocarriers to increase drug solubility, stability, and targeted delivery. Nanoparticles, liposomes, micelles, dendrimers, and nanotubes are among the most widely used nanocarriers designed to improve bioavailability and therapeutic efficiency [62].

8.2. Nanoparticles for drug delivery

Nanoparticles, typically ranging from 1 to 100 nm, have unique physicochemical properties that allow them to penetrate biological barriers, protect drugs from enzymatic degradation, and improve systemic circulation time. Polymeric nanoparticles, made from materials like poly (lactic-co-glycolic acid) (PLGA) and chitosan, enable sustained and controlled drug release, reducing dosing frequency and side effects [63]. In cancer therapy, gold and silver nanoparticles are employed for targeted drug delivery, ensuring that chemotherapeutic agents reach tumor cells with minimal impact on healthy tissues.

8.3. Hydrogels and cyclodextrin complexation

Cross-linked hydrophilic polymers in hydrogels offering moisture-sensitive and pH-responsive drug release also make them suitable for transdermal, ocular, and wound healing applications. Growth factors, as well as anti-inflammatory agents, have been delivered with hydrogels to promote tissue regeneration and healing. One such encapsulation method of a hydrophobic drug molecule uses cyclodextrins, cyclic oligosaccharides, which form inclusion complexes [64].

8.4. Microencapsulation for oral and injectable formulations

Oral drug delivery has widely used microencapsulation techniques, such as spray drying, coacervation, and emulsion-

Table 5. Selected clinical trials of terpenes.

Terpene	Formulation	Clinical indication	Study design and size	Key outcome	References
Limonene	Oral capsules	GERD, gallstones	Phase II, n = 43	Reduced gallstone size, improved bile flow	[26]
β -Caryophyllene	Essential oil (inhalation)	Anxiety, pain	Pilot, n = 30	Reduced pain scores, anxiolytic effect	[65]
Curcumin (polyterpene)	Nano-formulation	Osteoarthritis	RCT, n = 160	↓ Pain & inflammation, ↑ mobility	[66]
Taxol (Paclitaxel, diterpene)	Nab-paclitaxel	Breast cancer	Phase III, n = 454	↑ PFS (progression-free survival) vs. conventional Taxol	[67]
Fucoxanthin	Supplement capsule	Obesity, metabolic syndrome	Phase II, n = 151	↓ Body weight, improved lipid profile	[68,69]

based techniques, to protect drugs from stomach acid degradation. This is particularly applicable to probiotics, peptides, and protein-based drugs for controlling release in the intestines [70,71]. For the treatment of chronic diseases, the need to administer a drug formulation frequently can be reduced if extended drug release is achieved using injectable formulations featuring microparticles. Another strategy to enhance bioavailability, metabolic stability, and improve therapeutic activity involves chemical modifications of drug molecules. Each synthetic modification is a prodrug strategy, a nanocrystal formulation, all designed to improve pharmacokinetics and pharmacodynamics [72].

9. CHALLENGES AND FUTURE PROSPECTS

Terpenes, renowned for their diverse biological activities and potential therapeutic applications, have gained significant attention in various fields, including medicine, agriculture, and biotechnology. Despite their promising pharmacological and ecological roles, the clinical translation and large-scale application of terpenes face several challenges. Understanding these limitations and exploring innovative strategies to overcome them is crucial for unlocking their full potential. Moreover, future research directions must focus on enhancing the bioavailability, stability, and sustainable production of terpenes to facilitate their broader application in healthcare and industrial sectors [68]. One of the primary challenges in the clinical application of terpenes is their low bioavailability and poor water solubility. Many terpenes, particularly lipophilic monoterpenes and sesquiterpenes, have limited solubility in aqueous environments, which hinders their absorption and distribution in the human body. Another significant challenge is the lack of comprehensive toxicity and pharmacokinetic data for many terpenes [69]. Although terpenes are widely used in traditional medicine and as food additives, their safety profiles at higher doses or long-term exposure remain insufficiently studied. The complex chemical structures of some terpenes, such as furanoditerpenes and sesquiterpene lactones, can pose potential toxicological risks, including hepatotoxicity and allergenic effects [73]. To eliminate the limitations related to terpenes, it has been proposed to improve their bioavailability, stability, and therapeutic efficacy. This suggests that one potential alternative approach to terpene delivery is to use nanotechnology, such as liposomes, nanoparticles, and nanoemulsions as delivery systems that would be capable of encapsulating terpenes and improving solubility, stability, and

release of terpenes. The second strategy for improving the pharmacokinetic properties of terpenes is through chemical and structural modification. Research into improving the solubility and metabolic stability of terpenes has shown that conjugation of hydrophilic moieties or synthetic semi-synthetic derivatives can be performed with success [73,74].

9.1. Safety, toxicity, and regulatory status of terpenes

Although terpenes are widely utilized in pharmaceuticals, nutraceuticals, and cosmetics, their safety profiles vary depending on type, concentration, and route of administration. Monoterpenes such as limonene and menthol are generally recognized as safe (GRAS) by the U.S. Food and Drug Administration (FDA) when used within prescribed limits. However, high doses may cause gastrointestinal irritation or allergic reactions. Sesquiterpenes like β -caryophyllene exhibit low toxicity and have received approval as food additives [75,76]. Carotenoids (e.g., β -carotene and fucoxanthin) are considered safe at dietary levels, though excessive supplementation has been linked to adverse effects in specific populations such as smokers. Fucoxanthin, in particular, has been reported to influence lipid metabolism and exhibit favorable safety and metabolic profiles in preclinical and clinical studies [77]. Regulatory authorities, including the FDA and European Medicines Agency (EMA), emphasize dosage thresholds and standardized safety testing, ensuring that most terpenes used in therapeutic and commercial products remain within acceptable safety margins [76].

9.2. Future research directions

Future progress in terpene research will rely on interdisciplinary innovations that integrate chemistry, biology, engineering, and computational sciences:

- a) **Synthetic biology and metabolic engineering:** Engineering microbial platforms such as *E. coli*, *Saccharomyces cerevisiae*, or cyanobacteria for high-yield terpene biosynthesis can reduce reliance on overharvesting plant sources. Pathway optimization through promoter engineering, flux redirection, and enzyme engineering can enable scalable, eco-friendly production of complex terpenes such as Taxol or artemisinin analogs.
- b) **CRISPR/Cas genome editing:** Targeted genome editing offers precise control over terpene biosynthetic pathways. CRISPR-mediated knock-in/knock-out of terpene synthase genes in plants or microbes can enhance yield,

modify structural features, or generate novel derivatives with improved pharmacological profiles.

- c) **Computational and AI-driven discovery:** Artificial intelligence and machine learning models can accelerate the discovery of new terpenes and predict their pharmacological potential by integrating multi-omics datasets, docking simulations, and SAR analyses. AI-guided molecular design may also identify semi-synthetic terpene derivatives with optimized solubility, stability, and receptor selectivity.
- d) **Nanotechnology and smart delivery systems:** Combining terpenes with advanced delivery systems such as stimuli-responsive nanocarriers, biomimetic vesicles, and 3D-printed drug delivery platforms can address bioavailability challenges while enabling targeted release and reduced toxicity.
- e) **Green chemistry and bioprocessing:** The development of environmentally sustainable extraction methods (e.g., supercritical CO₂ extraction, microwave-assisted extraction, enzymatic biotransformation) will be essential for large-scale applications without ecological damage.
- f) **Systems biology and multi-target therapeutics:** Network pharmacology approaches can map terpene interactions with multiple biological targets, paving the way for multi-target therapeutics in cancer, neurodegeneration, and metabolic diseases.

10. CONCLUSION

Terpenes, with their remarkable structural diversity and multifunctional properties, occupy a unique position at the intersection of ecology, pharmacology, and biotechnology. Their ecological significance, ranging from plant defense and pollinator attraction to seed dispersal and stress adaptation, highlights their evolutionary importance, while their broad pharmacological activities, including antimicrobial, anti-inflammatory, anticancer, antioxidant, and neuroprotective effects, underscore their translational potential. Despite these promising attributes, clinical application of terpenes remains constrained by challenges such as low aqueous solubility, chemical instability, limited bioavailability, and incomplete pharmacokinetic and safety data. Advances in nanotechnology-based formulations, chemical modifications, and biotechnological strategies have shown considerable promise in overcoming these barriers, enhancing stability, solubility, and therapeutic efficacy. Moreover, the integration of emerging tools such as synthetic biology, metabolic engineering, CRISPR-based pathway optimization, and AI-driven drug discovery provides exciting opportunities to scale sustainable production and design novel terpene derivatives with improved drug-like properties. Looking forward, interdisciplinary collaborations spanning natural product chemistry, pharmacology, formulation science, and computational biology will be crucial for translating terpenes into next-generation therapeutics and sustainable industrial products. By bridging ecological insights, mechanistic understanding, and technological innovations, terpenes are poised to make significant contributions to precision medicine, nanomedicine, agriculture, and environmental sustainability, ultimately redefining their role as versatile biomolecules in both nature and human health.

11. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

12. ACKNOWLEDGEMENTS

The authors acknowledge the support from IFTM University, Moradabad.

13. FINANCIAL SUPPORT

This research received no external funding.

14. CONFLICT OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

15. ETHICAL APPROVALS

The study does not involve experiments on animals or human subjects.

16. DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

17. PUBLISHER'S NOTE

All claims expressed in this article are solely those of the authors and do not necessarily represent those of the publisher, the editors and the reviewers. This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

18. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing the manuscript and no images were manipulated using AI.

REFERENCES

1. Jahangeer M, Fatima R, Ashiq M, Basharat A, Qamar SA, Bilal M, *et al.* Therapeutic and biomedical potentialities of terpenoids-a review. *J Pure Appl Microbiol.* 2021;15(2):471–83. doi: <https://doi.org/10.22207/JPAM.15.2.04>
2. Del Prado-audelo ML, Cortés H, Caballero-Florán IH, González-Torres M, Escutia-Guadarrama L, Bernal-Chávez SA, *et al.* Therapeutic applications of terpenes on inflammatory diseases. *Front Pharmacol.* 2021;12:704197. doi: <https://doi.org/10.3389/FPHAR.2021.704197>
3. Proshkina E, Plyusnin S, Babak T, Lashmanova E, Maganova F, Koval L, *et al.* Terpenoids as potential geroprotectors. *Antioxidants.* 2020;9:529. doi: <https://doi.org/10.3390/ANTIOX9060529>
4. Yamada Y, Kuzuyama T, Komatsu M, Shin-Ya K, Omura S, Cane DE, *et al.* Terpene synthases are widely distributed in bacteria. *Proc Natl Acad Sci U S A.* 2015;112:857–62. doi: <https://doi.org/10.1073/PNAS.1422108112>

5. Elshafie HS, Camele I. An overview of the biological effects of some mediterranean essential oils on human health. *Biomed Res Int.* 2017;2017:9268468. doi: <https://doi.org/10.1155/2017/9268468>
6. Bunse M, Daniels R, Gründemann C, Heilmann J, Kammerer DR, Keusgen M, *et al.* Essential oils as multicomponent mixtures and their potential for human health and well-being. *Front Pharmacol.* 2022;13:956541. doi: <https://doi.org/10.3389/fphar.2022.956541>.
7. Koyama S, Heinbockel T. The effects of essential oils and terpenes in relation to their routes of intake and application. *Int J Mol Sci.* 2020;21:1558. doi: <https://doi.org/10.3390/IJMS21051558>
8. Sharifi-Rad J, Sureda A, Tenore G, Daglia M, Sharifi-Rad M, Valussi M, *et al.* Biological activities of essential oils: from plant chemoeology to traditional healing systems. *Molecules.* 2017;22:70. doi: <https://doi.org/10.3390/MOLECULES22010070>
9. Marshall B, Amritkar K, Wolfe M, Kaçar B, Landick R. Evolutionary flexibility and rigidity in the bacterial methylerythritol phosphate (MEP) pathway. *Front Microbiol.* 2023;14:1286626. doi: <https://doi.org/10.3389/FMICB.2023.1286626/FULL>
10. Bergman ME, Davis B, Phillips MA. Medically useful plant terpenoids: biosynthesis, occurrence, and mechanism of action. *Molecules.* 2019;24:3961. doi: <https://doi.org/10.3390/MOLECULES24213961>
11. Mosquera MEG, Jiménez G, Taberno V, Vinueza-Vaca J, García-Estrada C, Kosalková K, *et al.* Terpenes and terpenoids: building blocks to produce biopolymers. *Sustain Chem.* 2021;2:467–92. doi: <https://doi.org/10.3390/SUSCHEM2030026>
12. Ninkuu V, Zhang L, Yan J, Fu Z, Yang T, Zeng H. Biochemistry of terpenes and recent advances in plant protection. *Int J Mol Sci.* 2021;22:5710. doi: <https://doi.org/10.3390/IJMS22115710>
13. Kasahara H, Hanada A, Kuzuyama T, Takagi M, Kamiya Y, Yamaguchi S. Contribution of the mevalonate and methylerythritol phosphate pathways to the biosynthesis of Gibberellins in *Arabidopsis*. *J Biol Chem.* 2002;277:45188–494. doi: <https://doi.org/10.1074/jbc.M208659200>
14. Masyita A, Mustika Sari R, Dwi Astuti A, Yasir B, Rahma Rumata N, Emran TB, *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.* 2022;13:100217. doi: <https://doi.org/10.1016/J.FOCHX.2022.100217>
15. Siddiqui T, Khan MU, Sharma V, Gupta K. Terpenoids in essential oils: Chemistry, classification, and potential impact on human health and industry. *Phytomed Plus.* 2024;4:100549. doi: <https://doi.org/10.1016/J.PHYPLU.2024.100549>
16. Brock NL, Dickschat JS. Biosynthesis of terpenoids. In: Ramawat K, Mérillon JM, editors. *Natural products.* Berlin, Heidelberg: Springer; 2013:2693–732. doi: https://doi.org/10.1007/978-3-642-22144-6_121
17. Li C, Zha W, Li W, Wang J, You A. Advances in the biosynthesis of terpenoids and their ecological functions in plant resistance. *Int J Mol Sci.* 2023;24:11561. doi: <https://doi.org/10.3390/IJMS241411561>
18. Coca-Ruiz V, Suárez I, Aleu J, Collado IG. Structures, occurrences and biosynthesis of 11,12,13-Tri-nor-sesquiterpenes, an intriguing class of bioactive metabolites. *Plants.* 2022;11:769. doi: <https://doi.org/10.3390/PLANTS11060769>
19. Singh A, Singh L. Acyclic sesquiterpenes nerolidol and farnesol: mechanistic insights into their neuroprotective potential. *Pharmacol Rep.* 2025;77: 31–42. doi: <https://doi.org/10.1007/S43440-024-00672-8>
20. Chemistry LibreTexts. n.d. Chirality and Stereoisomers. [cited 2025 March 7] Available from: [https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Supplemental_Modules_\(Organic_Chemistry\)/Chirality/Chirality_and_Stereoisomers](https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Supplemental_Modules_(Organic_Chemistry)/Chirality/Chirality_and_Stereoisomers)
21. Kvittingen L, Sjursnes BJ, Schmid R. Limonene in citrus: a string of unchecked literature citations?. *J Chem Educ.* 2021;98:3600–7. doi: https://doi.org/10.1021/ACS.JCHEMED.1C00363/SUPPL_FILE/ED1C00363_SI_002.DOCX
22. Trepa M, Sułkowska-Ziaja K, Kała K, Muszyńska B. Therapeutic potential of fungal terpenes and terpenoids: application in skin diseases. *Molecules.* 2024;29:1183. doi: <https://doi.org/10.3390/MOLECULES29051183>
23. Rodrigues ACJ, Carlotto ACM, Gonçalves MD, Concato VM, Detoni MB, Santos YMD, *et al.* Exploring the leishmanicidal potential of terpenoids: a comprehensive review on mechanisms of cell death. *Front Cell Infect Microbiol.* 2023;13:1260448. doi: <https://doi.org/10.3389/FCIMB.2023.1260448>
24. Pattanaik B, Lindberg P. Terpenoids and their biosynthesis in cyanobacteria. *Life.* 2015;5:269. doi: <https://doi.org/10.3390/LIFE5010269>
25. Vavitsas K, Fabris M, Vickers C. Terpenoid metabolic engineering in photosynthetic microorganisms. *Genes.* 2018;9:520. doi: <https://doi.org/10.3390/GENES9110520>
26. Yang J, Lee SY, Jang SK, Kim KJ, Park MJ. Anti-inflammatory effects of essential oils from the peels of citrus cultivars. *Pharmaceutics.* 2023;15:1595. doi: <https://doi.org/10.3390/PHARMACEUTICS15061595>
27. Hou CY, Hazeena SH, Hsieh SL, Li BH, Chen MH, Wang PY, *et al.* Effect of D-limonene nanoemulsion edible film on banana (*Musa sapientum* Linn.) post-harvest preservation. *Molecules.* 2022;27: :6157. doi: <https://doi.org/10.3390/MOLECULES27196157>
28. Wei J, Yang Y, Peng Y, Wang S, Zhang J, Liu X, *et al.* Biosynthesis and the transcriptional regulation of terpenoids in tea plants (*Camellia sinensis*). *Int J Mol Sci.* 2023;24:6937. doi: <https://doi.org/10.3390/IJMS24086937>
29. Klawitter J, Weissenborn W, Gövon I, Walz M, Klawitter J, Jackson M, *et al.* B-caryophyllene inhibits monoacylglycerol lipase activity and increases 2-arachidonoyl glycerol levels *in vivo*: a new mechanism of endocannabinoid-mediated analgesia?. *S Mol Pharmacol.* 2024;105:75–83. doi: <https://doi.org/10.1124/MOLPHARM.123.000668/-/DC1>
30. Amalraj A, Jacob J, Varma K, Gopi S. Preparation and characterization of liposomal β -caryophyllene (rephyll) by nanofiber weaving technology and its effects on delayed onset muscle soreness (DOMS) in humans: a randomized, double-blinded, crossover-designed, and placebo-controlled study. *ACS Omega.* 2020;5:24045. doi: <https://doi.org/10.1021/ACSOMEGA.0C03456>
31. Nicolaou KC, Riemer C, Kerr MA, Rideout DR, Wrasidlo WW. Design, synthesis and biological activity of protaxols. *Nature.* 1993;364:464–6. doi: <https://doi.org/10.1038/364464a0>
32. Palumbo R, Sottotetti F, Trifirò G, Piazza E, Ferzi A, Gambaro A, *et al.* Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) as second-line chemotherapy in HER2-negative, taxane-pretreated metastatic breast cancer patients: prospective evaluation of activity, safety, and quality of life. *Drug Des Devel Ther.* 2015;9:2189. doi: <https://doi.org/10.2147/DDDT.S79563>
33. Xie C, Gu J, Zhu S. Progress in research on terpenoid biosynthesis and terpene syntheses of Lauraceae species. *Forests.* 2024;15:1731. doi: <https://doi.org/10.3390/F15101731>
34. Cox-Georgian D, Ramadoss N, Dona C, Basu C. Therapeutic and medicinal uses of terpenes. *Med Plants.* 2019;2019:333. doi: https://doi.org/10.1007/978-3-030-31269-5_15
35. Holopainen JK, Himanen SJ, Yuan JS, Chen F, Stewart CN. Ecological functions of terpenoids in changing climates. In: Ramawat K, Mérillon JM, editors, *Natural products.* Berlin, Heidelberg: Springer; 2013:2913–40. doi: https://doi.org/10.1007/978-3-642-22144-6_129
36. Al-Khayri JM, Rashmi R, Toppo V, Chole PB, Banadka A, Sudheer WN, *et al.* Plant secondary metabolites: the weapons for biotic stress management. *Metabolites.* 2023;13:716. doi: <https://doi.org/10.3390/METABO13060716>
37. Khwaza V, Aderibigbe BA. Antibacterial activity of selected essential oil components and their derivatives: a review. *Antibiotics.* 2025;14:68. doi: <https://doi.org/10.3390/ANTIBIOTICS14010068>
38. Rakoczy K, Szymańska N, Stecko J, Kisiel M, Maruszak M, Niedziela M, *et al.* Applications of limonene in neoplasms and non-

- neoplastic diseases. *Int J Mol Sci.* 2025;26:6359. doi: <https://doi.org/10.3390/IJMS26136359>
39. Huang AC, Osbourn A. Plant terpenes that mediate below-ground interactions: prospects for bioengineering terpenoids for plant protection. *Pest Manag Sci.* 2019;75:2368. doi: <https://doi.org/10.1002/PS.5410>
40. Boncan DAT, Tsang SSK, Li C, Lee IHT, Lam HM, Chan TF, *et al.* Terpenes and Terpenoids in Plants: interactions with Environment and Insects. *Int J Mol Sci.* 2020;21:7382. doi: <https://doi.org/10.3390/IJMS21197382>
41. Maffei ME. Sites of synthesis, biochemistry and functional role of plant volatiles. *South Afr J Botany.* 2010;76:612–31. doi: <https://doi.org/10.1016/J.SAJB.2010.03.003>
42. Liktör-Busa E, Keresztes A, Lavigne J, Streicher JM, Largent-Milnes TM. Analgesic potential of terpenes derived from *Cannabis sativa*. *Pharmacol Rev.* 2021;73:1269. doi: <https://doi.org/10.1124/PHARMREV.120.000046>
43. Wang Z, Chen Y, Huang A, Wen H, Wu Y, Xu X, *et al.* Design, synthesis and biological evaluation of novel β -caryophyllene derivatives as potential anti-cancer agents through the ROS-mediated apoptosis pathway. *RSC Med Chem.* 2025;16:3174–89. doi: <https://doi.org/10.1039/D4MD00951G>
44. Dahham S, Tabana Y, Iqbal M, Ahamed M, Ezzat M, Majid A, *et al.* The anticancer, antioxidant and antimicrobial properties of the sesquiterpene β -caryophyllene from the essential oil of *Aquilaria crassna*. *Molecules.* 2015;20:11808. doi: <https://doi.org/10.3390/MOLECULES200711808>
45. Mumu M, Das A, Emran TB, Mitra S, Islam F, Roy A, *et al.* Fucoxanthin: a promising phytochemical on diverse pharmacological targets. *Front Pharmacol.* 2022;13:929442. doi: <https://doi.org/10.3389/FPHAR.2022.929442/FULL>
46. Gammone MA, D’Orazio N. Anti-obesity activity of the marine carotenoid fucoxanthin. *Mar Drugs.* 2015;13:2196–4. doi: <https://doi.org/10.3390/MD13042196>
47. Huang Q, Chen H, Ren Y, Wang Z, Zeng P, Li X, *et al.* Anti-hepatocellular carcinoma activity and mechanism of chemopreventive compounds: ursolic acid derivatives. *Pharm Biol.* 2016;54:3189–96. doi: <https://doi.org/10.1080/13880209.2016.1214742>
48. Zhang DM, Tang PMK, Chan JYW, Lam HM, Au SWN, Kong SK, *et al.* Anti-proliferative effect of ursolic acid on multidrug resistant hepatoma cells R-HepG2 by apoptosis induction. *Cancer Biol Therapy.* 2007;6:1381–9. doi: <https://doi.org/10.4161/cbt.6.9.4528>
49. Mahizan NA, Yang SK, Moo CL, Song AAL, Chong CM, Chong CW, *et al.* Terpene derivatives as a potential agent against antimicrobial resistance (AMR) pathogens. *Molecules.* 2019;24:2631. doi: <https://doi.org/10.3390/MOLECULES24142631>
50. El Fannassi Y, Gharsallaoui A, Khelissa S, El Amrani MA, Suisse I, Sauthier M, *et al.* Complexation of terpenes for the production of new antimicrobial and antibiofilm molecules and their encapsulation in order to improve their activities. *Appl Sci.* 2023;13:9854. doi: <https://doi.org/10.3390/APPI13179854>
51. Kamran S, Sinniah A, Abdulghani MAM, Alshawsh MA. Therapeutic potential of certain terpenoids as anticancer agents: a scoping review. *Cancers.* 2022;14:1100. doi: <https://doi.org/10.3390/CANCERS14051100/S1>
52. Gonçalves ECD, Baldasso GM, Bicca MA, Paes RS, Capasso R, Dutra RC. Terpenoids, cannabimimetic ligands, beyond the cannabis plant. *Molecules.* 2020;25:1567. doi: <https://doi.org/10.3390/MOLECULES25071567>
53. De Cássia Da Silveira E Sá R, Andrade L, De Sousa D. A review on anti-inflammatory activity of monoterpenes. *Molecules.* 2013;18:1227. doi: <https://doi.org/10.3390/MOLECULES18011227>
54. Potocka W, Assy Z, Bikker FJ, Laine ML. Current and potential applications of monoterpenes and their derivatives in oral health care. *Molecules.* 2023;28:7178. doi: <https://doi.org/10.3390/MOLECULES28207178>
55. Meeran MFN, Al Tae H, Azimullah S, Tariq S, Adeghate E, Ojha S. β -Caryophyllene, a natural bicyclic sesquiterpene attenuates doxorubicin-induced chronic cardiotoxicity via activation of myocardial cannabinoid type-2 (CB2) receptors in rats. *Chem Biol Interact.* 2019;304:158–67. doi: <https://doi.org/10.1016/J.CBI.2019.02.028>
56. Andrade-Silva M, Correa LB, Candéa ALP, Cavalher-Machado SC, Barbosa HS, Rosas EC, *et al.* The cannabinoid 2 receptor agonist β -caryophyllene modulates the inflammatory reaction induced by *Mycobacterium bovis* BCG by inhibiting neutrophil migration. *Inflamm Res.* 2016;65:869–79. doi: <https://doi.org/10.1007/S00011-016-0969-3>
57. Schneider F, Pan L, Ottenbruch M, List T, Gaich T. The chemistry of nonclassical taxane diterpene. *Acc Chem Res.* 2021;54:2347–60. doi: <https://doi.org/10.1021/ACS.ACCOUNTS.0C00873>
58. Sati P, Sharma E, Dhyani P, Attri DC, Rana R, Kiyekbayeva L, *et al.* Paclitaxel and its semi-synthetic derivatives: comprehensive insights into chemical structure, mechanisms of action, and anticancer properties. *Eur J Med Res.* 2024;29:90. doi: <https://doi.org/10.1186/S40001-024-01657-2>
59. Kashyap D, Sharma AS, Tuli H, Punia SK, Sharma A. Ursolic acid and oleanolic acid: pentacyclic terpenoids with promising anti-inflammatory activities. *Recent Pat Inflamm Allergy Drug Discov.* 2016;10:21–33. doi: <https://doi.org/10.2174/1872213X10666160711143904>
60. Similie D, Minda D, Bora L, Kroškins V, Lugiņina J, Turks M, *et al.* An update on pentacyclic triterpenoids ursolic and oleanolic acids and related derivatives as anticancer candidates. *Antioxidants.* 2024;13:952. doi: <https://doi.org/10.3390/ANTIOX13080952>
61. Wróblewska-Luczka P, Cabaj J, Bargieł J, Luszczki JJ. Anticancer effect of terpenes: focus on malignant melanoma. *Pharmacol Rep.* 2023;75:1115. doi: <https://doi.org/10.1007/S43440-023-00512-1>
62. Lou J, Duan H, Qin Q, Teng Z, Gan F, Zhou X, *et al.* Advances in oral drug delivery systems: challenges and opportunities. *Pharmaceutics.* 2023;15:484. doi: <https://doi.org/10.3390/PHARMACEUTICS15020484>
63. Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MDP, Acosta-Torres LS, *et al.* Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnol.* 2018;16(1):1–33. doi: <https://doi.org/10.1186/S12951-018-0392-8>
64. Kurul F, Turkmen H, Cetin AE, Topkaya SN. Nanomedicine: how nanomaterials are transforming drug delivery, bio-imaging, and diagnosis. *Next Nanotechnol.* 2025;7:100129. doi: <https://doi.org/10.1016/J.NXNANO.2024.100129>
65. Montero AJ, Adams B, Diaz-Montero CM, Glück S. Nab-paclitaxel in the treatment of metastatic breast cancer: a comprehensive review. *Expert Rev Clin Pharmacol.* 2011;4:329–4. doi: <https://doi.org/10.1586/ECP.11.7>
66. Rivera-Pérez E, Escobar-Ortiz A, Pérez-Ramírez IF, Regalado-González C, Zubieta-Otero LF, Rodríguez-García ME, *et al.* Encapsulation of spray-dried curcumin nanoemulsions to develop a supplement with ingredients for the control of osteoarthritis. *J Drug Deliv Sci Technol.* 2023;82:104299. doi: <https://doi.org/10.1016/J.JDDST.2023.104299>
67. Mumu M, Das A, Emran T Bin, Mitra S, Islam F, Roy A, *et al.* Fucoxanthin: a promising phytochemical on diverse pharmacological targets. *Front Pharmacol.* 2022;13:929442. doi: <https://doi.org/10.3389/FPHAR.2022.929442>
68. Hosseini M, Pereira DM. The chemical space of terpenes: insights from data science and AI. *Pharmaceutics.* 2023;16:202. doi: <https://doi.org/10.3390/PH16020202>
69. Yadav H, Mahalvar A, Pradhan M, Yadav K, Kumar Sahu K, Yadav R. Exploring the potential of phytochemicals and nanomaterial: a boon to antimicrobial treatment. *Med Drug Discov.* 2023;17:100151. doi: <https://doi.org/10.1016/J.MEDIDD.2023.100151>

70. Jadhav LA, Mandlik SK. Nanocarriers in skin cancer treatment: emerging drug delivery approaches and innovations. *Nano TransMed.* 2025;4:100068. doi: <https://doi.org/10.1016/J.NTM.2024.100068>
71. Chehelgerdi M, Chehelgerdi M, Allela OQB, Pecho RDC, Jayasankar N, Rao DP, *et al.* Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. *Mol Cancer.* 2023;22:169. doi: <https://doi.org/10.1186/S12943-023-01865-0>
72. Markovic M, Ben-Shabat S, Dahan A. Prodrugs for improved drug delivery: lessons learned from recently developed and marketed products. *Pharmaceutics.* 2020;12:1031. doi: <https://doi.org/10.3390/pharmaceutics12111031>
73. Elbouzidi A, Haddou M, Baraich A, Taibi M, El Hachlafi N, Pareek A, *et al.* Biochemical insights into specialized plant metabolites: advancing cosmeceutical applications for skin benefits. *J Agric Food Res.* 2025;19:101651. doi: <https://doi.org/10.1016/J.JAFR.2025.101651>
74. Vaou N, Stavropoulou E, Voidarou C, Tsigalou C, Bezirtzoglou E. Towards advances in medicinal plant antimicrobial activity: a review study on challenges and future perspectives. *Microorganisms.* 2021;9:2041. doi: <https://doi.org/10.3390/MICROORGANISMS9102041>
75. Kim YW, Kim MJ, Chung BY, Bang DY, Lim SK, Choi SM, *et al.* Safety evaluation and risk assessment of D-limonene. *J Toxicol Environ Health B Crit Rev.* 2013;16:17–38. doi: <https://doi.org/10.1080/10937404.2013.769418>
76. Ricardi C, Barachini S, Consoli G, Marazziti D, Polini B, Chiellini G. Beta-caryophyllene, a cannabinoid receptor type 2 selective agonist, in emotional and cognitive disorders. *Int J Mol Sci.* 2024;25:3203. doi: <https://doi.org/10.3390/IJMS25063203>
77. Muradian K, Vaiserman A, Min KJ, Fraifeld VE. Fucosanthin and lipid metabolism: a minireview. *Nutr Metab Cardiovasc Dis.* 2015;25:891–7. doi: <https://doi.org/10.1016/J.NUMECD.2015.05.010>

How to cite this article:

Anjali KM, Raghav A, Chauhan AS, Kumar P. Natural terpenes: An overview of structural diversity and multifunctional applications. *J Appl Pharm Sci.* 2026;16(04):079-091. DOI: 10.7324/JAPS.2026.274026