Engineering in Life Sciences

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REVIEW OPEN ACCESS

Menthol and Its Derivatives: Exploring the Medical Application Potential

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Received: 10 October 2024 | **Revised:** 7 July 2025 | **Accepted:** 22 July 2025

Funding: This work was supported by the National Key Research and Development Program of China (2021YFC21037003).

Keywords: anti-cancer | medical applications | menthol | menthol derivatives | pharmacological effects

ABSTRACT

Menthol, a natural organic compound and the primary component of mint, exhibits diverse biological activities, including analgesic, anti-inflammatory, antibacterial, neuroprotective, and anticancer effects. The chemical modification of menthol, through processes such as esterification and amination, further enhances these activities, expanding its potential applications in drug development, agriculture, and food preservation. This review explores the structure-activity relationships (SAR) of menthol and its derivatives, emphasizing the significance of molecular modifications in enhancing their pharmacological effects. Research indicates that menthol and its derivatives can improve drug permeation, reduce inflammation, enhance memory, and even target cancer cells through various mechanisms. In addition, we examine the safety and pharmacokinetics of menthol and its derivatives to better understand their clinical potential. Although significant progress has been made in preclinical models, further research is necessary to fully elucidate their mechanisms of action and optimize their therapeutic efficacy in clinical settings. Continued innovation in drug delivery technologies and the development of novel menthol derivatives present promising prospects for future therapeutic applications.

1 | Introduction

Menthol is a monocyclic monoterpene ($C_{10}H_{20}O$) [1], widely used in pharmaceuticals, food, and cosmetics due to its cooling sensation and aroma [2, 3]. Its isomers, such as L-menthol and D-menthol, exhibit slight structural differences that affect their biological activities [4, 5]. Through chemical modifications like esterification and amination, certain menthol derivatives have been developed, some of which exhibit enhanced biological activities and pharmacological effects, such as potential treatments for irritable bowel syndrome and stronger analgesic properties [6, 7].

Through the *Web of Science*, a search using the keywords *menthol and its derivatives* (without additional search filters) yielded 372 research articles, 227 of which (approximately 61%) are related to pharmacology and pharmacy (see Figure S1). These studies cover the potential applications of menthol and its derivatives in the treatment of various diseases, including analgesic effects, anti-inflammatory properties, and antibacterial characteristics [8–12]. In particular, menthol and its derivatives have been extensively researched in the development of analgesics due to their ability to produce pain relief by stimulating specific receptors [8–10]. Additionally, the anti-inflammatory properties of menthol make

it an important candidate for treating chronic inflammation and related diseases [11, 12]. As research on menthol and its derivatives continues to deepen, scientists are exploring their potential applications in other fields, such as neuroprotection and anticancer therapy [13, 14]. Studies have shown that certain menthol derivatives may exert protective effects on the nervous system by modulating cellular signaling pathways or exhibit potential therapeutic effects against various cancers [14]. These findings not only enhance our understanding of the biological activities of menthol and its derivatives but also provide new directions for novel drugs' development.

This review provides a detailed examination of the current potential applications of menthol and its derivatives as drugs, focusing on aspects such as the structure-activity relationship (SAR), various pharmacological mechanisms, safety evaluations, and pharmacokinetics. As related research deepens, a better understanding of their mechanisms of action will pave the way for innovative therapeutic strategies. The exploration of menthol and its derivatives broadens their application range and necessitates continued research into their benefits and potential uses to advance modern medicine.

2 | SAR of Menthol and Its Derivatives

Multiple studies have demonstrated that the pharmacological effects of menthol and its derivatives are closely linked to their chemical structures [6, 15, 16]. The relationship between molecular modifications and biological activity, known as the SAR, plays a critical role in understanding how these compounds interact with biological targets, including receptors and enzymes [17, 18]. By analyzing the structural characteristics of menthol and its derivatives, researchers can identify the key factors responsible for producing therapeutic effects such as analgesia and anti-inflammation [19, 20], as well as inhibiting the transmission of vector-borne diseases by harmful mosquitoes [6, 21]. This section will explore how the characteristics of the chemical structure influence the pharmacological properties of menthol and its derivatives, providing insights for optimizing their potential in medical applications.

2.1 | Analgesic Effects Mediated by TRPM8 Receptor Activation

In 2006, Proudfoot et al. confirmed that menthol produces analgesic effects by activating the TRPM8 receptor [22]. Identifying and screening more effective TRPM8 ligands is crucial for enhancing analgesic effects. Sherkheli et al. conducted studies based on the structure of menthol and constructed several novel menthol derivative ligands [16]. The results revealed that five derivatives—CPS-368 (D-alanine-O-methyl conjugate of menthol), CPS-369 (D-alanine-O-ethyl conjugate of menthol), CPS-125 (sulfadiazine conjugate of menthol), WS-5 (N-alkylcarbonyl-amino acid ester of p-menthane), and WS-12 (Cyclohexanecarboxamide)—exhibited outstanding performance in TRPM8 selectivity experiments, with potency and efficacy improvements of up to six-fold and two-fold, respectively. WS-12, in particular, features a hexacyclic ring structure and an N-alkylcarbonyl side chain, which are critical for its high selectivity and potency in activating TRPM8 without affecting other thermo-TRP channels such as TRPV1-4 and TRPA1. These structural modifications highlight the importance of the hexacyclic ring and bulky N-alkylcarbonyl groups in enhancing the binding affinity and specificity of TRPM8 ligands [16]. Comparative analysis further demonstrated that all five menthol derivatives contain a hexacyclic ring structure, which is essential for their high potency. In contrast, derivatives lacking this structure, such as WS-23 (N,2,3-Trimethyl-2-isopropyl Butanamide), showed significantly reduced activity. Additionally, furanone compounds with a pentacyclcic ring structure exhibited no selective activity at all, underscoring the critical role of the hexacyclic ring in TRPM8 activation [23].

2.2 | Anti-Inflammatory Properties Through Structural Modifications

Menthol, known for its natural anti-inflammatory properties, can significantly enhance its activity through structural modifications targeting specific functional groups. Recent research has explored the SAR of menthol derivatives to enhance their therapeutic potential [20]. Kamble et al. employed computer-aided methods to design and synthesize new menthol derivatives by modifying the phenolic hydroxyl group (-OH) at the C3 position of the menthol scaffold [20]. This modification was achieved through esterification with aromatic and aliphatic carboxylic acids (e.g., acetyl chloride or benzoyl chloride), resulting in derivatives such as menthyl acetate and menthyl benzoate. The choice of the C3-OH modification site is critical, as this group directly participates in hydrogen bonding with inflammatory targets such as cyclooxygenase-2 (COX-2, PDB ID: 1CX2). The derivatives exhibited binding affinities up to 1.2–1.5 times stronger than reference drugs for antimicrobial activity and up to 1.3 times stronger for anti-inflammatory activity. ADMET analysis predicted good drug-likeness, indicating promising potential for further development.

2.3 | Insecticidal Activity and Structural Optimization

Menthol and its derivatives are important insecticidal components of essential oils (EOs), capable of effectively preventing the spread of vector-borne diseases [6]. Samarasekera et al. demonstrated that although thymol and menthol have similar molecular structures, the aromatic ring in thymol contributes to its superior mosquitocidal activity against *Aedes aegypti* and *Anopheles tessellatus* due to its aromaticity [6]. Further structural modifications were performed by introducing ester or amide groups at the C3 hydroxyl position of $_{L}$-menthol, resulting in derivatives such as menthyl chloroacetate, chloropropionate, dichloroacetate, and carboxamide. These modifications altered the polarity and conformation of the molecules, improving their interactions with mosquito neural receptors and significantly enhancing insecticidal activity. Among these, menthyl chloroacetate exhibited the highest efficacy due to the increased lipophilicity from the chlorine atom, facilitating penetration through the insect cuticle. However, excessive halogen substitution may reduce activity. In addition, modification of the carbonyl group (C═O) of $_{L}$-menthone to form menthone glyceryl acetal

introduced a hemiacetal ring structure, enhancing hydrogen bonding with target proteins and further improving insecticidal potency [6].

2.4 | Summary of SAR

From the above, it is evident that the SAR of menthol and its derivatives highlights the critical impact of molecular modifications on their pharmacological properties. Variations in chemical structure, such as the introduction of ester groups at the C3 hydroxyl group (—OH), halogen atoms at C8 or C9 positions, and acetal rings via C2 ketone modification, significantly influence their analgesic, anti-inflammatory, and mosquitocidal activities. Esterification enhances lipophilicity and membrane permeability, while halogenation strengthens electrostatic interactions with microbial targets. Acetal ring formation optimizes molecular geometry for binding to insect GABA (γ-Aminobutyric Acid) receptors. Compounds with specific structural features, such as a hexacyclic ring or aromaticity, demonstrate superior efficacy in TRPM8 receptor activation and insecticidal applications, underscoring the importance of structural optimization. Table 1 summarizes menthol and its known derivatives based on their SAR. These insights not only deepen our understanding of menthol's biological activity but also provide a foundation for the development of more effective therapeutic agents and insecticidal formulations.

3 | Pharmacological Effects of Menthol and its Derivatives

The previous section analyzed the impact of structural modifications of menthol and its derivatives on their pharmacological effects, highlighting that structural optimization offers significant potential for enhancing therapeutic efficacy. This section will further explore the broad pharmacological actions of menthol and its derivatives, focusing on their mechanisms and clinical significance in areas such as enhancing drug permeation, anti-inflammatory effects, analgesia, memory improvement, anticancer properties, gastrointestinal protection, and antibacterial, and insecticidal activities. A detailed analysis of these effects will not only deepen our understanding of their specific roles in different physiological systems but also provide theoretical support and research directions for their application in the treatment of various diseases.

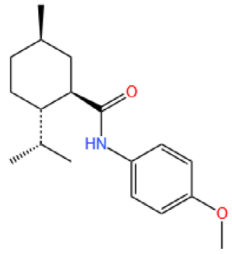
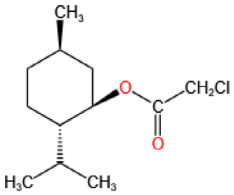
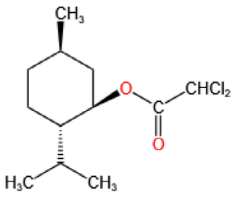
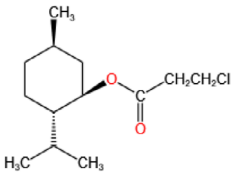
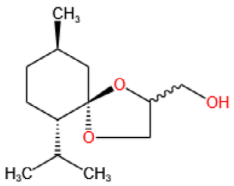
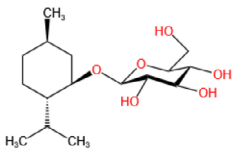
3.1 | Drug Permeation Effects

Menthol and its derivatives are widely used as penetration enhancers for transdermal drug delivery [24, 25]. Their ability to enhance drug permeation is attributed to their interactions with the stratum corneum (SC), the outermost layer of the skin. The SC is highly hydrophobic, making it difficult for hydrophilic drugs, such as polysaccharides, 5-fluorouracil (5-FU), and 5-aminolevulinic acid-based photodynamic therapy (ALA-PDT), to penetrate effectively [26]. Menthol and its derivatives disrupt the tightly packed lipid matrix of the SC by intercalating into the lipid bilayers, increasing their fluidity and creating transient pores. This enhances the diffusion coefficients of drugs, improving their permeability [27, 28]. This effect is particularly pronounced for hydrophilic drugs, which typically struggle to penetrate the highly hydrophobic SC. Additionally, menthol and its derivatives can interact with keratin proteins in the SC, leading to partial denaturation and further reducing the skin barrier function. These combined effects facilitate the penetration of both hydrophilic and lipophilic drugs [27, 28].

Olivella et al. found that L-menthol significantly enhanced the transdermal delivery of quercetin (Q) in carbopol gel (CG) [29]. Using Franz diffusion cells, the addition of 1.95% L-menthol increased quercetin permeation by 17 times. L-menthol was approximately nine times more effective than dimethylformamide (DMF) at the same concentration. This enhancement is due to L-menthol's direct action on the skin membrane, promoting relaxation and improving drug permeation. The team led by Zhao et al. synthesized O-acylmenthol derivatives and saturated fatty acid O-ethylmenthol (MET) using L-menthol for the development and testing of new penetration enhancers [30]. They tested the percutaneous absorption enhancing effects of these compounds on five model drugs (5-fluorouracil, isosorbide dinitrate, lidocaine, ketoprofen, and indomethacin). The experimental results showed that menthol derivatives with different chain lengths exhibited varying enhancement effects on different drugs. The C14 acyl chain in O-acylmenthol derivatives aligns with the hydrophobic core of the SC, while the terminal ester group (—COOR) interacts with hydrophilic regions. This dual interaction disrupts lipid packing, explaining its superior enhancement for hydrophilic drugs like 5-FU [30]. In contrast, C6-C10 chain derivatives showed better enhancement for lipophilic drugs, as their shorter chains preferentially interact with the lipid-rich regions of the SC, facilitating the permeation of lipophilic compounds [31]. Clemente et al. used PerMM software to simulate the in vitro permeability of menthol and its prodrugs 1c and 1g [32]. The results indicated that menthol and its prodrugs can cross biological membranes via a "flip-flop" mechanism. This prediction was subsequently validated through experiments using a biomimetic artificial membrane (BAM), which showed that the menthol prodrugs (1c and 1g) had higher apparent permeability coefficients (Papp) compared to menthol itself, as well as good stability. This demonstrates that the use of simulation technology can successfully predict the penetration-enhancing effects of certain menthol derivatives, saving time and resources in subsequent drug development.

Overall, menthol and its derivatives have shown great potential as penetration enhancers in transdermal drug delivery. These compounds can effectively improve the skin permeability of both hydrophilic and lipophilic drugs, providing a solid foundation for further optimization of transdermal drug delivery systems. By combining in vitro experiments and computational simulations, researchers can more accurately predict the mechanisms of action of these derivatives, thereby accelerating the drug development process. The effects of additional menthol derivatives as penetration enhancers are presented in Table 2. These research findings not only serve as a reference for the development of new penetration enhancers but also offer more efficient transdermal delivery options for different types of drugs. This will provide important support for personalized treatment and non-invasive drug delivery in the future.

TABLE 1 | The structural changes of menthol derivatives lead to enhanced pharmacological effects.

Menthol derivatives	Structural formula	Structural changes	Enhanced pharmacological effects	References
Derivative WS-12		Introducing a six-membered ring structure based on menthol.	The cooling and analgesic effects are enhanced by 40%.	[16]
Menthyl chloroacetate		Introducing a chlorine atom and an acetate group.	Enhanced insecticidal activity against *Aedes aegypti* and *Anopheles* spp. and antibacterial effects against *Escherichia coli* and *Staphylococcus aureus*, with an increase of 30%–50%.	[6]
Menthyl dichloroacetate		Introducing two chlorine atoms and an acetate group.		
Menthyl chloropropionate		Introducing a chlorine atom and a propionate group.		
Menthone glyceryl acetal		Converting the carbonyl group to an acetal group based on menthone.		
(−)-menthol β-d-glycoside		Introducing a sugar molecule (β-D-glucose)	The cooling intensity applied to the skin is approximately enhanced by 70%.	[109]

3.2 | Anti-Inflammatory Effects

Menthol and its derivatives have garnered attention for their anti-inflammatory properties, making them potential candidates for therapeutic applications in treating inflammatory conditions. Their ability to modulate inflammatory responses stems from their interactions with key signaling pathways and inflammatory mediators. This section explores the mechanisms by which menthol and its derivatives exert anti-inflammatory effects and their potential applications in the management of various inflammatory diseases.

Ghori et al. produced an oily formulation containing menthol (OFCMT) and applied it to the inflamed paws of rats [33]. The results showed that inflammation was significantly reduced in the rats treated with OFCMT compared to the control group. The team suggested that menthol played a key role in the anti-inflammatory effect, specifically by inhibiting the synthesis of cyclooxygenase (COX) and reducing the production of prostaglandin E2 (PGE2), a key inflammatory mediator. This mechanism is similar to that of indomethacin, a well-known COX inhibitor [33]. Researchers developed a mixed herbal medicine composed of 30%–55% menthol and 14%–32% menthone and

TABLE 2 | This summary of recent reports on drug permeation effects of menthol derivatives.

Menthol derivatives	Tested drugs	Effectiveness	References
$_{L}$-menthyl acetate	5-aminolevulinic acid (ALA)	30 h, 1.7× increase in permeation.	[110]
3-*iso*-butylmenthol	ketoprofen	8 h, 2.0× increase in E_f[1].	[101]
2-isopropyl-5-methylcyclohexyl tetradecanoate (C14 alkyl chain)	5-fluorouracil (5-FU)	P[2] increased by 1.34×.	[30]
2-isopropyl-5-methylcyclohexyl hexanoate (C6 alkyl chain)	isosorbide dinitrate (ISDN)	P[2] increased by 1.91×.	[30]
2-isopropyl-5-methylcyclohexyl heptanoate (C7 alkyl chain)	indomethacin (IM)	P[2] increased by 3.70×.	[30]
2-isopropyl-5-methylcyclohexyl 2-hydroxypanoate (M-LA)	lidocaine (LD)	P[2] increased by 3.20×.	[111]
thiomenthol derivatives	ketoprofen	8 h, 15.0× increase in E_f[1].	[112]
p-menthane derivatives	paroxetine	Accumulation increased by 2.3×.	[113]
menthone	puerarin	ER[3] increased by nearly 31.60×.	[114]
p-menth-4(8)-en-3-ol	5-fluorouracil	ER[3] increased by nearly 3.08×.	[115]

[1]Enhancement factor.
[2]Permeability coefficient.
[3]Enhancement ratio.

investigated its therapeutic effects on mice infected with *Schistosoma mansoni* [34]. The results showed not only a reduction in the number of eggs in the mice but also an 84% decrease in blood eosinophils, along with a decline in inflammatory cytokines IL-4 and IL-10 levels. This suggests that herbal compounds composed of menthol and its derivatives can modulate the immune response by suppressing the production of pro-inflammatory cytokines and regulating Th2-mediated inflammation, which is critical in schistosomiasis [34]. Additionally, the anti-inflammatory effects of menthol in inflammatory bowel diseases (IBD) have also been confirmed. Bastaki et al. administered menthol orally to Wistar rats (50 mg/kg/day) to investigate its therapeutic effects on acetic acid-induced colitis [35]. The results showed that menthol reduced myeloperoxidase (MPO) activity and malondialdehyde (MDA) levels while increasing glutathione (GSH) levels. These findings indicate that menthol alleviates oxidative stress, a key driver of inflammation in IBD, by enhancing antioxidant defenses and reducing lipid peroxidation [35]. Additionally, menthol significantly reduced the levels of pro-inflammatory cytokines, such as IL-1, IL-23, and TNF-α, but had no significant effect on IL-6 levels. This indicates that menthol effectively improved the condition of IBD rats through its anti-inflammatory effects. Another study utilized mentha arvensis essential oil (MAEO), containing menthol, menthone, and menthyl acetate, to effectively inhibit the ERK/NF-κB signaling pathway in mice with atopic dermatitis (AD), thereby reducing the transcription of pro-inflammatory genes and mitigating inflammation [36].

Menthol and its derivatives exhibit significant anti-inflammatory properties across various inflammation models, from atopic dermatitis to schistosomiasis and inflammatory bowel diseases. Whether applied topically or administered orally, menthol has demonstrated efficacy in reducing inflammatory markers, improving oxidative stress responses, and mitigating symptoms in animal models [37, 38]. As our understanding of menthol's mechanisms of action deepens, it is conceivable that its role in managing inflammatory diseases may expand, offering new avenues for treatments that are both effective and well-tolerated.

In recent years, numerous preclinical studies have demonstrated the anti-inflammatory effects of menthol and its derivatives through mechanisms such as cytokine suppression, immune modulation, TRP channel activation, and antioxidant activity [39, 40], However, the clinical translation of these findings remains limited. Most of the current evidence is derived from in vitro and animal studies [39, 40], while well-designed, large-

scale clinical trials are still lacking [40]. Furthermore, the activation of TRPM8 and TRPA1 by menthol may produce paradoxical effects depending on concentration, tissue type, and disease condition, potentially leading to hyperalgesia or even pro-inflammatory responses under certain circumstances [39, 41]. In addition, safety concerns such as gastrointestinal irritation, reflux aggravation [40], and off-target effects related to its low receptor selectivity require further investigation [41]. Therefore, future research should focus on optimizing delivery systems, developing more selective derivatives [41], and conducting rigorous randomized controlled trials to comprehensively evaluate and translate the therapeutic potential of menthol and its derivatives into clinical practice for inflammatory disease management.

3.3 | Analgesic Effects

Menthol and its derivatives are well-known for their analgesic properties and are widely used in both traditional and modern medicine for pain relief. In addition to the pain-relieving effects through interactions with transient receptor potential (TRP) channels, particularly TRPM8 [16, 22], as previously mentioned, other inflammatory mediators and ion channels involved in nociception have also been discovered to contribute to its analgesic effects. The analgesic mechanisms of menthol and its derivatives involve multi-target modulation, including TRP channel activation, opioid receptor agonism, GABAergic system potentiation, and ion channel blockade, which synergistically suppress nociceptive signaling at both peripheral and central levels.

Researchers conducted hotplate and abdominal constriction tests on mice to investigate the analgesic effects of (−)-menthol. The results showed that (−)-menthol produced analgesia by activating κ-opioid receptors (KOR), and this effect could be blocked by opioid receptor antagonists. This suggests that (−)-menthol binds to KOR, triggering the release of endogenous opioid peptides (e.g., dynorphin) and inhibiting cAMP-dependent pain signaling pathways [19]. However, the other isomer, (+)-menthol, did not alter the pain threshold in mice, highlighting the stereospecificity of menthol's interaction with opioid receptors [19]. The structure and analgesic activity of the menthol derivative WS-12 have already been thoroughly discussed, while the research team led by Liu et al. conducted an in-depth study on its mechanism of action [42]. They further confirmed that WS-12 is a selective TRPM8 agonist, and its analgesic effect could be blocked by naloxone (an opioid receptor antagonist), indicating that it exerts its effects by activating endogenous opi-oid-dependent analgesic pathways. Moreover, compared to menthol, WS-12 demonstrates better selectivity and fewer side effects. Pan et al. induced inward and outward currents in dorsal horn neurons using menthol, achieving central analgesic effects [43]. Menthol activates γ-aminobutyric acid type A (GABAA) receptors by binding to the β-subunit, enhancing chloride ion influx and hyperpolarizing neurons, thereby reducing nociceptive transmission [43]. Concurrently, menthol blocks voltage-gated Na^+ and Ca^{2+} channels in a use-dependent manner, suppressing repetitive firing and action potential amplitude in nociceptors. This dual action—GABAA activation and ion channel blockade—synergistically decreases neuronal excitability in the spinal cord, contributing to its central analgesic effects [43].

It is evident that from activating TRPM8 to modulating opioid receptors, ion channels, and directly acting on nerve cells, menthol and its derivatives exhibit significant analgesic properties through various mechanisms. These diverse pathways not only enhance their analgesic effects but also provide opportunities for more targeted pain management strategies in future research. However, there are still gaps in understanding the full scope of their mechanisms, and despite the development of new derivatives, their contributions to expanding knowledge in this area have been limited. Further research is needed to uncover more precise molecular pathways and to better explore how different menthol derivatives can be optimized for enhanced efficacy in diverse pain models.

3.4 | Memory Improvement Effects

As early as the Ming Dynasty in China, the famous medical doctor Lan Mao recorded in *Di-an Nan Ben Cao* that mint can "clear the head and various wind-related disorders." In short, it was believed to refresh the brain. In recent years, modern pharmacological research has provided deeper insights into menthol and its derivatives, confirming their potential to enhance cognitive functions, especially memory. Menthol and its derivatives exert memory-enhancing effects through multiple mechanisms, including modulation of neurotransmitter systems, promotion of neurotrophic factor activity, and reduction of oxidative stress and neuroinflammation. These mechanisms synergistically improve synaptic plasticity, neuronal survival, and cognitive function. This section will explore the scientific basis of menthol's effects on memory enhancement and its potential to improve Alzheimer's disease (AD), analyzing its mechanisms of action and experimental evidence from preclinical and clinical studies.

Decker et al. demonstrated that the aroma of L-menthol can enhance short-term memory in cockroaches and is related to the storage and retrieval of cognitive information [44]. This effect is attributed to menthol's ability to modulate olfactory sensory neurons and enhance the release of neurotransmitters such as acetylcholine (ACh) and glutamate, which are critical for memory formation. Nerve growth factor (NGF) supports the enhancement of memory function by promoting neuronal growth, maintenance, and synaptic plasticity. Further studies have expanded on this by investigating how menthol affects cognitive functions in more complex organisms and disease models. Kiran et al. tested how different concentrations of peppermint oil (PO) containing menthol affected NGF transport across the olfactory epithelium and its brain absorption in rats, using in vitro and in vivo experiments [45]. The results showed that PO significantly enhanced the bioavailability of NGF, with 0.5% PO increasing NGF bioavailability in the brain by approximately eight-fold in the in vivo studies, effectively improving the memory ability of the rats. This suggests that menthol enhances NGF transport by modulating the permeability of the olfactory epithelium and blood-brain barrier (BBB), thereby promoting neuronal growth and synaptic plasticity [45].

AD, a major neurodegenerative disease-causing memory impairment, is characterized by key pathological features such as β-amyloid plaque deposition, Tau protein tangles, and BBB dysfunction [46–49]. The accumulation of these abnormal proteins obstructs signal transmission between neurons, disrupting neural networks responsible for memory formation and storage. Studies have found that menthol and nicotine work synergistically to protect against neurodegenerative diseases. These effects include enhancing neuroblastoma cell viability by activating the JNK pathway, inhibiting caspase-3 activation by amyloid β1-42, and promoting the expression of anti-apoptotic proteins such as Bcl-xl [13]. Liu et al. modified liposomes with menthol to create menthol-modified quercetin liposomes (Men-Qu-Lips) and investigated their potential to cross the BBB and treat AD [50]. The results demonstrated that Men-Qu-Lips had high encapsulation efficiency, crossed the BBB, improved oxidative stress and neuroinflammation, protected neurons, and enhanced memory and learning abilities in aged mice. Additionally, AD patients exhibit symptoms such as neuronal degeneration [51], synaptic damage [52], and reduced acetylcholine (ACh) neurotransmitter function [53], with ACh being a neurotransmitter closely associated with memory and cognition [54]. This systematically damages the brain regions involved in memory processing. In a study by Daryadel et al., eight menthol sulfamates (2a–h) were synthesized and tested for their inhibitory effects on the acetylcholinesterase (AChE) enzyme [55]. Among them, derivative 2e showed the strongest inhibition of AChE, with an efficient inhibition constant (Ki) of 111.17 ± 52.36 nM. This result suggests that such menthol sulfamates and their derivatives could be potential drug candidates for the treatment of AD by enhancing cholinergic signaling through the inhibition of AChE, thereby improving memory and cognitive function in AD models.

In conclusion, menthol and its derivatives present promising potential for memory enhancement and neuroprotection, particularly in improving short-term memory and treating neurodegenerative diseases such as AD. As research continues to uncover their mechanisms and therapeutic benefits, menthol-based compounds could become powerful tools in addressing memory impairment and protecting cognitive function. However, current studies are primarily focused on experimental models, and large-scale clinical data supporting their application in actual treatment are still lacking. Additionally, while the mechanisms of menthol's effects have been partially elucidated, its specific role in different neural pathways and potential interactions with other drugs require further exploration.

3.5 | Anti-Cancer Effects

Menthol and its derivatives have garnered significant attention for their potential anti-cancer properties. A large body of research from cell and animal models [56, 57], as well as some clinical data, suggests that menthol can exert inhibitory effects and therapeutic outcomes on various types of cancer, including liver cancer [58], skin cancer [59], and prostate cancer [60]. Its anti-cancer activity is believed to be mediated through a range of mechanisms, including inhibiting cancer cell proliferation [61] and metastasis [62], suppressing tumor angiogenesis [63], blocking cell division [64], and inducing apoptosis [65]. In this section, we will explore the mechanisms by which menthol and its derivatives exert anti-cancer effects in separate subsections and review key preclinical findings that support their potential role in cancer therapy.

3.5.1 | Inhibition of Tumor Proliferation, Metastasis, and Angiogenesis

In research on the metabolism of carcinogenic substances, N-acetyltransferase (NAT) is frequently mentioned because it participates in the metabolic processes of various carcinogens, especially aromatic amines and heterocyclic amines [66]. Lin et al. were the first to discover in their liver cancer cell experiment that high doses of menthol can inhibit NAT activity by competitively binding its terpene backbone to the acetyl-CoA binding pocket, thereby blocking the N-acetylation of 2-aminofluorene [61]. Because menthol inhibits this metabolic process, it reduces DNA damage, thereby suppressing the proliferation of tumor cells [67]. Another study on gastric cancer found that menthol reduced Benzo(a)pyrene (BaP)-induced DNA damage and achieved this by decreasing the proliferation marker Ki-67 and the apoptosis marker caspase-3 in forestomach cells. This demonstrates that menthol protects against DNA damage by enhancing the activity of DNA repair enzymes and reducing oxidative stress, thereby inhibiting the growth of existing cancer cells in the early stages of gastric cancer [68].

Tumor metastasis is one of the primary reasons for cancer progression, leading to the spread of cancer cells to other organs, increasing treatment complexity, and raising mortality rates [69]. Therefore, inhibiting tumor metastasis is a key strategy in the fight against cancer. Studies have confirmed that both TRPM8 and TRPA1 are ion channel proteins that respond to menthol [70, 71]. Several research teams have confirmed that TRPM8 is a key therapeutic target for prostate cancer. Menthol suppresses cancer cell metastasis by inhibiting focal-adhesion kinase and protein tyrosine kinase 2 (PTK2) [62, 72].

Tumor angiogenesis supplies more oxygen and nutrients to the tumor. Folkman [73] was the first to propose a therapeutic strategy aimed at inhibiting tumor angiogenesis. Later, Carmeliet discovered that vascular endothelial growth factor (VEGF) is one of the key factors in tumor angiogenesis [74]. Walcher et al.'s study found that menthol, as a TRPM8 agonist, can reduce VEGF-induced calcium transients and whole-cell currents, thereby inhibiting the formation of new blood vessels in uveal melanoma (UM) [57].

3.5.2 | Inhibition of Cell Cycle

Inhibiting the cell cycle can prevent cancer cells from further spreading through proliferation and division, particularly by interfering with key cell cycle regulatory proteins and checkpoints to control tumor growth [75]. Kim et al. found that menthol can induce G2/M phase arrest in prostate cancer PC-3 cells, thereby inhibiting further tumor growth [76]. The mechanism was identified through DNA microarray analysis, which revealed that menthol significantly suppresses the expression of polo-like kinase 1 (PLK1), a key regulator of G2/M phase progression. Fatima et al.'s research found that menthol can also arrest human

epidermoid carcinoma (A431) cells in the G2/M phase, thereby inhibiting the cell growth cycle through the suppression of cyclin-dependent kinases (CDKs) and cyclins, which are essential for cell cycle progression [56].

3.5.3 | Induction of Apoptosis

In cancer therapy, inducing apoptosis has become one of the key strategies, as apoptosis is a programmed, non-inflammatory form of cell death [77]. Faridi et al. were the first to propose the signaling pathway of $_{L}$-menthol-induced apoptosis [78]. Their research team used a variety of techniques, including gene chip analysis, proteomics, and in silico simulation, to study the regulation of gene and protein expression in human adenocarcinoma cells (Caco-2 cell line) in response to $_{L}$-menthol treatment. The results showed that L-menthol promotes apoptosis by inhibiting the HSP90 protein and AKT survival pathway and releasing the pro-apoptotic factor BAD. This study provides a solid theoretical foundation for future research. Furthermore, enzymes such as hyaluronidase play a crucial role in promoting tumor invasion and metastasis by degrading hyaluronic acid (HA) in the extracellular matrix, thus facilitating the spread of cancer cells [79]. The research team led by Faridi et al. further found that menthol also inhibits the expression of hyaluronidase or interferes with its structure, preventing the degradation of HA, impairing the migration ability of skin cancer cells, and ultimately leading to apoptosis [56].

In conclusion, menthol and its derivatives demonstrate anticancer potential by inhibiting tumor proliferation, metastasis, angiogenesis, and inducing apoptosis and cell cycle arrest. Preclinical studies provide strong support, particularly in liver, skin, and prostate cancers. To better illustrate the role of menthol and its various derivatives in treating different types of cancer, Table 3 summarizes the relevant research findings and the mechanisms of action of different derivatives on various cancers. However, challenges remain in translating these findings to clinical applications, including issues such as bioavailability, optimal dosing, and potential side effects. Future research should focus on elucidating the molecular mechanisms of menthol's multi-target effects, optimizing its derivatives for selective modulation of cancer-related pathways, and developing targeted delivery systems to enhance therapeutic efficacy.

3.6 | Antibacterial and Insecticidal Effects

Menthol and its derivatives have garnered significant attention for their dual antibacterial and insecticidal properties, showing strong potential as natural alternatives to synthetic chemicals. These properties make menthol an appealing candidate in both food preservation, where it can inhibit harmful bacteria, and pest control, where it disrupts the nervous systems of insects. The antibacterial effects of menthol are primarily attributed to its ability to disrupt bacterial cell membranes [80], while its insecticidal activity is closely linked to its impact on the nervous systems of pests [81]. Understanding these mechanisms is crucial for exploring the broad applications of menthol-based compounds across various industries.

The menthol-containing EOs derivatives 1–8 exhibited varying antibacterial activities against *Clostridium perfringens, Salmonella typhimurium, Salmonella enteritidis*, and *Escherichia coli* strains. Among them, compounds 1 and 2 demonstrated particularly strong antibacterial effects and have good water solubility without producing a strong odor, showing potential for direct application in feed additives or packaging coatings [82]. These derivatives likely enhance antibacterial activity by increasing the penetration of menthol into bacterial membranes and improving its interaction with membrane proteins [82]. The menthol-containing EO of Japanese mint (*Mentha arvensis* L.) achieved a 100% mortality rate against 15 species of fungi, including *Helminthosporium oryzae*, and also demonstrated a 99% mortality rate against *Candida* and *Staphylococcus* within 1 h. This broad-spectrum activity is attributed to menthol's ability to disrupt fungal cell walls and membranes, similar to its effects on bacterial cells [83]. The study found that menthol-modified nanodiamond (ND-menthol) particles have a significant inhibitory effect on the biofilm formation of Gram-positive bacteria (*Staphylococcus aureus*) and Gram-negative bacteria (*E. coli*) [84]. The antibacterial mechanism is primarily related to their impact on the structure and function of the cell membrane. Menthol is believed to penetrate the fatty acid chains in the lipid bilayer, altering membrane fluidity and disrupting lipid arrangement, leading to noticeable structural and morphological changes on the cell surface, thereby damaging the cell membranes of both Gram-positive and Gram-negative bacteria.

After conducting repellency tests of $_{L}$-menthol against four harmful insects, including *Callosobruchus maculatus* F., *Rhyzopertha dominica* F., *Sitophilus oryzae* L., and *Tribolium castaneum* Herbst, it was found that when the concentration reached 0.353 μg/cm^2, the repellency rate could reach 82%–100% [85]. This high repellency is due to menthol's ability to activate TRP channels in insect sensory neurons, causing discomfort and deterring feeding [85]. Additionally, menthyl propionate exhibited high contact toxicity against the four insects, while menthyl acetate showed strong ovicidal activity against the eggs of *Tribolium castaneum* Herbst. Nikitin et al. found that (−)-(1*R*,2*S*,5*R*)-menthol has no toxic effect on nematodes, but its dithiophosphoric derivatives, including O,O-di-(−)-menthyldithiophosphoric acid, can cause nematode death, with the toxicity being dose-dependent [86]. The dithiophosphoric group enhances the interaction of menthol derivatives with nematode neuronal receptors, leading to paralysis and death [86]. However, this toxic effect has a lag phase, reaching its maximum value after 24 h at 191.5 μg/mL. It shows promise as a nematicide for controlling plant-parasitic nematodes. Jankowska et al. reviewed that menthol-containing EOs can exert neurotoxic effects on the insect nervous system, specifically through the octopaminergic system [87]. Menthol can increase cAMP and calcium levels in nerve cells, preventing octopamine from binding to its receptors, ultimately leading to the insect's death.

3.7 | Other Effects

Studies have found that oral administration of menthol is effective in protecting the gastrointestinal tract. A dosage of 50 mg/kg menthol provided 88.62% protection against ethanol-induced

TABLE 3 | The mechanisms of action of menthol or its derivatives in different cancers.

Menthol or its derivatives	Cancers	Mechanism of Action	References
Menthol	Gastric cancer	• Reduces the toxicity of benzo[a]pyrene (BaP); • Lowers proliferation marker Ki-67 and apoptosis marker caspase-3, inhibiting excessive proliferation of gastric cancer cells	[68]
	Prostate cancer	• Downregulates PTK2, inhibits cancer cell metastasis; • Induces G0/G1 phase and G2/M phase cell cycle arrest, inhibiting tumor growth; • Activates TRPM8 channels, inducing apoptosis.	[62, 72, 76]
	Uveal melanoma	• Activates TRPM8, reduces VEGF-induced calcium transients and whole-cell currents, inhibiting angiogenesis.	[57]
	Bladder cancer	• Induces mitochondrial membrane depolarization through TRPM8, leading to cell death.	[116]
	Leukemia	• Enhances autophagic resistance of leukemia cells by upregulating caspase-3, BAX, p53, and downregulating MDM2.	[117]
	Colon adenocarcinoma	• Induces apoptosis by inhibiting HSP90 protein and AKT survival pathway, releasing pro-apoptotic factor BAD.	[78]
(−)-Menthol	Liver cancer	• Inhibits NAT activity, blocks the N-acetylation of 2-aminofluorene, inhibits tumor cell proliferation.	[61]
Neomenthol	Skin cancer	• Induces apoptosis by inhibiting hyaluronidase activity; • Induces G2/M phase cell cycle arrest, inhibiting tumor growth; • Inhibits tubulin polymerization.	[56, 79]
	Ehrlich ascites carcinoma	• Induces apoptosis by inhibiting hyaluronidase activity.	[56]
Menthol-Doxorubicin Conjugate (2c)	Leukemia/ Uveal melanoma	• Activates apoptosis through Caspase-8.	[118]
Menthol-Doxorubicin Conjugate (2d)	Leukemia	• Activates apoptosis through Caspase-8.	
	Uveal melanoma	• Activates apoptosis through Caspase-9.	

gastric ulcers and 72.62% protection against indomethacin-induced gastric ulcers [88]. The specific mechanism involves menthol increasing gastric mucus secretion by stimulating the expression of mucin genes (e.g., MUC5AC) and enhancing the production of prostaglandin E2 (PGE2) through the activation of cyclooxygenase-1 (COX-1) [88]. These effects strengthen the gastric mucosal barrier, reducing the impact of ulcer-inducing agents such as ethanol and nonsteroidal anti-inflammatory drugs (NSAIDs) [89].

$_{L}$-menthol can also activate the cold-sensitive receptors TRPM8 and TRPA1, promoting the browning of white adipose tissue (WAT) into brown adipose tissue (BAT)-like cells. This process, known as "browning," increases the expression of uncoupling protein 1 (UCP1), which enhances mitochondrial thermogenesis and energy expenditure [90]. This mechanism may bypass the traditional β-adrenergic pathway, thus avoiding the side effects associated with excessive stimulation.

Menthol, as a natural compound, exhibits a wide range of biological activities. This article provides a summary of the pharmacological effects and mechanisms of menthol and its derivatives through visual representation (see Figure 1), offering valuable reference for future research. In addition to the previously mentioned applications, such as anti-inflammatory, antibacterial, neuroprotective effects, and respiratory health benefits, further exploration of the potential mechanisms of menthol and its derivatives is highly anticipated. They show great promise

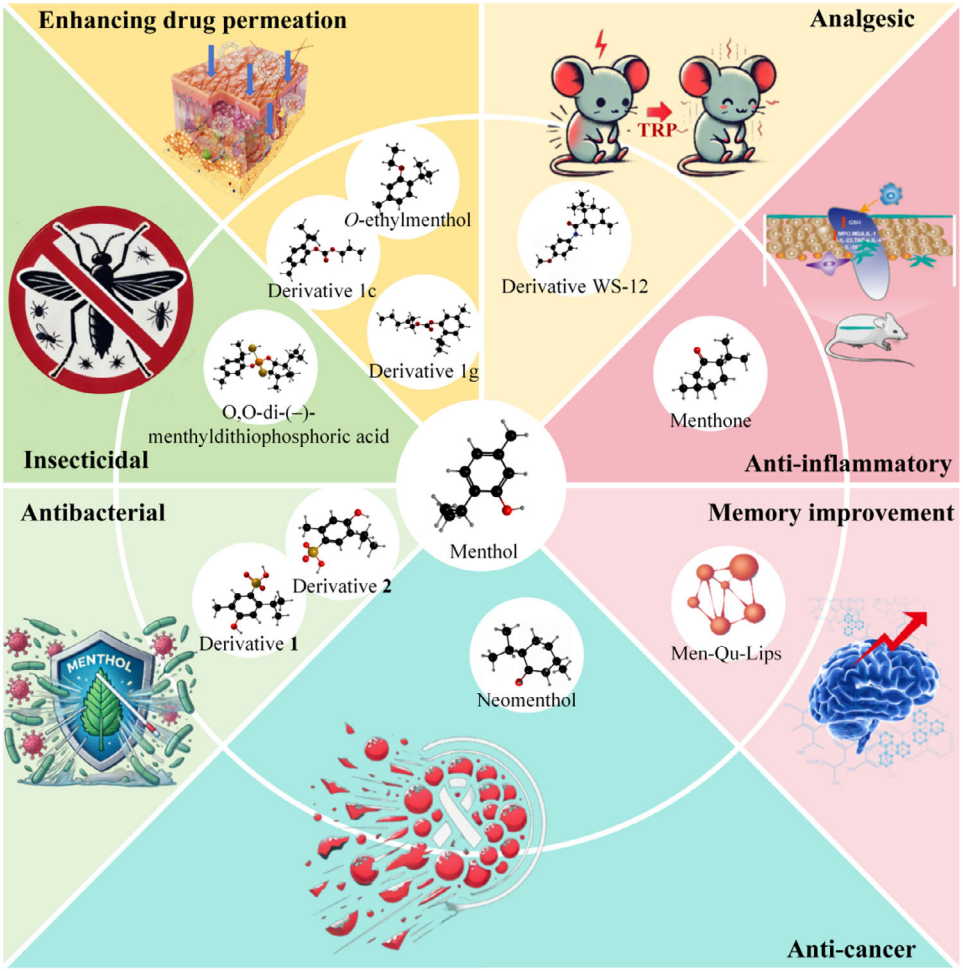


FIGURE 1 | Overview of the main pharmacological effects and mechanisms of menthol and its derivatives (Among them, Derivative 1c and 1g are from study [32], Derivative WS-12 is from study [16], Menthone is from study [34], Men-Qu-Lips is from study [50], Neomenthol is from study [57] and [79], Derivative 1 and 2 are from study [82], and O,O-di-(–)-menthyldithiophosphoric acid is from study [86].).

in fields such as drug development, agricultural pest control, and food preservation, making them important targets for continued research and development.

4 | Safety Profile and Pharmacokinetics of Menthol and Its Derivatives

The previous sections have introduced the wide applications of menthol and its derivatives in pharmaceuticals and personal-care products. Subsequently, understanding their safety and pharmacokinetics is crucial to minimizing potential adverse effects while ensuring therapeutic efficacy for specific diseases. This section gathers safety and pharmacokinetic reports of menthol and its derivatives from the literature, aiming to provide valuable data for further research and the development of new drugs containing menthol and its derivatives.

4.1 | Safety Profile of Menthol and Its Derivatives

This section will focus on discussing the safety profile of menthol and its derivatives, including their toxicity thresholds, potential adverse effects, elimination processes, structural safety analysis, and safety differences across various biological species.

As early as 1976, Opdyke [91] found that excessive consumption of menthol can cause adverse effects on the gastrointestinal and nervous systems, such as vomiting, coma, and convulsions. Moreover, when the dosage exceeds 50–150 mg/kg, it can be lethal. Menthol is commonly used as an additive in over-the-counter medications to relieve pain or respiratory discomfort. However, frequent use of such products without paying attention to the dosage may pose potential health risks. A case from the United States described an 86-year-old man who had been consuming large amounts of menthol-containing cough drops for 20 years, resulting in coma, severe skin lesions, and kidney failure. After being hospitalized and discontinuing the menthol-containing cough drops, his symptoms gradually improved [92]. A case report from India discussed a severe poisoning incident caused by the ingestion of a large amount of PO, which is rich in menthol and menthone [93]. A 40-year-old woman developed symptoms of coma, respiratory depression, low blood pressure, and bradycardia after ingesting the oil. She was eventually saved through mechanical ventilation and treatment with vasopressor medications [93]. However, another case involving a 21-year-old

man from India was less fortunate. While cleaning a peppermint factory's storage tank, he inhaled a large amount of menthol, leading to symptoms of coma, seizures, intermittent hematuria, and acute kidney failure [94]. Despite receiving a series of intensive treatments, he unfortunately passed away 10 days later. These cases also emphasize the importance of safety monitoring and controlling intake when using menthol, especially in industrial settings and over-the-counter products, where prolonged or high-dose exposure can lead to serious or even fatal health consequences.

In toxicity studies on rats and mice, Fischer 344 rats were fed $_{L}$-menthol at concentrations up to 15,000 ppm for 13 weeks, with high-dose male rats developing interstitial nephritis. The No Observed Adverse Effect Level (NOAEL) was determined to be 7500 ppm (750 mg/kg/day). In the same study, B6C3F1 mice showed reduced weight gain and interstitial nephritis in high-dose female groups, with a NOAEL of 2000 ppm (300 mg/kg/day). Overall, menthol caused adverse effects in rats and mice at high doses but was considered safe at lower doses [95]. In the reproductive toxicity study, Sprague Dawley rats were administered various doses of menthol (up to 16,000 ppm). The results showed significant weight reduction in offspring from the high-dose group, with a NOAEL for reproductive toxicity of 8000 ppm (419 mg/kg/day). This indicates that high doses of menthol may affect development, but it is considered safe at lower doses [95].

The potential safety risks associated with structural modifications of menthol and its derivatives have long been a focal point of research. Mirokuji et al. conducted a systematic safety assessment of four menthol derivatives ($_{L}$-menthyl 2-methylbutyrate, $_{DL}$-menthyl octanoate, $_{DL}$-menthyl palmitate, and $_{DL}$-menthyl stearate) using the evaluation procedure of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) [96]. Structurally, these derivatives are esters formed by menthol and simple carboxylic acids (such as 2-methylbutyric acid, octanoic acid, palmitic acid, and stearic acid). Their chemical structures lack known toxic groups or complex functional groups, and they are metabolized into harmless products. Moreover, their daily intake levels are well below the safety thresholds, making them safe for use as food flavoring agents. However, pulegone, a monoterpene ketone, contains an α,β-unsaturated ketone group in its structure, which generates reactive intermediates (such as epoxides) during metabolism. These intermediates bind to GSH in liver cells, leading to GSH depletion, oxidative stress, and hepatocyte damage [97]. Menthofuran, a major metabolite of pulegone, is structurally related to pulegone and also exhibits potential toxicity, particularly at high doses, where it may cause liver and kidney damage. The European Medicines Agency recommends a lifelong acceptable exposure dose of 0.75 mg/kg body weight for pulegone and menthofuran [98]. In the treatment of irritable bowel syndrome (IBS), the maximum daily dose of PO is 540 mg, with the combined amount of pulegone and menthofuran being only 0.54 mg/day, significantly below the maximum acceptable dose [99].

In summary, menthol and its derivatives are generally considered safe at low doses, but high doses or prolonged exposure may cause adverse effects on organ systems such as the gastrointestinal tract, nervous system, liver, and kidneys. A summary of the safety and potential toxicity of menthol and its common derivatives (see Table 4), including their NOAEL, potential reproductive toxicity, and effects on organ systems, provides a comprehensive understanding of their safety profile. Although structural modifications of these compounds typically exhibit low safety risks, certain modifications may introduce new toxic groups or alter metabolic pathways, potentially leading to health hazards. Future research should further investigate the effects of different structural modifications on toxicity and metabolism, particularly focusing on safety assessments under high-dose or long-term exposure conditions, to ensure their broad safety in food and pharmaceutical applications.

4.2 | Pharmacokinetics of Menthol and Its Derivatives

Analyzing the pharmacokinetics of menthol and its derivatives is crucial, as it reveals their absorption, distribution, metabolism, and excretion processes. Understanding the behavior of menthol and its derivatives under different doses and routes of administration helps optimize their use in medical and everyday products, ensuring optimal therapeutic efficacy while minimizing health risks caused by overexposure or adverse reactions.

In the study by Gelal et al., 12 subjects ingested 100 mg of menthol capsules and mint candy or mint tea containing 10 mg of menthol [2]. By analyzing menthol metabolites in plasma and urine, as well as related physiological indicators, the study concluded that the plasma half-life of menthol ranged from 42.6 to 56.2 min, with a peak plasma concentration (C_{max}) of 16.73 ± 5.53 μmol/L, and the time to reach C_{max} ranged from 35 to 87 min. Additionally, the bioavailability of both intake methods was similar, with urinary recovery rates of 45.6% for menthol capsules and 56.6% for mint candy/tea. Hiki et al. evaluated the tolerability, pharmacokinetics, and preliminary efficacy of l-menthol during upper gastrointestinal endoscopy [100]. The study found that after spraying the $_{L}$-menthol preparation (NPO-11) directly onto the gastric mucosa, it was rapidly absorbed, reaching its peak plasma concentration within 1 h, with a C_{max} of 32.89 ± 32.00 ng/mL at the 80 mg dose. Additionally, 65%–68% of the $_{L}$-menthol was excreted in the urine as a glucuronide conjugate within 24 h, indicating efficient metabolism and clearance. The absorption rate (R_p) and efficacy (C_{max} and AUC) increased linearly with the dose, demonstrating that the pharmacokinetics of l-menthol are predictable across different dosages. Obata et al. investigated the percutaneous absorption enhancement of ketoprofen using l-menthol-derived cyclohexanol compounds [101]. The study found that applying these synthesized compounds in hydrogel formulations significantly improved the transdermal absorption of ketoprofen in rats. Among the 35 compounds tested, the C-3 iso-butyl substituted compound (compound 12) demonstrated the strongest absorption enhancement effect, with an enhancement factor (E_f) of 6.63, which was significantly higher than that of O-ethylmenthol (E_f = 3.40). The optimal log *p* value for promoting absorption was found to be around 3.28, balancing both high absorption rates and minimal skin irritation. Additionally, the apparent penetration rate (R_p) and efficacy (C_{max} and AUC) showed dose-dependent increases, with compound 12 achieving the highest Rp value of 3.93 mg/h/cm^2, indicating that the pharmacokinetics of these l-menthol derivatives are predictable across different dosages.

TABLE 4 | Safety and potential toxicity of menthol and its common derivatives.

Menthol or its derivatives	Test objects	NOAEL	Potential toxicity	References
Menthol	Fischer 344 rats	7500 ppm	Interstitial nephritis (≥15,000 ppm).	[95]
	B6C3F1 mice	2000 ppm	Reduced body weight gain, interstitial nephritis, and perivascular lymphoid hyperplasia (≥15,000 ppm).	
	Sprague Dawley Rats	8000 ppm	Inhibited offspring development (≥16,000 ppm).	
Menthyl isovalerate	Fischer 344 rats	7500 ppm	Interstitial nephritis (≥15,000 ppm).	[119]
	B6C3F1 mice	2000 ppm	Reduced body weight gain, interstitial nephritis, and perivascular lymphoid hyperplasia (7500 ppm and 15,000 ppm).	
	Pregnant rabbits	425 mg/kg/day	No developmental toxicity was observed.	
$_{L}$-menthyl methylether	*Salmonella typhimurium* strains	5000 μg/plate	No mutagenic effects were observed.	[120]
	Sprague Dawley Rats	800 mg/kg/day	No reproductive or repeated dose toxicity was observed.	
	THP-1 cell line	5000 μg/mL	Although a positive response was observed, it will not cause skin sensitization at the current usage concentration.	
$_{L}$-menthyl lactate	Fischer 344 rats	300 mg/kg/day	Increased liver weight and hepatocyte vacuolation (≥400 mg/kg/day).	[121]
	B6C3F1 mice	185 mg/kg/day	No developmental toxicity was observed.	
	Pregnant rabbits	425 mg/kg/day	No developmental toxicity was observed.	
$_{L}$-menthyl D-lactate	Sprague Dawley Rats	5 mg/kg/day	Wet fur, red/brown mouth staining, increased water intake, liver weight increase, and kidney damage with eosinophilic material in male rats (≥1000 mg/kg/day).	[122]
		300 mg/kg/day	No developmental toxicity was observed.	
Menthyl acetate	CD (SD) SPF rats	150 mg/kg/day	Two female rats died postpartum. The remaining rats exhibited hematuria, perineal infection, and varying degrees of organ damage (≥500 mg/kg/day).	[123]
	Fish (*Danio rerio*)	—	The median lethal concentration (LC50) is 6.72 mg/L.	
	Chinese hamster lung fibroblast cells (V79)	—	No significant gene mutations were observed.	
	Human peripheral blood lymphocytes	—	No significant chromosomal damage.	
$_{L}$-menthyl 2-methylbutyrate	Fischer 344 rats	380 mg/kg/day	No developmental toxicity was observed.	[96]
$_{DL}$-menthyl octanoate				
$_{DL}$-menthyl palmitate				
$_{DL}$-menthyl stearate				

Feng et al. studied the pharmacokinetics of $_L$-menthol in rats using both inhalation and intravenous injection methods [102]. The results showed that the half-life of $_L$-menthol was 8.53 h following inhalation and 6.69 h after intravenous injection, with maximum plasma concentrations of 118.82 and 143.61 mg/L, respectively. The bioavailability of $_L$-menthol via inhalation was 50.24%. Another study [103] investigated the anti-parasitic activity of menthol and its novel prodrug (menthol-pentanol) against *Echinococcus multilocularis* in a mouse model, to optimize menthol's pharmacokinetic properties. The results showed that the lipophilicity of menthol-pentanol significantly increased, with its ClogP value rising from 3.23 to 6.22, suggesting an improvement in its bioavailability and antiparasitic activity.

5 | Conclusions and Future Perspectives

This review highlights the diverse pharmacological applications of menthol and its derivatives, including their roles in pain relief, anti-inflammatory effects, anticancer activity, antibacterial properties, and neuroprotection. Structural modifications of menthol have been shown to significantly enhance its biological activity by targeting specific receptors and signaling pathways, improving drug permeability, and inhibiting cancer cell proliferation and metastasis. These multifunctional properties, combined with ongoing research into their safety and pharmacokinetics, position menthol and its derivatives as promising candidates for drug delivery systems, cancer therapy, and disease management. However, several challenges remain. Most studies are still limited to preclinical models, with only a few progressing to clinical trials [104, 105], leading to a lack of robust clinical data to confirm their efficacy and safety in humans. Moreover, the majority of preclinical studies were conducted in rodents using diverse dosing regimens and experimental protocols, making it difficult to perform consistent and reliable comparisons across different menthol derivatives. The mechanisms of action, particularly their interactions with specific receptors and signaling pathways, are not yet fully understood [68, 106]. In addition, the development of novel menthol derivatives remains limited, necessitating further innovation in chemical synthesis and structural optimization.

Future research should prioritize advancing clinical trials to validate therapeutic potential, elucidating molecular mechanisms through multi-omics approaches, and designing derivatives with improved bioavailability and reduced side effects. Innovations in drug delivery technologies, such as prodrug design and nanotechnology, could further enhance their therapeutic utility [107, 108]. With continued interdisciplinary efforts, menthol-based compounds hold great promise as versatile therapeutic agents, bridging gaps between natural product discovery and modern pharmaceutical development.

Author Contributions

Conceptualization: Jing Zhang. Writing–original draft: Jing Zhang and Yupei Hu. Review and editing: Jing Zhang, Yupei Hu, and Zheng Wang. Editing: Jing Zhang, Yupei Hu, and Zheng Wang.

Acknowledgments

The authors gratefully acknowledge the National Key Research and Development Program of China (2021YFC21037003) for the financial support.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting file 1: elsc70039-sup-0001-FigureS1.pdf