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Review

A Narrative Review on the Bioactivity and Health Benefits of Alpha-Phellandrene

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Abstract: Aromatic essential oils play a significant role in pharmaceuticals, food additives, cosmetics, and perfumery. Essential oils mostly comprise aliphatic hydrocarbons, monoterpenoids, sesquiterpenoids and diterpenes. Plant extracts comprise a complex mixture of terpenes, terpenoids, aliphatic and phenol-derived aromatic components. Terpenes are a significant class of hydrocarbons with numerous health benefits. These biological functions of essential oil components are examined in vitro and in vivo studies. Some studies evaluated the properties and functions of α-phellandrene (α-PHE). Detailed evaluation to determine the functions of α-PHE over a spectrum of health care domains needs to be initiated. Its possible mechanism of action in a biological system could reveal the future opportunities and challenges in using α-PHE as a pharmaceutical candidate. The biological functions of α-PHE are reported, including anti-microbial, insecticidal, anti-inflammatory, anti-cancer, wound healing, analgesic, and neuronal responses. The present narrative review summarizes the synthesis, biotransformation, atmospheric emission, properties, and biological activities of α-PHE. The literature review suggests that extended pre-clinical studies are necessary to develop α-PHE-based adjuvant therapeutic approaches.

Keywords: α-phellandrene; essential oils; terpenes; health benefits

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1. Introduction

Plant-based medicines are playing a vivid role in health care. Plant-derived essential oils are one of the prominent sources of bioactive molecules, including volatile lipophilic compounds with strong aromas. Essential oils are composed of hydrocarbons and their derivatives, such as alcohols, acids, esters, aldehydes, ketones, amines, nitrogen and sulfur compounds, oxygenated terpenes, terpenoid hydrocarbons and sesquiterpenes [1,2]. Essential oils are isolated from plants through various distillation processes, such as hydro and steam distillation, effleurage, maceration, supercritical, microwave-assisted, and solvent extractions [1]. Other chromatographic techniques, such as column, thin layer, high-pressure liquid chromatography, mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, gas chromatography/mass spectrometry (GC/MS), liquid chromatography/mass spectrometry, and Fourier-transform infrared spectrophotometry were also used in the characterization and identification of compounds in the essential oils [1].

Monoterpenes are the most important constituents of essential oils. α-phellandrene (α-PHE) is a cyclic monoterpene with two double bonds in a heterocyclic ring (endocyclic) [3]. It was named after *Eucalyptus phellandra (E. phellandra)*, the plant from where α-PHE was first isolated. α-PHE is a natural plant-derived compound with various medicinal properties, found useful in the pharmaceutical, food, cosmetic and perfume industries [4,5]. Phellandrene (PHE) compounds are prevalently used in fragrances [6]. PHE is found in plants, such as Angelica and Eucalyptus, and due to its pleasant scent, it has been used

in fragrances [7]. *E. microtheca*, *E. viminalis*, and *E. dives* primarily emit α-PHE into the atmosphere, and the α-PHE produces particle nucleation due to monoterpene oxidation, observed over Eucalypt forests [8,9]. In the indoor environment, α-PHE is used in cleansing products, detergents, and room fresheners [10]. α-PHE interacts with the local environment when it is emitted. α-PHE is an important component for ozonolysis and produces a significant, blue-colored haze due to nocturnal nucleation over the Eucalypt forests [11].

Though several studies have detailed the pharmacological activities of α-PHE, the biological activities of α-PHE still need to be studied in detail. α-PHE can potentially be used to manage inflammatory diseases, such as osteoarthritis, rheumatoid arthritis, allergies, etc. Some adverse events may occur in the use of α-PHE. For example, any topical application of α-PHE can cause skin irritations, and oral administration of α-PHE may result in nausea, vomiting, diarrhea, and intestinal disturbances [12]. This review aimed to summarize the necessary details of α-PHE, including synthesis and biological functions.

2. Properties of Phellandrene

Phellandrenes comprise alpha-phellandrene (α-PHE) and beta-phellandrene (β-PHE), prominently found in eucalyptus plant species. PHEs are also present in other plants, such as mint, black pepper, parsley, cinnamon, lavender, pine, ginger grass, water fennel, and dill [13]. PHEs are herbaceous with different aromas, which have been known for their anti-fungal [14], anti-inflammatory, anti-hyperalgesic, anti-depressant [15], analgesic [16] and anti-cancer activity [17,18]. Plant-derived secondary metabolites comprise different active components, most prevalently, terpenes, alkaloids, and phenolic compounds [19]. The compounds are extracted from the medicinal plants via various methods, which yield a complex liquid mixture of chemicals, including terpenes, terpenoids, aliphatic and aromatic compounds and characteristic volatile properties, and are mostly lipophilic [4,16]. The monoterpene α-PHE is one of the predominant constituents of many plant species. The list of the representative plant species containing α-PHE is summarized in Table 1, and pictures of the few representative plant species are displayed in Figure 1.

Table 1. The list of representative plant species that are reported to have α-Phellandrene.

S. No.	Plant Species	α-Phellandrene Content (%) #	References
1	*Curcuma zedoaria* (Christm)	14.93	[20]
2	*Xylopia aromatica* L.	2.2–6.4	[21]
3	*Rosmarinus officinalis* L.	0.1–0.4	[22]
4	*Eucalyptus dives*	17.4	[23]
5	*Eucalyptus staigeriana*	8.8	[23]
7	*Schinus terebinthifolius* Raddi	15.7	[24]
		34.38	[25]
6	*Schinus molle* L.	46.52	[25]
8	*Solanum erianthum* D. Don.	17.5	[26]
9	*Thymus kotschyanus* Boiss. and Hohen.	10.8	[27]
10	*Cupressus atlantica* Gaussen	5.5	[28]
11	*Anethum graveolens* L.	32	[29]
12	*Myrica gale* L.	8	[30]
13	*Ligusticum mutellina* L. Crantz	23.4	[31]
14	*Ligusticum marginatum*	50.2	[32]
15	*Artemisia feddei*	5.78	[33]

Table 1. *Cont.*

S. No.	Plant Species	α-Phellandrene Content (%) #	References
16	*Bursera morelensis*	1	[34]
17	*Monodora myristica* (Gaertn.)	34.4	[35]
	Monodora myristica (Gaertn.) Dunal	53	[36]
18	*Piper nigrum*	8.56	[37]

α-PHE content (%) in the essential oil of the respective plants.

Figure 1. The pictures of the few representative plant species reported to have α-phellandrene [38].

3. Chemistry and Synthesis of α-PHE

Tea and lemon tree oils have high p-cymene and other monoterpenoids [39,40]. γ-Terpinene (1-isopropyl-4-methyl-1,4-cyclohexadiene) and α-PHE (5-isopropyl-2-methyl-1,3-cyclohexadiene) with the molecular formula $C_{10}H_{16}$ are grouped under the class of monoterpenes. In α-PHE, the cis-1, 3-diene chain is inserted into the 6-membered ring. Photooxidation of α-PHE revealed that the ring structure of α-PHE opens to produce a cyclohexatriene-type product [41]. Like γ-terpinene, α-PHE can also exhibit three structural conformations due to the internal rotation of the exocyclic isopropyl group. The three conformers can be identified using experimental IR spectra. The UV-induced photoreaction results in the reorganization of the π-system. At $\lambda > 200$ nm, new bands are produced in the spectrum of α-PHE; this shows that the α-PHE seems to be photolabile under UV-C light [41].

In solution, α-PHE exists in folded conformation with the left-handed diene helix [42]. The diene helix is left handed in the axial conformer, and in the equatorial conformer, it is right handed. In α-PHE, (R)-(−)-5-isopropyl-2-methyl-1,3-cyclohexadiene possesses the quasi-axial-isopropyl group to sustain in solution [43]. α-PHE exists as an axial-isopropyl conformer in conformational equilibrium, and its stability is due to the presence of the CH/π hydrogen bond [44]. The electron transfer catalysis reaction of (R)-α-PHE with 4-methoxystyrene produces mixed cycloaddition products [45].

Upon photoexcitation, the ground state and excited state dynamics of α-PHE were studied using broadband femtosecond UV absorption spectroscopy [46]. The ring-opening

dynamics of α-PHE were examined using picosecond time-resolved UV resonance Raman spectroscopy [47]. In the matrix isolation experiment, α-PHE photochemistry and ground state conformational size were intermediate between 1,3-cyclohexadiene (CHD) and 7-dehydrocholesterol, provitamin D3 (DHC) [41].

Synthesis of α-PHE from (R)-carvone through the batch process was reported by Sen and Grosch [48] and, through the continuous-flow process, by [49]. In Sen and Grosch's model of α-PHE synthesis, R-carvone converted to the unsaturated ketone with the help of Wilkinson's catalyst (Rh $(PPh_3)_3Cl$) and toluene. Unsaturated ketone converted to N-tosyl hydrazone in the presence of tosyl hydrazide resin ($TsNHNH_2$) and tetrahydrofuran (THF). With the help of methyllithium (2MeLi) and diethylether (Et_2O), N-tosyl hydrazone converted into (S)-α-PHE, and the yield was 48% [48] (Figure 2). In the continuous-flow process model, R-carvone was subjected to reduction with the help of a metal nanoparticle as a catalyst in the first reactor. Then the condensation was carried out in the second reactor with $TSNHNH_2$ and acid resin as the catalyst. The steam from the second reactor was linked with the third reactor, which contains a strong base, n-butyllithium (nBuLi). The organic phase was collected and dried in the presence of disodium sulphate (Na_2SO_4) and filtered with alumina, which yielded crude α-PHE. The product was then purified using flash chromatography and distilled to produce 96% pure α-PHE [49] (Figure 3).

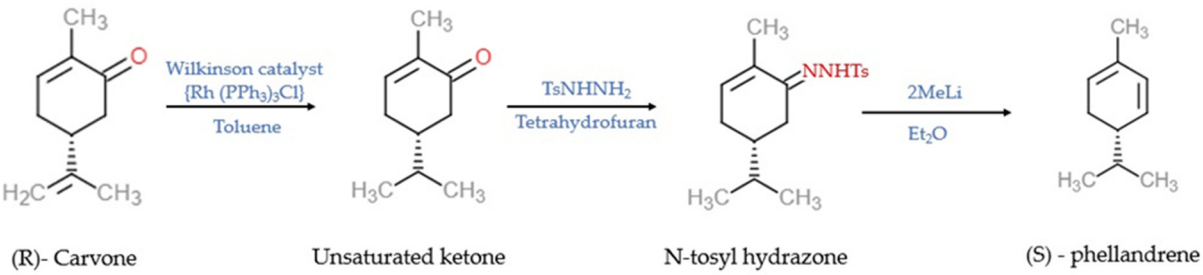

Figure 2. The batch process model of the synthesis of (S)—phellandrene [48]. Chemical structures were drawn using free online ChemDoodle Web software (https://web.chemdoodle.com/demos/2d-sketcher, accessed on 22 August 2022).

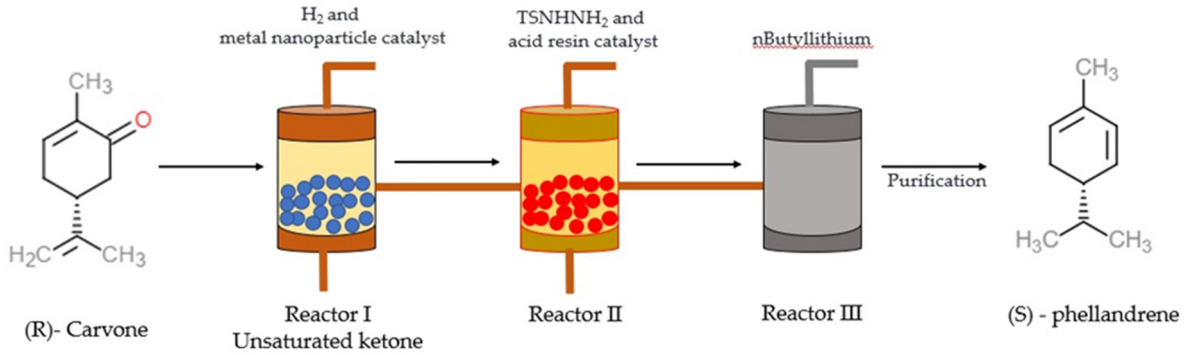

Figure 3. The illustration describes the process of (S)—phellandrene synthesis using a continuous-flow process [49]. Chemical structures were drawn using free online ChemDoodle Web software (https://web.chemdoodle.com/demos/2d-sketcher, accessed on 22 August 2022).

4. Biotransformation of α-PHE

Generally, fragrance compounds exist as single enantiomers. The diversity in sensory properties of fragrance is associated with different types of enantiomers. The chemical synthesis or derivatizations of stereo-, enantio- and regioselective forms can be made by the biotransformation method. The stereo- and enantioselective chiral compound biotransformations were found useful in pharmaceutical and chemical industries in commercial-scale applications [50].

α-PHE exists in two enantiomer forms, such as (−)-(R) and (+)-(S), with varied physicochemical and olfactory properties [5]. İşcan et al. bio-transformed enantiomerically pure (−)-(R)-α-PHE using 16 microorganisms, including bacteria, yeasts, and fungi. Organisms, such as *Escherichia coli (E. coli)*, *Escherichia coli O157-H7*, *Staphylococcus aureus (S. aureus)*, *Staphylococcus aureus MRSA*, *Staphylococcus epidermidis (S. epidermis)*, *Pseudomonas aeruginosa (P. aeruginosa)*, *Enterobacter aerogenes (E. aerogenes)*, *Proteus vulgaris (P. vulgaris)*, *Salmonella typhimurium (S. typhimrium)*, *Bacillus cereus (B. cereus)*, *Bacillus subtilis (B. subtilis)*, *Agrobacterium tumefaciens (A. tumefaciens)*, *Erwinia carotovora subsp. carotovora (E. carotovora subsp. carotovora)*, *Peudomonas syringae pv. Phaseolicola (P. syringae pv. phaseolicola)*, and *Pseudomonas syringae pv. tomato* (*P. syringae pv. tomato*) and *Serratia marcescens*, were used in the biotransformation of (−)-(R)-α-PHE [5]. (−)-(R)-α-PHE biotransformation yielded six metabolites namely, 5-p-menthene-1,2-diol, 6-hydroxypiperitone, α-PHE epoxide, cis-p-menth-2-en-1-ol, p-mentha-1(7), 5-dien-2-ol and carvotanacetone. The resulting metabolites were screened by chromatographic techniques, and their biological activities were examined against pathogenic microorganisms. The anti-bacterial activity of α-PHE and the compound 5-p-menthene-1,2-diol were analyzed. Among these two metabolites, 5-p-menthene-1,2-diol showed significant anti-microbial and anti-candidal (anti-fungal) activity compared to α-PHE [5].

In other studies, α-PHE was bio-transformed into other metabolites using different organisms. Three different metabolites, 5-p-menthene-1,2-diol, p-mentha-1(7), 5-dien-2-ol and 5-p-menthen-2-one, were synthesized by *Corynespora cassiicola (C. cassiicola*) (DSM 62474) (Figure 4) [51]. Biotransformation of α-PHE by *Alternaria alternata* produces 5-p-menthen-1, 2-diol with anti-microbial activity [52].

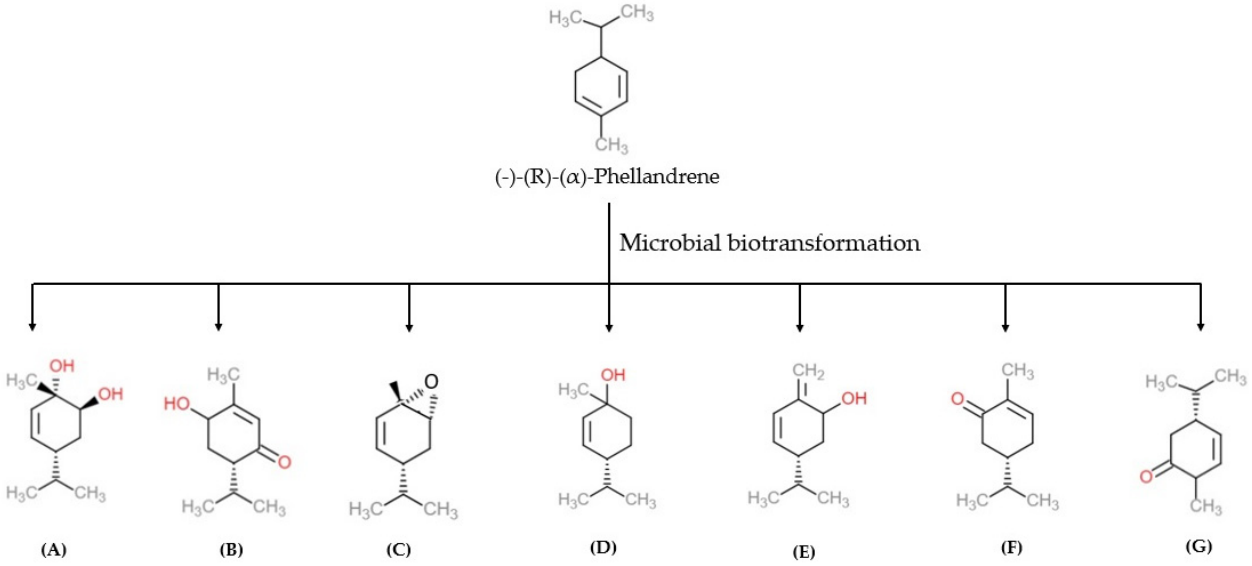

Figure 4. The microbial biotransformation of (−)-(R)-(α)-phellandrene produces different products namely (**A**) 5-p-menthene-1,2-diol, (**B**) 6-hydroxypiperitone, (**C**) α-PHE epoxide, (**D**) cis-p-menth-2-en-1-ol, (**E**) p-mentha-1(7), 5-dien-2-ol, (**F**) carvotanacetone, (**G**) 5-p-menthen-2-one [5]. Chemical structures were drawn using free online ChemDoodle Web software (https://web.chemdoodle.com/demos/2d-sketcher, accessed on 22 August 2022).

The chemical transformation of α-PHE by photo-oxidation and electrochemical processes has been reported [53]. (−)-(R)-α-PHE was also bio-transformed by fungal species such as *Fusarium heterosporium (F. heterosporium)*, *Aspergillus alliaceus (A. alliaceus)*, *Yarrowia lipolitica (Y. lipolitica)*, *Alternaria alternata (A. alternata)*, *Saccharomyces cerevisiae (S. cerevisiae)*, *Kluyveromyces la ctis (K. lactis)*, *Neurospora crassa (N. crassa)*, *Fusarium solani (G. solani)*, *Fusarium culmorum (F. culmorum)*, *Botrytis cinerea (B. cineria)*, *Aspergillus flavus (A. flavus)*, *Phanerochaete chrysosporium (P. chrysosporium*), and *Devosia riboflavina (D. riboflavina)* strains [5].

5. α-PHE in Atmospheric Emission

Naturally, the monoterpenes play an important function in the atmosphere's chemistry and influence the atmosphere's oxidative capacity, which results in the formation and development of the tropospheric ozone and the secondary organic aerosol (SOA), which cause changes in climate and health [54,55]. The biogenic emission sources exceed the emission level of volatile compounds globally into the atmosphere; in this scenario, the monoterpenes produce a significant proportion of non-methane hydrocarbons [56]. α-PHE is the most reactive monoterpene, known for its tropospheric degradation and aerosol formation [57]. The ozonolysis changes of α-PHE and other associated mechanisms were studied. The results showed that when α-PHE reacts with ozone, one of the double bonds in α-PHE opens and releases SOA with 10 carbons. Then, the second addition of ozone causes fragmentation and produces SOA with three or seven carbons [57].

6. Bioactivities of α-PHE

Several studies recognized that medicinal plants are rich sources of secondary metabolites. Among the secondary metabolites, essential oils have been reported for several pharmacological activities and were also used in cosmetics and agricultural industries [4,58]. This section summarizes the reported bioactivities of α-PHE. The bioactivities of α-PHE are summarized in Table 2.

6.1. Insecticidal Property of α-PHE

The *Curcuma longa* leaves essential oil (CLLEO), rich in α-PHE, has insecticidal properties against the third instar stage larvae of the Australian sheep blowfly (*Lucilia cuprina*). The study by Chabaan et al. revealed the insecticidal activity of CLLEO by comparing it with commercially available α-PHE. The third instar larvae were placed over CLLEO spread over the filter paper with varying concentrations, such as 0.15 to 2.86 μL/cm^2 and commercial α-PHE (0.29–1.47 μL/cm^2). The insecticidal activities, such as progressive darkness in the body of larvae, reduced movement, cuticle color change, and the death of the larvae, were observed. The vacuolar degeneration, brain damage and neurotoxicity were observed. Henceforth, α-PHE can be considered an eco-friendly method of pest control [59,60].

Table 2. The reported bioactivities of α-phellandrene.

Study Model	Details of α-PHE and EO Used	Experimental Condition	Study Results	References
Insecticidal activity				
Third instar stage larvae (L3) of the Australian blowfly *Lucilia cuprina*	Commercial α-PHE and *Curcuma longa* leaves EO (CLLEO).	L3 larvae were kept on tissue paper infused with 0.15–2.86 mL/cm^2 of CLLEO and 0.29–1.47 mL/cm^2 of α-PHE dissolved in ethanol. Toxicity was observed at 6, 24 and 48 h.	• Intensive darkening of the L3 body. • Reduced movement and color changes in the cuticle of the larva and dead after 6 and 24 h of α-PHE and CLLEO treatment.	[59]
Third instar stage larvae (L3) of the Australian blowfly *Lucilia cuprina*	Commercial α-PHE and *Curcuma longa* leaves EO (CLLEO).	L3 larvae were kept on tissue paper infused with 0.15–2.86 mL/cm^2 of CLLEO and 0.29–1.47 mL/cm^2 of α-PHE s dissolved in ethanol. Toxicity was observed at 6, 24 and 48 h.	• CLLEO and α-PHE exposure cause damage to the cuticle, brain, and fat body of L3. • Vacuolar degeneration and pyknotic profiles detected in L3 brain. • Reduced neurotoxicity.	[60]
Anti-microbial activity				
Penicillium cyclopium	Commercial α-PHE and Nonanal	6mm diameter discs of *P. cyclopium* inoculum were taken out from culture and placed at the center of Petri dishes containing α-PHE (0, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75 and 2.00 mL/L) and Nonanal (0, 50, 100, 150, 200, 250, 300, 350 and 400 µL/L)	• Mycelial growth of *P. cyclopium* was affected depends on the dosage. • The cell constituents were released. • Shrunken mycelium, depressed conidia and distorted hyphae were observed.	[14]
Swiss male mice and Wistar male rats. Macrophages were isolated from the peritoneal cavity of the mice.	Commercial α-PHE	Mice were treated with α-PHE and saline before (1 h) the treatment with 0.75% acetic acid, 2% formalin, capsaicin (2 mg/paw), glutamate (20 mmol/paw), 1% carrageenan. The anti-nociceptive effect of α-PHE and mechanical hypernociception were analyzed.	• Oral administration of α-PHE significantly reduced abdominal writhing induced by acetic-acid and capsaicin-induced licking response. • 50 mg/kg α-PHE reduced licking response in the formalin test. • α-PHE reduced licking and biting response in glutamate test. • α-PHE 50 mg/kg significantly reduced withdrawal response in carrageenan-induced hypernociception test.	[16]

Table 2. *Cont.*

Study Model	Details of α-PHE and EO Used	Experimental Condition	Study Results	References
Spared Nerve Injury (SNI) induced hyperalgesia in Wistar rats.	Commercial (R)-(+)-phellandrene, α-limonene and *Schinus terebinthifolius* fruits EO	Commercial (R)-(+)-phellandrene (10 mg/kg) and α-limonene (10 mg/kg) and *S. terebinthifolius* EO (3, 30 and 100 mg/kg) were treated with SNI-induced hyperalgesia rats.	• Reduced mechanical induced hypernociception and depression-like behavior. • (R)-(+)-limonene and α-PHE reduced mechanical hyperalgesia and depressive-like activity. • α-PHE inhibited mechanical and cold sensitivity and the Forced swim test.	[15]
S-180 inoculated Swiss mice female. Melanoma B-16/F-10 and S-180 murine cells.	Commercial α-PHE	Animals were separated into seven groups as follows: Sham treated, vehicle-treated (pregabalin 10 mg/kg), positive control (25 mg/kg of 5-fluorouracil), and α-PHE in doses of 6.25, 12.5, 25 and 50 mg/kg orally by gavage once a day.	• Mechanical sensitivity in mice increased significantly. • α-PHE treatment showed antinociceptive responses. • α-PHE treatment showed anti-proliferative activity. • α-PHE treatment reduced malondialdehyde, and TNF-α and IL-1β.	[61]
Immune responses				
BALB/c mice	Commercial α-PHE	BALB/c mice were divided into five groups; I: normal diet; II: olive oil vehicle as positive control; other groups III, IV and V: α-PHE at 1, 5 and 25 mg/kg dissolved in olive oil for 27 days.	• α-PHE treatment did not significantly affect body weight. • α-PHE treatment increased CD3, CD 11b, CD19, and Mac-3 levels. • α-PHE significantly enhanced the phagocytic activity. • Significantly increased the NK cell activity and B-cell and T-cell proliferation.	[62]
Litopenaeus vannamei White shrimp	Commercial α-PHE	*L. vannamei* was administered with α-PHE (4,8 and 12 μg/g) and challenged against *V. alginolyticus* (2×10^5 CFU/shrimp). Non-pre-treated shrimps as controls. Shrimp survival was observed. The immune responses, gene expression and hemocytes morphology, were studied.	• Survival of shrimp increased. • PO, RB, and SOD activities, Phagocytic and lysozyme activities were higher in the α-PHE treated group. • The expression of immune genes was increased. • α-PHE treatment reduced the flattening of hemocytes and pseudopodia.	[63]

Table 2. *Cont.*

Study Model	Details of α-PHE and EO Used	Experimental Condition	Study Results	References
Anti-cancer activity				
Human liver cancer (J5) cells	Commercial α-PHE	J5 cells were treated with 0, 10, 30, or 50 mM of α-PHE for 0, 6, 12, 24, or 48 h. The cytotoxic effects and expressions of Bax, Bcl-2, PARP, and caspase-3 proteins were studied. The necrotic cells level, ROS, MMP, ATP and LDH levels in J5 cells were investigated.	• α-PHE treatment reduced the viability of J5 cells. • Bax, Bcl-2, PARP and caspase-3 protein levels were not changed. • ROS level was increased, and MMPs were decreased. • ATP level was decreased. • LDH leakage, NO production and J5 necrotic cell death were increased.	[17]
Human liver cancer (J5) cells	Commercial α-PHE	J5 cells were treated with 0, 10, 30, or 50 mM of α-PHE. The expression levels of cytoplasmic proteins PI3K-I, PI3K-III, Akt, mTOR, phosphorylated Bcl-2 (p-Bcl-2), Beclin-1, LC3-II, p53, TIGAR, phosphorylated IκB (p-IκB), IκB, and NF-κB (p65) and nuclear p53, DARM, and NF-B were evaluated.	• α-PHE induced apoptosis and autophagy in J5 cells. • PI3K-I, Akt proteins reduced, mTOR proteins increased the phosphorylation of Bcl-2, Beclin-1, PI3K-III, and LC3-II proteins. • α-PHE induces pre-autophagosome formation. • Increased Nuclear p53 and DRAM proteins. Decreased cytoplasmic p53, and TIGAR proteins • α-PHE was involved in autophagosome formation.	[64]
WEHI-3 murine leukemia cells	Commercial α-PHE	WEHI-3 cells were treated with α-PHE (0, 10, 20, 30, and 50 μM) for 48 h. DNA damage and condensation and DNA repair associated-proteins expression were analyzed.	• α-PHE significantly reduced cell viability and induced DNA damage, condensation, and fragmentation in a dose-dependent way. • α-PHE decreased p53, MGMT, DNA-PK, and BRCA-1 expression. • Increased p-p53, p-H2A.X, 14-3-3σ, and MDC1 expression.	[65]

Table 2. *Cont.*

Study Model	Details of α-PHE and EO Used	Experimental Condition	Study Results	References
Male BALB/c mice injected with WEHI-3 murine leukemia cells	Commercial α-PHE	WEHI-3 injected mice were treated with 25 and 50 mg/kg of α-PHE. After 2 weeks, immune responses and macrophage phagocytic and NK cell activities were studied.	• α-PHE treatment reduced the spleen weight of WEHI-3 treated mice. • α-PHE treatment increased CD3 and CD11b and reduced the CD19. • α-PHE treatment increased the Mac-3 cell population. • α-PHE treatment affects phagocytic activity and NK cell activity. • α-PHE treatment increased the T-cell and B-cell proliferation.	[66]
WEHI-3 murine leukemia cell line	Commercial α-PHE	WEHI-3 cells were treated with 10 μM of α-PHE or vehicle for 48 h. The cells were analyzed for expression of DNA damage-related genes, cell cycle and apoptotic cell death.	• α-PHE treatment upregulated the DNA damage inducer transcript-4, DNA fragmentation factor, cyclin G2, cyclin-dependent kinase inhibitor 2D and IA (p21) and apoptosis genes such as BCL2/adenovirus EIB interacting protein 3, associated factor 3, BCL2-modifying factor, caspase-8. • DNA damage-associated genes TATA box BP, cyclin F2 and death box polypeptide 33, apoptosis genes growth arrest-specific 5 and ATP synthase were down-regulated.	[67]

Table 2. *Cont.*

Study Model	Details of α-PHE and EO Used	Experimental Condition	Study Results	References
WEHI-3 murine leukemia cell line	Commercial α-PHE	WEHI-3 cells were treated with 0, 5, 10, 30, 40, and 50 µM of α-PHE. The cytotoxicity effect of α-PHE was assessed.	• α-PHE causes damage to leukemia cells in a dose-depended manner. • α-PHE treatment affected ROS production. • α-PHE induces Ca^{2+} production and caspase 8, 9 and 3 in a time-dependent manner. • α-PHE induces mitochondria-dependent apoptosis. • The level of Fas, Fas-L, Caspase-8, Bax, Bad, tBid, AIF, Endo G, cytochrome c, Caspases-9,3 and 12, PARP, ATF-6a, GRP78 and GADD153 were increased after α-PHE treatment. • α-PHE decreased Bcl-2 and Mcl-1 expressions in WEHI-3 cells.	[18]
Anti-inflammatory activity				
Wistar male rats and Swiss mice	Commercial α-PHE	Before carrageenan injection, rats or mice were treated with vehicle or α-PHE (50, 100, or 200 mg/kg) or dexamethasone (0.5 mg/kg).	• Carrageenan injection induced neutrophil migration. • Pre-treatment with α-PHE (50, 100, and 200 mg/kg) significantly prevented inflammatory cell accumulation in the cavities. • α-PHE attenuated TNF-α, IL-6 expression. • α-PHE inhibited leukocyte rolling and prevented mast cell degranulation.	[68]
Wistar male rats and Swiss mice	Commercial α-PHE	Before carrageenan injection, rats or mice were treated with vehicle or α-PHE (50, 100, or 200 mg/kg) or dexamethasone (0.5 mg/kg).	• α-PHE treatment reduced histamine and Substance P-induced paw edema. • α-PHE treatment reduced ear edema induced by croton oil, TPA and arachidonic acid.	[69]

Table 2. *Cont.*

Study Model	Details of α-PHE and EO Used	Experimental Condition	Study Results	References
Male *Mus musculus* mice of Swiss albino lineage. Wound healing activities	Commercial α-PHE	Mice were treated with tween (vehicle control), ifosfamide (IFOS; negative control), Mesna (positive control), and α-PHE.	• IFOS-induced urinary bladder toxicity was prevented by α-PHE treatment. • α-PHE treatment decreased the activity of myeloperoxidase, malondialdehyde, nitrite/nitrate, and prevented the depletion of superoxide dismutase and reduced glutathione in bladder tissues. • α-PHE significantly reduced TNF-α but did not affect the IL-1β level. • α-PHE treatment showed anti-inflammatory properties against pathological conditions.	[70]
Fibroblasts (L929), macrophages and human embryonic renal cells (HEK 293) transfected with the luciferase-expressing gene	Commercial α-PHE and Terpinolene	For the cytotoxicity study: Fibroblasts and macrophages were treated with terpinolene and α-PHE. For wound healing study: Fibroblasts were exposed to 10, 100 and 200 μM of terpinolene and α-PHE.	• α-PHE showed better antioxidant activity than terpinolene. • Terpinolene and α-PHE did not exhibit a cytotoxic effect against macrophages but enhanced proliferation and migration of fibroblasts in a dose-dependent way. • Suppressed the NO production and inhibited the superoxide anion in LPS-stimulated macrophages. Terpinolene and α-PHE reduced the release of IL-6, TNF-α, and NF-kB.	[71]

Table 2. *Cont.*

Study Model	Details of α-PHE and EO Used	Experimental Condition	Study Results	References
Male CD-1 mice and fibroblasts	Commercial α-PHE and α-Pinene	The mice's back skin was shaved, and an incision was made. Mice were divided into groups I: untreated skin without wounds, group II: untreated wounds (negative control), group III: wounds treated with Recoverón NC® (positive control), group IV: cosmetic grade mineral oil (vehicle), and the next four groups treated with α-pinene and α-PHE at 0.1 and 0.01 mg/mL concentrations for 10 days.	• α-pinene and α-PHE treatment did not affect the cell viability and did not stimulate fibroblast proliferation. • No alteration in morphology of fibroblasts. • α-pinene and α-PHE showed the highest wound closing speeds. • Histopathological study showed that α-pinene and α-PHE-treated skin presented some dermal collagen fiber bundles and blood microvasculature vessels inside the mononuclear infiltrate.	[34]

CLLEO, *Curcuma longa* leaves essential oil; SNI, spared nerve injury; EO, essential oil; TNF-α, tumor necrosis factor-α; IL-1β, interleukin 1β; CD3, CD 11b, and CD19, cluster of differentiation 3, 11b, and 19; Mac-3, macrophage; NK cell, natural killer cell; B cell, B lymphocyte; T cell, T lymphocyte; CFU, colony forming unit; PO, phenoloxidase, RB, respiratory bursts, SOD, superoxide dismutase; THC, total hemocyte count; ROS, reactive oxygen species; MMP, mitochondrial membrane potential; ATP, adenosine tri-phosphate; LDH, lactate dehydrogenase; PI3k, phosphatidylinositol 3 kinases; Akt, protein kinase B; mTOR, mammalian target of rapamycin; TIGAR, Tp53-induced glycolysis and apoptosis regulator; DRAM, damage-regulated autophagy modulator; NF-κB, nuclear factor-κB; MGMT, O6-methylguanine-DNA methyltransferase; DNA-PK, DNA-dependent protein kinase; BRCA-1, breast cancer protein; p-H2A.X, phosphorylated histone 2A X variant protein; MDC-1, mediator of DNA damage check point 1 protein; PARP, poly ADP ribose polymerase; ATF, activating transcription factor; GRB, glucose regulated protein; GADD, growth arrest and DNA damage inducible protein; TPA, 12O-tetradecanoylphorbol-13-acetate; IFOS, ifosfamide; LPS, lipopolysaccharide.

6.2. Anti-Microbial Properties of α-PHE

Generally, essential oils possess anti-microbial activity against microbes, including bacteria and fungi such as *Candida albicans*, *Bipolaris* sp., *Alternaria alternate*, *Cuvularia lunata* and *Fusarium oxysporium* [72–76]. α-PHE, β-PHE, ocimene, myrcene, limonene and α-caryophyllene showed in vitro anti-microbial activities against *Bacillus* sp., *Escherichia coli*, *Candida albicans*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* [77,78]. α-PHE inhibited the growth of *Salmonella choleraesuis (S. choleraesius)*, *E. coli* and *B. subtilis* [71], *Micrococcus luteus*, *Rhodococcus rhodochorus (R. rhodochorus)*, *Arthobacter protophormiae (A. protophormiae)* and *S. aureus* [79] and *Aspergillus flavus* [80].

Gram-positive bacteria are more highly prone to be affected by essential oils than Gram-negative bacteria [81]. Gram-negative bacteria's outer hydrophilic polysaccharide membrane is a barrier against hydrophobic essential oils [82,83]. The anti-bacterial mechanism of essential oils could be the lipophilicity of essential oils causing expansion of cell membrane, which increases membrane fluidity and permeability, and disturbs membrane proteins, which indulge in respiration ion transport in microbes, subsequently causing cell death because of the leakage of ions and cellular contents [84–87].

In the case of anti-fungal activity, α-PHE decreases the lipid content and alters the fungal hyphae, thus disturbing the membrane integrity [88,89]. α-PHE and nonanal showed inhibition of mycelial growth of *Penicillium cyclopium* in a dose-dependent way. The inhibitory action is directly proportional to the concentration of α-PHE. Complete mycelial growth inhibition was observed at the concentration of ≥1.35 mL/L of α-PHE. The minimum inhibitory (MIC) and minimum fungicidal concentration (MFC) of 1.7 and 1.8 mL/L of α-PHE were observed, respectively. Nonanal was relatively more efficient than α-PHE in inhibiting fungal growth (0.10 mL/L for complete inhibition). The MIC and MFC of nonanal against *P. cyclopium* were 0.3 and 0.4 mL/L, respectively.

The effect of α-PHE on the release of cell components was evaluated by measuring the optical density (OD_{260}) values. The OD values of α-PHE treated *P. cyclopium* suspension were profoundly higher than the nonanal treated samples. α-PHE also disturbs the shape, structure and appearance of hyphae and conidia of *P. cyclopium* and causes the leakage of potassium ion (K^+) after 30 min of α-PHE treatment (1.520 µg/mL) [14].

6.3. Analgesic Property of α-PHE

Pain is one of the common unpleasant experiences among people having physical injuries and mental illnesses, such as emotional, cognitive, and social issues [90]. α-PHE exerts antinociceptive effects in acute nociception models. The oral administration of α-PHE was found to be more effective. α-PHE exerts its anti-nociceptive activity through glutamatergic, nitrergic, opioid, cholinergic and adrenergic systems [16].

The anti-nociceptive activity of α-PHE in the nociception mice model was studied. Oral administration of α-PHE (3.125, 6.25 and 12.5 mg/kg) significantly inhibited the acetic acid-induced abdominal writhing in mice. The injection of 50 mg/kg α-PHE reduced the paw-licking time in mice injected with 2% formalin compared to the control. Nociception was also drastically reduced with α-PHE (3.125, 6.25, 12.5 mg/kg) injection in capsaicin (2 µg/paw) treated mice, which confirms the anti-nociceptive effect of α-PHE. Declines in the licking and biting behavior were observed in the mice with glutamate-induced nociception. The inhibitory effects of α-PHE may be due to its regulatory effects on the histamine, serotonin, and prostaglandin E2 (PGE2) [16].

The essential oil extracted from *Schinus terebinthifolius* Raddi fruits is comprised of α-pinene, β-pinene, sabinene, z-salven, α-funebrene, (R)-(+)-limonene, myrcene and α-PHE [24]. The terpene α-PHE from *S. terebinthifolius* showed anti-hyperalgesic and anti-depressant effects in spared nerve injury (SNI)-induced experimental hyperalgesia and depression rat models. *S. terebinthifolius* essential oil reduced the hypernociception, depression-like behavior and immobility induced by SNI. This study could open new possibilities for developing novel anti-hyperalgesic and anti-depressive drugs for treating chronic pain and depression due to neuropathy and infections [15].

The anti-nociceptive ability of α-PHE was studied in a Sarcoma-180 (S-180) hypernociception mice model. Nociception was induced by implanted S-180 into the axillary region of mice for 8 days. α-PHE (6.25, 12.5, 25 and 50 mg/kg) was orally administrated to mice on the first day of S-180 inoculation. Acute α-PHE treatment reduced peritumoral mechanical sensitivity for up to 180 min and antinociception in a dose-dependent way [64]. Another study reported that the essential oil from the *Eucalyptus* genus reduced the S-180-induced nociception without affecting rodent tumor growth. This showed that the analgesia does not depend on tumor reduction [91].

6.4. Immune Responses of α-PHE

The role of α-PHE on the immune responses was analyzed in the murine cells. BALB/c mice were treated with α-PHE (1, 5 and 25 mg/kg) or olive oil (vehicle control) for 27 days with the standard laboratory diet. The results showed that α-PHE did not significantly affect the body weight compared to the control group. α-PHE supplementations increased the cluster of differentiation (CD) 3 (at 1 mg/kg), CD19 (at 5 and 25 mg/kg), and Mac-3 (Macrophages) (at 25 mg/kg) levels and repressed the CD11b level (at 5 and 25 mg/kg). α-PHE promoted the phagocytotic activity of macrophages, NK cell activity, and B- and T-cell proliferation. The results indicated that α-PHE did not induce any toxic effects in murine cells but impacted the activities of immune cells [62].

The impact of α-PHE on infections, susceptibility, and other non-specific immune responses, such as the levels of total hemocyte count (THC), phenoloxidase (PO) activity, respiratory bursts (RB), superoxide dismutase (SOD), and the phagocytic and lysozyme activity of white shrimp (*Litopenaeus vannamei*) were reported. In detail, white shrimps were individually treated with α-PHE (4, 8 and 12 μg/g on day 1). On the second day, they were administered 10 μL of Vibrio alginolyticus suspension (1×10^7 CFU) or saline (control). Shrimp survival or sustainability was observed after 12, 24, 36, 48, 60 and 72 h. The survival rate of white shrimp was increased in the α-PHE treated group. The PO and SOD activity of shrimp was significantly higher in the α-PHE treatment than in the control group. No significant changes were observed in THCs, and the shrimp's RB activity was higher than in the control. The expression of prophenoloxidase, LPS- and β-1,3-glucan binding protein and peroxinectin were also significantly increased. Shrimp treated with *V. alginolyticus* showed affected hemocytes that displayed flattened, shrinkage and pseudopodia. α-PHE (8 and 12 μg/g) treated shrimp hemocytes were less flattened and showed pseudopodia [63].

6.5. Anti-Cancer Property of α-PHE

α-PHE exhibits potent anti-cancer properties against various cancer types, such as lung cancer [92], human breast and prostate cancer [27], and human liver tumor [17,64]. Lin et al. (2014) demonstrated the role of α-PHE in the activation of immune responses under leukemic conditions, this would potentially initiate additional studies concerning α-PHE treatment for leukemia [68]. α-PHE in the essential oil of *Solanum erianthum* possesses anti-cancer activities against human breast cancer cells (Hs 578T) and human prostate cancer cells (PC-3) [26].

WEHI-3 murine leukemia cells treated BALB/c mice were co-treated with α-PHE (25 mg/kg and 50 mg/kg), and the changes were measured. The results showed that α-PHE did not significantly reduce the body weight of animals. The weight of the spleen was reduced in the α-PHE group compared to the control groups. A high dose of α-PHE (50 mg/kg) stimulated the B-cell and T-cell proliferation in WEHI-3 treated group, which indicated that α-PHE enhanced the immune responses, increased phagocytosis and NK cell cytotoxic activity in the leukemia WEHI3 cells of treated mice [67]. The macrophages exhibit inflammatory responses during tissue damage or pathogens invasion, which could maintain tissue homeostasis [93]. The NK cells are involved in recognizing and clearing off the pathogen-infected cells [94].

The cytotoxic and autophagy-inducing functions of α-PHE in human liver cancer cells were reported. Human liver cancer (J5) cells were treated with 0, 10, 30 or 50 μM of α-PHE for 24 h. J5 cells treated with 30 or 50 μM α-PHE showed cell 61% and 51% of viability, respectively. α-PHE treated cells showed about 21–46% cell viability after 48 and 72 h of treatment, which was significantly decreased compared to the control group [64].

The α-PHE effect on pre-autophagosome and autophagosome formation was also examined in J5 cells using monodansylcadaverine (MDC) staining. Additionally, 30 or 50 μM α-PHE for 24 h showed more MDC-stained J5 cells than the control. The involvement of α-PHE in the autophagy-associated regulatory protein signal transduction pathway was studied by evaluating proteins such as PI3K-I, III, Akt, mTOR, phosphorylated BCl-2 (pBCl-2), Beclin-1, LC3-II, p53, TIGAR, pIκB, IκB, NF-κB also nuclear p53, DARM, and NF-κB. The predominant autophagy-inducing proteins PI3K-I, Akt and mTOR were suppressed by α-PHE. Autophagosome-formation modulating proteins PI3K-III, pBCl-2, Beclin-1, and LC3-II were significantly increased in the α-PHE treated cells compared to control. The p53, DRAM, NF-κB, Beclin-1 and pIκB were also increased after 24 h of α-PHE treatment. α-PHE increases the translocation of NF-κB into the nucleus from the cytoplasm. The cytoplasmic p53, NF-κB, TIGAR and IκB were significantly reduced. Thus, the α-PHE induced the autophagy of human liver tumor cells, thereby reducing its viability [64].

Schinus molle L. derived α-PHE induced the DNA damage and repair associated protein expression was evaluated in WEHI-3 murine leukemia cells. Among different concentrations of α-PHE, 50 μM of α-PHE treated WEHI-3 cells showed reduced cell viability. Comet assay described the dose-dependent effect on DNA damage, condensation, and fragmentation. α-PHE also induced DNA damage by suppressing the expression of DNA repair-associated proteins, such as p53, O6-methylguanine DNA methyltransferase (MGMT), DNA-dependent protein kinase (DNA-PK) and BRCA-1. α-PHE inhibited the translocation of pH2A.X and MDC-1 from the cytosol to nuclei in WEHI-3 cells. α-PHE induced caspase 3,8 and 9 activities in a time-dependent way and induced cytochrome c release from mitochondria of WEHI-3 cells, which shows that α-PHE can induce apoptosis by mitochondrial-dependent pathways. α-PHE upregulated the apoptosis regulating proteins such as Bax, Bad, tBid, Endo G, PARP, Caspase 3, 9, 12, ATF-6a, GRP78 and GADD153 and reduced the Bcl2 and Mcl 1, indicating that α-PHE could promote cell death through mitochondrial and endoplasmic reticulum pathways [65].

The functional role of α-PHE in DNA damage, cell cycle and apoptotic regulatory genes in WEHI-3 cells were reported. WEHI-3 cells were treated with 10 μM α-PHE for 24 h and then subjected to cDNA microarray analysis. The results indicated that α-PHE treatment upregulated the DNA damage-inducer transcript 4 and DNA fragmentation factor. The cell cycle checkpoint genes, such as cyclin G2 and cyclin-dependent kinases inhibitor 2D and p21, were upregulated. Apoptotic genes, such as BCL2/adenovirus EIB interacting protein 3, XIAP-associated factor 1, BCL2 modifying factor, caspase 8, and FADD-like apoptosis regulator genes, were upregulated. The genes TATA box-binding protein, cyclin E2, growth arrest-specific 5, Gm5426, and death box polypeptide were downregulated [67].

6.6. Anti-Inflammatory Properties of α-PHE

The anti-inflammatory property of α-PHE was studied using the carrageenan-induced peritonitis mice model. Mice were treated with commercial α-PHE at various concentrations (50, 100 or 200 mg/kg). After one hour of α-PHE treatment, the animals were injected with diluted carrageenan. After 4 h of carrageenan injection, the mice were sacrificed, and the levels of proinflammatory cytokines IL-6 (Interleukin-6) and TNF-α (tumor necrosis factor-α) were measured by ELISA. The leukocyte rolling and adhesion were examined with the help of the real-time intravital microscopy method. Mast cell degranulation in the mesenteric tissue was also determined. The examined results showed that the carrageenan-injected air pouch or peritoneum produced leukocyte influx, which inhibited the α-PHE treated group. Reduced TNF-α and IL-6 could exert the leukocyte influx control by α-PHE.

α-PHE and dexamethasone reduced the influx of total leukocytes, thereby reducing the neutrophils rolling or endothelial adherence [67].

The migration of leukocytes into the joints of rheumatoid arthritis patients can induce the secretion of ROS, proteases, cytokines, and prostaglandins, which could be harmful to the synovial tissues, bone, and cartilage [95]. In addition to the influx of pro-inflammatory cytokines, carrageenan also induces the expression of cyclo-oxygenase-2 (COX-2) and PGE2 [96,97]. Moreover, in addition to the inhibition of TNF-α and IL-6 in carrageenan-induced animal models, α-PHE also modulated the other inflammatory mediators, such as leukotriene B4, IL-8 and C5a [98–101]. The inhibitory effect of α-PHE might be associated with the reduced TNF-α and IL-6 release and regulation of the adhesion molecules in the endothelial cells and polymorphonuclear cells [102,103].

α-PHE, because of its anti-inflammatory property, could be used to inhibit hemorrhagic cystitis (HC), one of the side effects of the clinical usage of ifosfamide (IFOS). The neuroprotective role of α-PHE was evaluated in the IFOS-induced HC mouse model. HC can lead to bladder constriction, anemia, urinary tract infections, renal failure, and hydronephrosis, which might lead to death [104]. α-PHE prevents IFOS-induced HC by suppressing oxidative stress and inflammation. Mice that received α-PHE (25 and 50 mg/kg) showed a reduction in cell loss, hemorrhage and edema in bladder tissue compared to the control group. A dose of 25 mg/kg of α-PHE increased the antioxidant score, restored IL-1β and TNF-α, and reduced bladder damage. α-PHE at 12.5, 25 and 50 mg/kg doses reduced vascular protein leakage. The lower concentration of α-PHE could prevent the damage caused by IFOS. These findings furthermore support the use of α-PHE as a potential therapeutic compound. [70]. α-PHE also proved to be an effective cytoprotective agent that can potentially reduce the proinflammatory cytokines [68], controlling inflammation and protecting from free radicals [105]. α-PHE proved to have anti-dematogenic properties in acute inflammation models [69].

6.7. Wound-Healing Activities of α-PHE

Wound healing requires complex processes that involve growth factors, cytokines and different types of cells and their interactions [106,107]. α-PHE possesses promising efficiency for treating skin wounds by reducing inflammation and oxidative stress through the regulation of nitric oxide (NO), superoxide anion (O^{2-}), TNF-α and IL-6 [71]. The first level of defense in wound healing is the migration of dermal fibroblasts to the site of injury, which is an important step in cutaneous wound repair [106]. The inflammatory phase is a critical period in wound healing, producing pro-inflammatory cytokines by macrophages regulates the healing process. Both in vitro and in vivo studies demonstrated that α-PHE stimulates fibroblast proliferation and migration to the wound site, suppresses the overproduction of pro-inflammatory cytokines and reduces intracellular NO and superoxide anion, thereby reducing oxidative stress [71]. α-PHE also attenuates neutrophil migration and mast cell degranulation and contributes to wound healing [69].

The synthesis, maturation and deposition of collagen is an important characteristic feature of the wound-healing process [108]. The migration of fibroblasts into the wound bed and the formation of an extracellular matrix of granulation tissue is another feature of wound healing [109]. The essential oil of *Bursera morelensis* promoted fibroblast migration to the wound site and initiated collagen synthesis [110]. α-pinene and α-PHE treatments showed wound-healing activity, with improved scar tissue and collagen deposition [34].

6.8. Neuronal Properties of Terpenes

The plant-derived secondary metabolites, such as alkaloids, flavonoids, and triterpenes, can avert the breakdown of acetylcholine and improve cognitive performance [111]. Cognitive and memory processes are well coordinated by the cholinergic system of the central nervous system (CNS). Plants belonging to the genera *Mentha* produce high monoterpenes and sesquiterpenes [5]. Essential oil from the peppermint plant *(Mentha piperita)* showed cholinergic inhibitory activity and GABAA/nicotinic receptor binding properties,

which increases cognition in healthy adults. Monoterpene-rich plant extracts, such as *Melissa* and *Rosmarinus* genera, involve cholinergic and GABAergic neurotransmission that affects mood and cognitive performance [112]. Borneol, a bicyclic monoterpene, possesses radical scavenging activity [113] and is reported to have neuroprotective functions in both in vivo and in vitro models of AD [114].

α-PHE inhibited the nociception induced by formalin. The formalin-induced nociception involves the first phase-neurogenic pain due to the chemical stimuli of both the myelinated and unmyelinated afferent fibers [115]. The second phase occurs because of inflammatory mediators, such as serotonin, histamine, prostaglandins, bradykinin, and changes in the spinal dorsal horn's neurons [116].

The intraplantar injection of glutamate activates N-methyl D-aspartate (NMDA) and α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate (non-NMDA) receptors by NO release and intracellular Ca^{2+} concentration. Calcium initiates NO synthase [117], which releases the pro-inflammatory cytokines, ROS, that enhance inflammatory reactions [118]. α-PHE could inhibit NO production by inhibiting the interaction of glutamate with its receptors [16]. Although α-PHE has not been involved in any study related to neuroprotective effects, other terpenes have found applications in neuronal functions. However, more studies on α-PHE and its role in CNS functions are required. The bioactivities of α-PHE are represented in Figure 5.

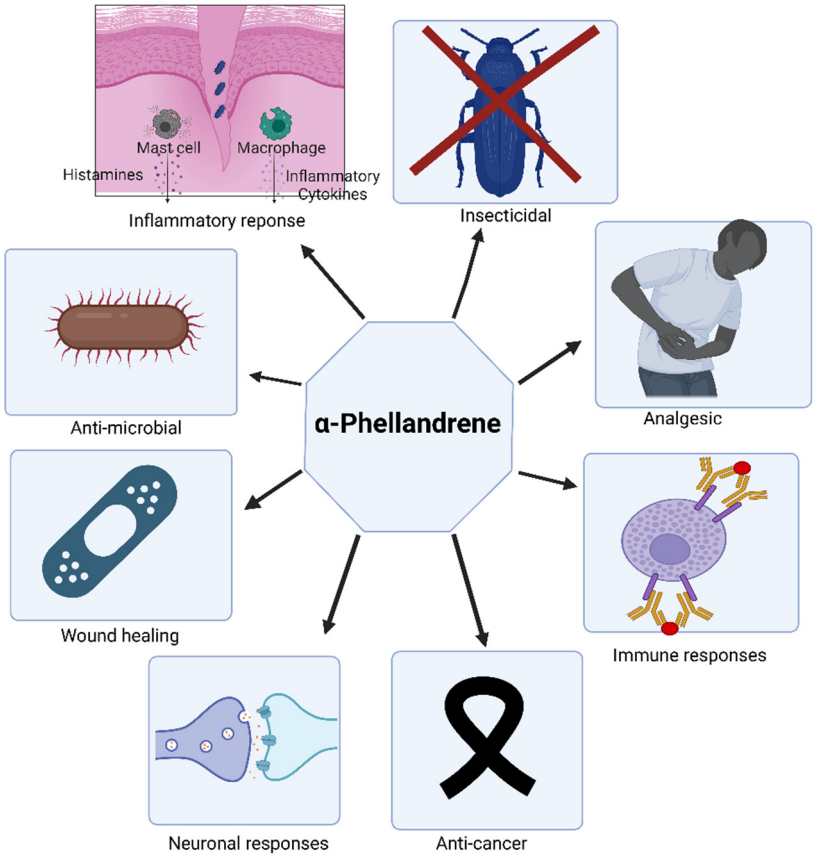

Figure 5. The biological functions of α-PHE involve insecticidal, anti-microbial, analgesic, immune, inflammatory, neural-response, anti-cancer, and wound-healing effects. (Figure created using BioRender.com accessed on 29 August 2022).

7. Possible Mechanism of Action of α-PHE

The anti-microbial activities of phellandrene or other terpenes were more effective against Gram-positive bacteria. The anti-fungal activity of α-PHE involves alteration in the mycelial morphology, disturbed membrane stability, and increased ions and other cell materials leakage [84]. α-PHE can induce changes in lipid content and fatty acid content

of the cells and cause K^+ leakage, increase in extracellular pH and further destroy fungal or microbial cells [14]. α-PHE might exert anti-inflammation activity by preventing NF-kB activity, reducing the production of TNF-α and IL-6 from LPS-stimulated macrophages [68,119], pro-inflammatory enzymes [120] and through inhibition of neutrophil infiltration and mast cell degranulation [68].

The possible analgesic effect of α-PHE could involve glutamatergic, opioid, nitrergic, cholinergic and adrenergic systems [16]. The nociceptive receptors, such as the transient receptor potential (TRP) family, including TRPM8 and TRPA1, mediate the analgesic effect [121,122]. α-PHE might have antihyperalgesic activity against cold sensitivity, SNI-induced hyperalgesia, and depression-like behavior in rats. This enables α-PHE to be used in treating pain resulting from neuropathy and infections and is clinically involved in developing new antinociceptive drugs [15]. The antinociceptive effect of α-PHE was reverted by an opioid receptor antagonist, naloxone, which indicates that antinociceptive activities depend on the opioid system [61].

The pain modulation pathways are associated with GABA in the mammalian brain [123]. GABA is the inhibitory neurotransmitter, so GABAergic neurons inhibit the release of excitatory neurotransmitters, such as serotonin, dopamine, glutamate, and acetylcholine [124]. α-PHE positively contributes to the GABAergic system by enhancing GABA's inhibitory activity and reducing neuronal excitability [124], which might provide the antinociceptive effects for α-PHE. During oncogenic pain, the activation of immune responses leads to TNF-α release, which later releases prostaglandins and pro-inflammatory amines that cause hyperalgesia [125]. Thus, α-PHE, through the GABAergic and opioid pathways, reduces the cytokines TNF-α, IL-1β, IL-4 and IL-6, consequently strengthening effective antinociception.

α-PHE exhibits wound-healing efficiency because the terpenes possess an adhesive effect on the skin, which initiates the healing effect [126]. Terpenes, such as α-PHE and α-pinene, act as primary agents in repairing wounds by providing good tensile strength for scar and accelerating wound closure [127]. α-PHE favors wound-healing activities by inducing the proliferation and migration of fibroblasts, which stimulate wound closure. α-PHE decreases intracellular NO levels and superoxide anion, thereby inhibiting oxidative stress and boosting cutaneous wound healing [71].

The enzymes lipoxygenase-5 (LOX-5) and cyclooxygenase II (COX II) regulate the arachidonic acid pathway of inflammation [12]. LOX-5 is important for leukotriene production by neutrophils and other related inflammatory mediators responsible for NF-kB activation, which is a sign of early-stage joint inflammation in gout patients [120,128]. α-PHE inhibits COX-II and LOX-5 enzyme activity in a dose-dependent manner, comparable to the standard anti-inflammatory drug diclofenac sodium [12]. The possible mechanisms of action of α-PHE are presented in Figure 6.

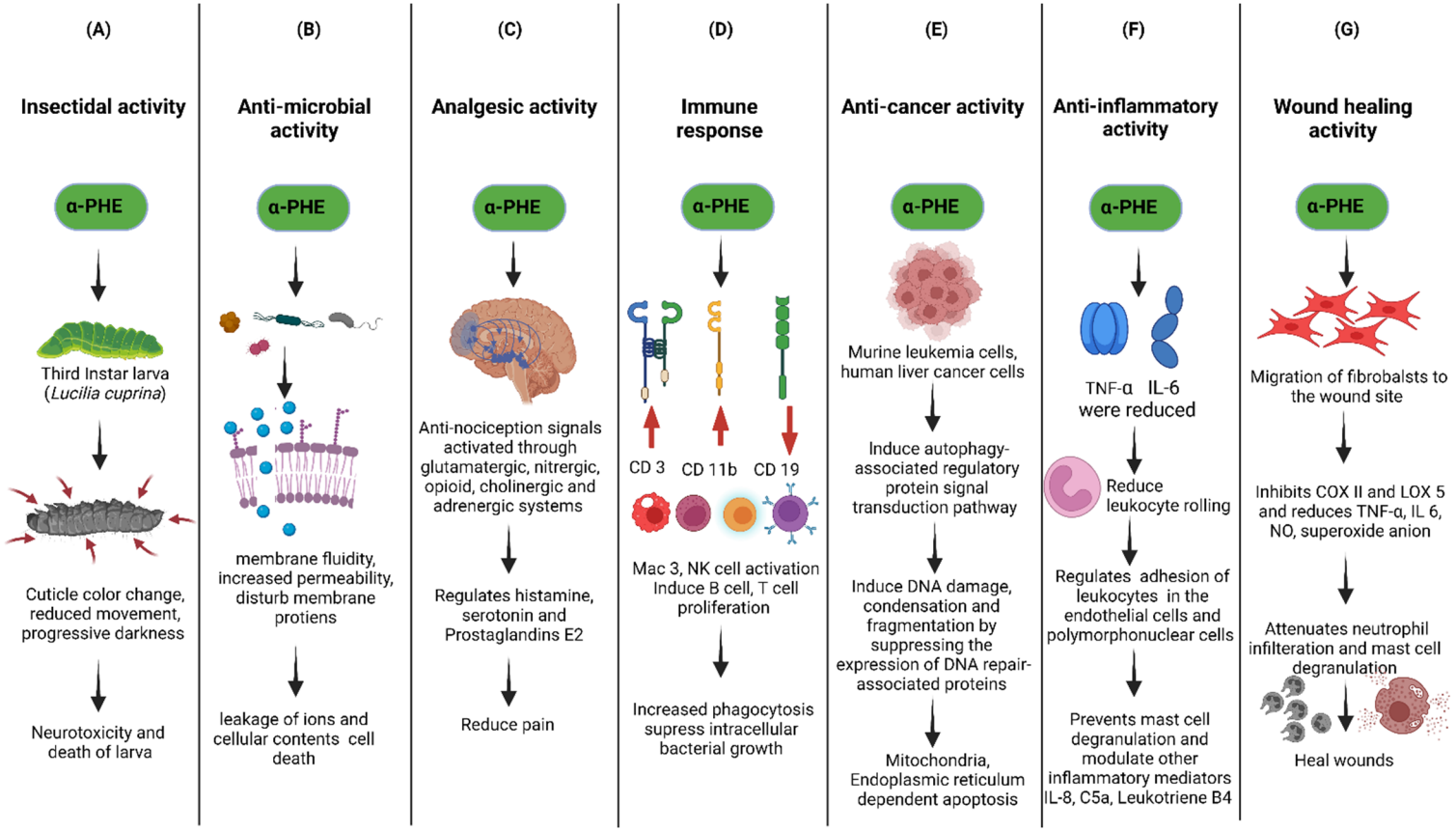

Figure 6. The possible mechanism of α-PHE: (**A**) α-PHE exhibit insecticidal activity by inducing neurotoxicity and death of insect in the larval stage. (**B**) Anti-microbial activity of α-PHE occurs by increased membrane permeability, fluidity, and leakage of ions from the microbial cells. (**C**) α-PHE showed anti-nociception activity by regulating neurotransmitters through various signaling pathways such as opioid, GABA, glutamatergic, nitrergic, cholinergic and adrenergic systems. (**D**) The immune response of α-PHE is exhibited through macrophages and NK cell activation, T-cell and B-cell proliferation. (**E**) Anti-cancer activity of α-PHE is associated with inducing autophagy-associated protein pathways and DNA damage. (**F**) The anti-inflammatory properties of α-PHE are carried out by reducing TNF-α, and IL6, regulating other inflammatory mediators, and preventing mast cell degranulation. (**G**) α-PHE wound healing property works by inhibiting COX II, LOX 5, TNF-α, IL6, and superoxide anions and inducing activated fibroblasts' migration to the wound site. (Figure created using BioRender.com, accessed on 29 August 2022).

8. Conclusions and Future Prospectus

Essential oils and their components have functional attributes in various fields, including the food, cosmetic and pharmacology industries. α-PHE-containing essential oils have been used in conventional treatments of certain diseases and infections. α-PHE has been reported for its several biological activities. Notably, α-PHE exerts anti-microbial, antioxidant, anti-nociception, anti-tumor, and anti-inflammatory activities. In vitro and in vivo studies have proven the pharmacological importance of α-PHE. However, more studies are needed to acknowledge the bio-properties and the pharmacokinetics of α-PHE. Similarly, though the role of α-PHE in several activities is explained, the existing evidence is insubstantial and not conclusive in confirming the mechanism of action of α-PHE. Apart from the beneficial effects, any topical application of α-PHE can cause skin irritations, and oral administration may result in nausea, vomiting, diarrhea, and intestinal disturbances, so intensive studies on the adverse effects of α-PHE are required. Collectively, the current literature review suggests that extended pre-clinical studies are vital to developing safe α-PHE-based adjuvant therapeutic approaches.

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