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Review

D-Limonene: Promising and Sustainable Natural Bioactive Compound

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Abstract: The discovery of antibiotics and pesticides has greatly contributed to the social and economic development of human society but, due to the long-term irrational application, it has led to drug-resistant microorganisms, environmental damage, and other hazards, so the selection of alternative natural, safe, and non-hazardous bioactive substances is an effective solution for this problem. D-limonene is a bioactive compound widely present in various plant essential oils, exhibiting excellent broad-spectrum bioactivity and promising prospects for development and clinical application. This review provides a detailed overview of the biological activities of D-limonene, emphasizing its antimicrobial, anthelmintic, insecticidal, and medicinal potential. While nanoencapsulation technology shows promise in improving the physicochemical properties of D-limonene and enhancing its practical applications, it is also crucial to comprehensively evaluate the potential side effects of D-limonene before use.

Keywords: D-limonene; preparation; antimicrobial activity; anthelmintic activity; pharmacological activity; application; nanotechnology

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1. Introduction

Since their discovery, antibiotics and pesticides have been used to combat microbial contamination and crop production, but due to long-term uncontrolled misuse, they have led to serious hazards, such as the widespread spread of drug-resistant microorganisms, global environmental pollution, and incalculable losses to public health and safety [1–3]. Under this critical situation, the concept of green and sustainable development has been accepted by the public so researchers hope to find green methods to replace the long-term use of antibiotics and pesticides, among which, plant essential oils, due to their origin from natural plants, have reliable safety and excellent biological activity. This is one of the research directions that researchers have high hopes [4,5].

Plant essential oils are the main source of aromatic plant odors, which are mainly derived from the roots, stems, leaves, and other organs of plants and have long been used in culinary and medical applications in the historical record [6]. With deeper research, it has been found that plant essential oils have excellent antioxidant activity, antimicrobial activity, and other biological activities [7], which are mainly derived from the constituents of plant essential oils, which are dominated by terpenes and phenyl terpenoids, of which monoterpenoids are the most common [8] and, thus, natural compounds have been incorporated into the study of natural antimicrobial substances. Among the many natural compounds, limonene, due to its widespread presence in the essential oils of various plants, such as *Citrus bergamia*, *Citrus deliciosa*, *Montanoa quadrangularis*, *Juniperus oxycedrus*, *Citrus unshiu*, and *Bursera graveolens* [9,10], and excellent bioactivity has been considered by researchers as a potential sustainable natural active compound [11,12].

Limonene (1-methyl-4-isopropenylcyclohex-1-ene), also known as dipentene, is a natural monocyclic monoterpene that is a colorless liquid with two optical isomers: dextrorotatory D or (+) limonene and levorotatory L or (-) limonene and a racemic mixture (DL-limonene), which have different bioactivities, which may be attributed to the fact that different spatial structures result in different affinities for the active site [13,14]. Limonene in natural plant essential oils is mainly dominated by D-limonene, which is widely found in the peels of citrus and other fruits as a plant biomarker volatile organic compound with a content of up to 80% or more [15], whereas L-limonene is found in *Cymbopogan nardus* and *Cymbopogan citratus*, with a content of about 3% [16]; therefore, D-limonene has been extensively studied compared to L-limonene, so this paper will mainly describe the current status of D-limonene research but, in some studies, the authors did not specify the configuration of limonene. It is classified as "generally recognized as safe" (GRAS) by the U.S. Food and Drug Administration and is widely used in the food and cosmetic industries [13]. Additionally, D-limonene also has analgesic, anti-inflammatory [17,18], antioxidant [19], neuroprotective [20], and antimicrobial [21] effects and has hence received extensive attention from researchers.

In recent years, research on the practical applications of D-limonene has continued; however, despite its proven bioactivity, its hydrophobicity, volatility, and sensitivity to heat, light, oxygen, and moisture are affected by environmental factors (e.g., oxygen, light, and temperature) when applied directly to food systems and its oxidation gives off unpleasant odors, which, together with its own strong aromatic odor, can interfere with the sensory properties of the food to which they are added [22], which limits its application in food [23,24]. Currently, researchers are improving the physicochemical properties and bioactivity of D-limonene by producing new materials, such as nanoemulsions and nanofilms, through encapsulation and other techniques, and applying them in practical applications [25]. For instance, nanoemulsions of sodium caseinate and D-limonene in specific ratios were generated using high-pressure homogenization, which significantly improved preservation and thermal stability. The original particle size was maintained even after storage at 4 °C for 60 days and heating at 90 °C for one hour and the antibacterial activity was also significantly enhanced, with the minimum inhibition concentrations (MICs) reduced from 12.5, 7.8, and 7.8 μL/mL to 3.13, 3.13, and 1.56 μL/mL for E. coli, *Bacillus subtilis*, and *S. aureus*, respectively [23]; Shao et al. [26] homogenized Ulva fasciata polysaccharide with 0.15% *w*/*w* D-limonene into nanoemulsions and applied these to strawberries and they found that, although the elasticity of strawberries in the experimental group was slightly reduced compared to the control group, there were significant advantages in terms of color, morphology, texture, and weight loss.

Although studies have described the antibacterial and antifungal activity of D-limonene, detailed analyses of its mechanism of action are lacking and there is still a lack of research on other bioactivities, such as anthelmintic activity and pharmacological activity, possible modes and mechanisms of action, and enhancement of its biological activity by techniques such as nanoencapsulation. Therefore, this paper focuses on the antibacterial and antifungal mechanism of action of D-limonene; describes the anthelmintic activity, insecticidal activity, pharmacological activity, and antiviral activity of D-limonene; and discusses the current application of technologies, such as nanoencapsulation, for enhancement of the bioactivity and improvement of the physical properties of D-limonene.

In this review, we mainly searched for articles in English from databases of Web of Science (https://www.webofscience.com/wos/, accessed on 15 May 2024), NCBI (https://pubmed.ncbi.nlm.nih.gov/, accessed on 21 March 2024), and X-mol (https://www.x-mol.com/, accessed on 15 May 2024) and considered the most recent research. The keyword "Limonene" was used alone or in combination with, for example, "production", "essential oil", "antimicrobial activity", "antibacterial activity", "antifungal activity", "antibiofilm activity", "anthelmintic activity", "insecticidal activity", "antioxidant", "anti-inflammatory" "antiviral activity", and "application".

2. Production of D-Limonene

Natural plant extraction and biotransformation are the main methods for D-limonene production [27–29].

2.1. Natural Plant Extraction: Adding Value to Waste

The fruit and vegetable industry produces a large amount of peel waste every year, causing great economic waste and environmental burden [30]. The extraction of high-value chemical substances from fruit peels can not only effectively alleviate this problem, but can also achieve sustainable development and promote economic cycles [31]. D-limonene is widely present in essential oils extracted from the peels and leaves of natural plants and its content depends on the plant species and cultivar [32–35]; notably, D-limonene is present in large amounts (up to 98.54%) in citrus (Table 1). Natural plant extraction of D-limonene can be performed using organic solvent extraction, new bio-based solvent extraction, and natural deep eutectic solvent extraction [36–38]. These methods are safer than chemical pyrolysis, but the yield is affected by differences in the extraction methods, solvent dosages, and even the plant raw materials, which can be subject to seasonal, climatic, and geographical factors [36,39–44]. Therefore, the production of D-limonene via efficient bioconversion is an attractive strategy [29].

Table 1. Source and composition of D-limonene.

Plant (Essential Oil)	Parts	Composition (%)	Ref.
Citrus × sinensis	Fruit peels	98.54	[45]
Citrus × aurantium	Fruit peels	93.70	[46]
Citrus reticulata	Fruit peels	91.65	[45]
Citrus deliciosa	Fruit peels	91.27	[45]
Tetradium daniellii	Leaves, Fruits	72.71	[47]
Hyptis Jacq	Leaves, Fine stems	72.60	[48]
Cymbopogon citratus	-	71.00	[49]
Citrus unshiu	Fruit peels	70.22	[50]
Citrus maxima	Fruit peels	67.58	[51]
Citrus × limon	Dry leaves, Fruit peels	62.97	[52]
Citrus × latifolia	Fruit peels	54.71	[53]
Bursera graveolens	Fruits	43.60	[54]
Citrus medica	Leaves, Fruits	39.77	[47]
Psidium guajava	Leaves	38.01	[55]
Citrus bergamia	-	21.47	[56]
Zanthoxylum schinifolium	-	21.24	[57]
Litsea cubeba	Fruits	14.30	[58]
Zanthoxylum armatum	Leaves, Fruits	10.70	[47]

2.2. Biotransformation: A New Direction for Future Development

Biotransformation to high-value natural products is a direction to explore as an alternative to extraction from natural plants, usually using metabolic engineering and biosynthetic engineering to process microorganisms for sustainable production [59]. For example, using the methylerythritol 4-phosphate pathway or the mevalonate-dependent pathway [60], the introduction of a specific gene fragment into the test bacterium and induced expression for the synthesis of D-limonene resulted in D-limonene production up to 0.15 g/(L·h) under ideal conditions [61]. The yield of D-limonene obtained by metabolic engineering depends on the strain, the type of exogenous gene introduced, the incubation temperature, and other factors [29,62,63]. In addition to the methylerythritol 4-phosphate pathway and mevalonate-dependent pathways, the isopentenol utilization pathway and the isoprenoid alcohol pathway have also been used to produce D-limonene, with reported maximum yields of approximately 0.7 μg/(L·h) and 10.42 μg/(L·h), respectively [59,64–66]. Alternatively, the alcohol-dependent hemiterpene pathway has been suggested as a promising pathway for terpene production; however, its use for D-limonene production has not been reported to date [63]. Biotransformation as an alternative method to extract D-limonene from natural plants has the advantages of high concentration and yield and has great potential for expanding production. However, D-limonene has a certain degree of cytotoxicity, which greatly reduces the adaptability of engineered cells, and the specificity and inefficiency of the biosynthetic enzyme pathway in heterologous hosts hinder the large-scale production of D-limonene by microorganisms. In addition, because of public health, environmental protection, and other considerations, some regions, such as the European Union, have set the most stringent scrutiny standards for the application of genetically modified organisms, which has limited the promotion of genetically modified microorganisms, so plant essential oil extraction is still the main method to produce D-limonene [59,67,68].

3. Antimicrobial Activities of D-Limonene

3.1. Antibacterial and Antifungal Activity of D-Limonene

D-limonene is a monocyclic monoterpene with excellent antimicrobial properties and has received considerable attention from researchers. Numerous studies have reported the inhibitory activity and mechanisms of action of D-limonene against bacteria and fungi. The MICs and minimum bactericidal/fungicidal concentrations (MBCs/MFCs) of 11 bacteria and 14 fungi are listed in Table 2 (colony forming unit, CFU), indicating that D-limonene has a relatively broad antimicrobial spectrum, and it can be found that the antimicrobial activity of D-limonene is correlated with microbial species, number of viable microorganisms and strains, and D-limonene concentration. In addition, a study found that D-limonene reduced the D-value (Decimal reduction Times) of *L. monocytogenes* in carrot juice, but lipids and fibers led to significant changes in the D-value, suggesting that the food matrix interfered with the antimicrobial activity of D-limonene, but the mechanism is still unclear [69]. Other than the antimicrobial activity studies listed in Table 2, the inhibitory effect of D-limonene on multiple drug resistance (MDR) strains and its synergistic effect with antimicrobial drugs are also important.

Table 2. The antimicrobial activity of D-limonene.

Categories	Species	Strain	CFU/mL	MIC	MBC/MFC	Ref.
Bacteria	*Aeromonas hydrophila*	MF 372510	1×10^5	6.4 mg/mL	6.4 mg/mL	[21]
	Escherichia coli	ATTC 25922	1×10^6	16 μL/mL	32 μL/mL	[70]
			1×10^6	10 mg/mL	40 mg/mL	[71]
		ATCC 8739	1×10^8	1 μg/mL	-	[72]
			1×10^8	12.5 μL/mL	-	[23]
		CIP 54127	1×10^6	12.5 mg/mL	-	[73]
		O157:H7	-	50 μL/mL	-	[74]
	Staphylococcus aureus	CIP 4.83	1×10^6	12.5 mg/mL	-	[73]
		ATCC 6538	1×10^8	1 μg/mL	-	[72]
			1×10^8	7.81 μg/mL	-	[23]
		ATCC 43300	5×10^5	3 mg/mL	8 mg/mL	[75]
		ATCC 25923	5×10^5	3 mg/mL	3 mg/mL	[75]
			5×10^5	10 mg/mL	-	[76]

		ST30-t019	5×10^5	15 mg/mL	-	[76]
		ST5-t311	5×10^5	20 mg/mL	-	[76]
		-	5×10^5	7.9 mg/mL	12.9 mg/mL	[75]
	Mycobacterium tuberculosis	H37Ra	-	64 μg/mL	-	[77]
		ATCC 25177	1.5×10^8	32 μg/mL	-	[78]
	Enterococcus faecalis	-	1×10^6	12.5 mg/mL	-	[73]
	Listeria monocytogenes	ATCC 35152	1×10^6	12.5 mg/mL	-	[73]
		FSCC 178006	10^6–10^7	20 μL/mL		[79]
	Streptococcus uberis	-	1×10^6	3.3 mg/mL	210 mg/mL	[80]
	Streptococcus mutans	UA 159	1×10^8	21 mg/mL	-	[81]
	Lactobacillus acidophilus	-	1×10^6	40 mg/mL	80 mg/mL	[71]
	Salmonella	-	1×10^6	1.25 mg/mL	40 mg/mL	[71]
	Bacillus subtilis	ATCC 6633	1×10^8	7.81 μg/mL	-	[23]
			1×10^8	1 μg/mL	-	[72]
Fungi	*Saccharomyces cerevisiae*	ATCC 9763	1×10^8	0.5 μg/mL	-	[72]
	Fusarium sporotrichioides	ITEM 692	-	10 μL/mL	-	[82]
	Fusarium langsethiae	ITEM 11020	-	5 μL/mL	-	[82]
	Fusarium graminearum	ITEM 6477	-	5 μL/mL	-	[82]
	Candida albicans	ATCC 90028	-	0.31 mg/mL	0.62 mg/mL	[83]
			1×10^7	300 μg/mL	400 μg/mL	[84]
	Candida glabrata	ATCC 90030	-	0.31 mg/mL	1.25 mg/mL	[83]
	Candida parapsilosis	ATCC 27853	-	0.31 mg/mL	1.25 mg/mL	[83]
		URM 6404	-	256 μg/mL	-	[85]
		HAM 26	-	512 μg/mL	-	[85]
	Candida krusei	ATCC 6258	-	0.07 mg/mL	0.62 mg/mL	[83]
	Candida tropicalis	SH 1	1×10^7	20 μL/mL	40 μL/mL	[86]
	Bacillus cereus	ATCC 33018	1×10^7	2.5 mg/mL	>40 mg/mL	[87]
	Phytophthora capsici	LT 263	5×10^4	20 mg/L	-	[88]
	Trichophyton rubrum	KCTC 6345	1×10^5	5 μL/mL	-	[89]
	Trichophyton rubrum	MTCC 296	-	2 μL/mL	6 μL/mL	[90]
	Sclerotinia sclerotiorum	BRM 29673	-	200 μL/mL	-	[45]

3.2. Inhibition of MDR Strains by D-Limonene

Trials have revealed the potential of D-limonene to resist MDR bacterial and fungal contamination and exhibited synergistic effects with antimicrobials. For clinically isolated MDR *Mycobacterium tuberculosis* strains T1 1558, H1 47, and Beijing 1, D-limonene at concentrations of 128, 128, and 256 μg/mL, respectively, inhibited their growth; potentiated the inhibitory effects of antimicrobial drugs ethambutol, rifampicin, and isoniazid; and reduced the MICs by two-fold at subinhibitory concentrations and by eight-fold for the non-resistant strains [78]. In another study, D-limonene was found to have a synergistic effect with gentamicin, reducing the MIC values of resistant *S. aureus* and *E. coli* from 13.71 μg/mL and 30 μg/mL to 4 μg/mL and 20.1 μg/mL, respectively [91]; for MDR fungi, such as *Candida tropicalis*, *Candida parapsilosis*, *Candida metapsilosis*, *Candida krusei*, *Candida lusitaniae*, D-limonene in the concentration range of 16–64 μg/mL can inhibit their growth [92]; and D-limonene acts synergistically with fluconazole to resensitize fluconazole-resistant strains of *C. albicans* and inhibit their growth and biofilm formation [93]. This may be due to the increased permeability of the antimicrobial agent by D-limonene or to D-limonene's lipophilic properties, which allow D-limonene to cross the cell wall and alter the permeability of the cell membrane [75,94]; another view also suggests that this may be due to the different targets of natural antimicrobial compounds and clinical drugs [95].

In addition, researchers have suggested that the microbial efflux pump (EP) is associated with microbial drug resistance and allows the excretion of antimicrobial substances, thereby reducing their intracellular concentrations [96,97]; one study found that D-limonene could act as an inhibitor of the efflux pump (EP) and synergistically with ciprofloxacin to inhibit drug-resistant *S. aureus,* reducing the MIC from 32 μg/mL to 3.17 μg/mL, better than carbonyl cyanide m-chlorophenylhydrazone from 32 μg/mL to 10.07 μg/mL, and molecular docking showed that this could be due to competition or non-competitive inhibition caused by D-limonene [98]. Several experiments have shown that D-limonene and antimicrobials have different synergistic effects against gram-positive and gram-negative bacteria, which may be due to the difference in cell wall structure between the two bacteria [99].

Although D-limonene is considered to be a potential substance against MDR strains, unfortunately, D-limonene was found to have no synergistic effect with penicillin in experiments, whereas D-limonene had an antagonistic effect with norfloxacin and elevated MIC value against *E. coli* MDR strains in the experiments, which may be due to chelation resulting in reduced antimicrobial effect [91,94,100].

3.3. Antibiofilm Activity of D-Limonene

It has been widely reported that biofilms formed by fungi or bacteria are found on the surfaces of foods, medical equipment, soil, and other substrates, thus posing serious threats to public safety [101,102]. Biofilms are large numbers of microorganisms aggregated together, attached to the surface of organisms (e.g., meat tissue) or abiotic (e.g., processing equipment) [103] and enclosed in an extracellular matrix [104] (Figure 1). The biofilm matrix is generally composed of water and extracellular polymeric substances (EPSs), mainly composed of polysaccharides, proteins, nucleic acids, lipids, dead microbial cells [105,106]), flagella, and other adhesive fibers [103], thereby enhancing their resistance to drying, liquid flow, antimicrobial agents, disinfectants, and other methods [106]. Biofilm formation is an adaptation strategy of microorganisms to their environment and it also increases their virulence, resulting in greater pathogenicity [107]. Statistics have shown that more than 80% of recurrent microbial diseases and chronic infections are associated with biofilm formation [108]. Therefore, it is important to investigate biofilm inhibition and removal.

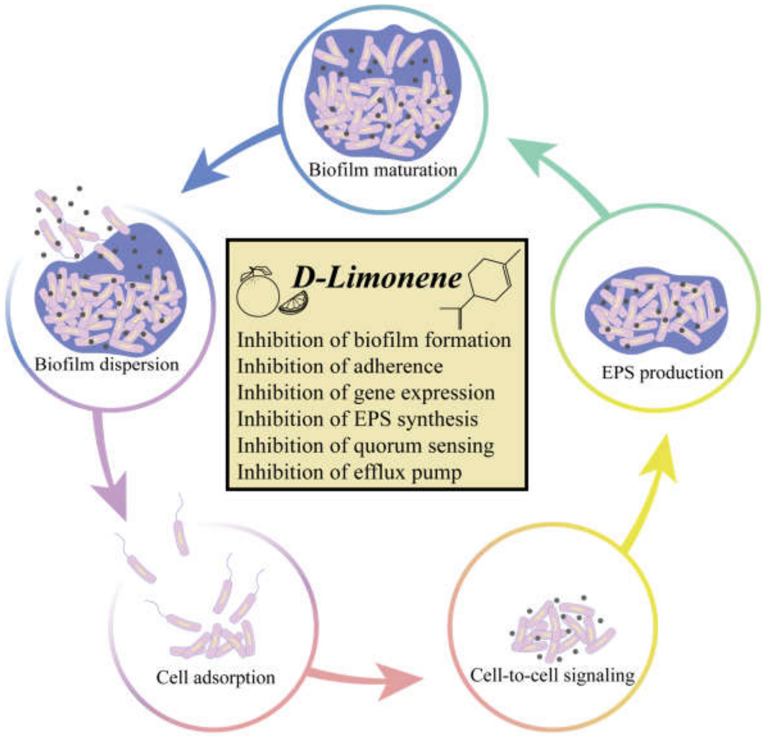

Figure 1. The formation of biofilm.

Table 3 lists some of the reports on the D-limonene inhibition of microbial biofilm formation, indicating that the inhibitory activity on biofilm is related to the microbial species, number of viable microorganisms and strains, and D-limonene concentration. The biofilm inhibition of *Streptococcus mutans* has been reported to be 94.88% and 46.62% at D-limonene concentrations of 10.5 mg/mL and 2.625 mg/mL [81]. However, for *Streptococcus uberis*, the inhibition rate was 88.25% at a concentration of 3.3 mg/mL, thus indicating that the biofilm inhibitory activity of D-limonene on different microorganisms is variable [80].

Table 3. The antibiofilm activity of D-limonene.

Species	Strain	CFU/mL	MBIC	Inhibition Rate	Ref.
Aeromonas hydrophila	MF 372510	1×10^5	51.2 mg/mL	-	[21]
Escherichia coli	O157:H7	-	25 µL/mL	92%	[74]
Streptococcus pyogenes	SF 370	2×10^3	400 µg/mL	83%	[109]
	St 38	2×10^3	400 µg/mL	95%	[109]
Streptococcus uberis	-	1×10^6	3.3 mg/mL	88.25%	[80]
Streptococcus mutans	UA 159	1×10^8	10.5 mg/mL	94.88%	[81]
Candida albicans	ATCC 90028	1×10^7	300 µg/mL	87%	[84]

4. Antimicrobial Mechanism of D-Limonene

4.1. Antibacterial and Antifungal Mechanism of D-Limonene

4.1.1. Damage to Cell Membranes and Cell Walls

The most intuitive and obvious effect of D-limonene on microorganisms is the disruption of cell membranes and cell walls (Figure 2). In several experiments, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) showed that the overall shape, cytoplasmic homogeneity, and cell wall thickness of bacterial and fungal cells were significantly changed after D-limonene treatment. In addition, it includes increased cell membrane permeability, altered membrane potential, and decreased heat resistance; leakage of intracellular substances, such as proteins, lipids, and nucleic acids, was also observed and even cell lysis at high concentrations, which may be due to the lipophilic and hydrophobic properties of D-limonene that promote lipid solubilization in the plasma membrane [70,77,79,86,110–114]. However, unlike bacteria, D-limonene affects ergosterol and β-1,3-glucan, which are unique to fungi. Ergosterol in fungal cell membranes is responsible for maintaining cell function and integrity and a decrease in its level can lead to cell death [115]; in one study, D-limonene without cosolvent had no effect on the ergosterol content in yeast cell membranes [116] but, in another study, D-limonene-Tween 80 cosolvent could reduce the ergosterol content in the *Saccharomyces cerevisiae* cell membrane, which may be due to the fact that Tween 80 improved D-limonene permeability [117]. Interestingly, 107 mg/L D-limonene ceased the growth of yeast but D-limonene-Tween 80 cosolvent did not cause a growth disturbance for reasons that are not clear [116]. In addition, preventing biofilm formation by inhibiting the quorum sensing (QS) system and EP system is also one of the properties of D-limonene in inhibiting microbial growth, which will be described in the biofilm section.

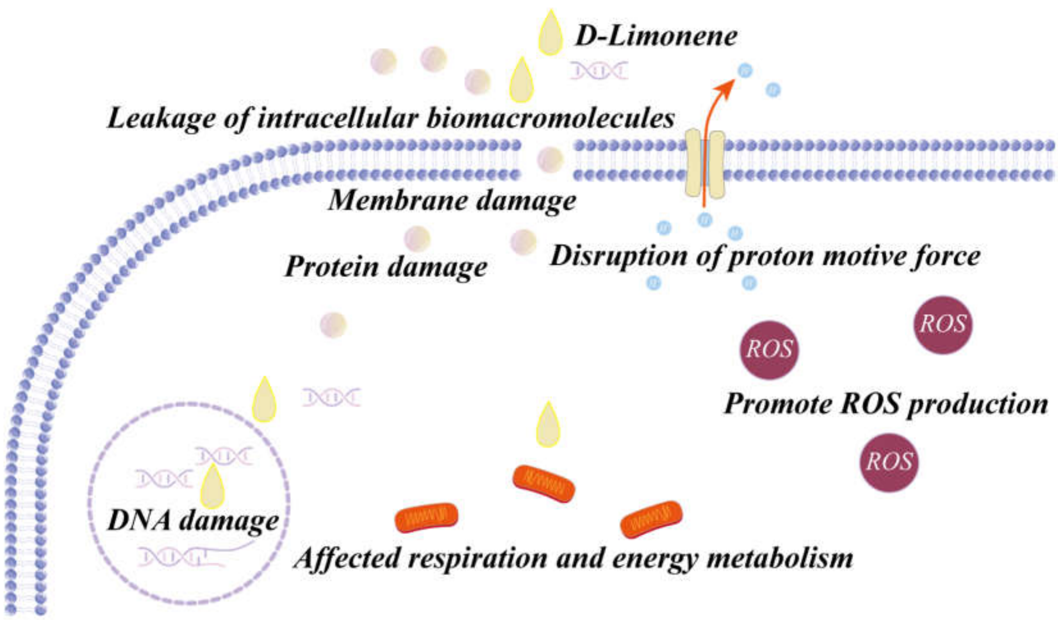

Figure 2. The antimicrobial mechanisms of D-limonene.

4.1.2. Effects on Lipids, Proteins, and Nucleic Acids

Studies at the subcellular level, including lipids, proteins, and nucleic acids, similarly revealed the antimicrobial activity of D-limonene. A study shows that D-limonene prevents lipid molecules from being tightly packed and alters the properties of the condensed phase, resulting in smaller and fewer structural domains, which causes membrane fluidization in a bacterial model [111] and, in another, the normal modification of nascent proteins by the endoplasmic reticulum of *C. albicans* was affected by 20 μL/mL of D-limonene treatment [118]. Notably, SDS-PAGE results showed a reduction in one plasmid band in D-limonene-treated *E. coli* compared to the control group, presumably due to a change in the *E. coli* DNA helix conformation, which may affect the stability and subsequent degradation susceptibility of *E. coli* [70].

4.1.3. Disturbance of Energy Metabolism

Moreover, modulations of energy metabolism pathways are also ways for D-limonene to inhibit microorganism growth. According to transcriptomics studies, D-limonene at a MIC of 20 μL/mL interfered with the transcription of key enzyme genes of the glycolysis pathway, tricarboxylic acid cycle, and oxidative phosphorylation pathway in *C. tropicalis* [118] and, in another study, the ATP concentration of *L. monocytogenes* decreased significantly after exposure to D-limonene, the activity of the respiratory chain I-V complex decreased, and the protein units were downregulated, which indicated that D-limonene could inhibit the synthesis of the respiratory chain complex proteins in *L. monocytogenes*, interfering with its respiratory function and energy metabolism, which led to the death of the cells [79]. D-limonene can also interfere with the synthesis of cellular ATP by inhibiting the respiratory complex and the ATPase in *C. albicans*, thereby affecting the respiratory intensity and energy metabolism [114].

4.1.4. Interference with Gene Expression

As the research got deeper, the mechanism of action of D-limonene at the gene level was revealed. After D-limonene treatment, the expression of *dpeE1*, a gene downstream of the cell wall synthesis, and *clgR*, a gene that protects cell membrane integrity in *M. tuberculosis*, thereby disrupted cell integrity, as well as *Streptococcus pyogenes* virulence-associated genes *covR* and *sepB* by 53% and 16%, respectively, and *covS* and *mga* being downregulated by 26% and 57%, respectively, with no significant difference in the expression levels of *srv* and *luxS*, indicating that D-limonene reduced the surface-mediated virulence factors of *S. pyogenes* [109,119]. And for fungi, it was shown that D-limonene induced disruption of the specific cell differentiation program of *C. parapsilosis*, leading to apoptosis, and also arrested the cell cycle of *C. albicans* in the G1 phase and the abundancies of 52 proteins were significantly changed (≥two-fold), 33 of which were upregulated and 19 downregulated. Furthermore, qPCR demonstrated that *C. albicans* cell wall and cell membrane damage stress genes (*KRE 9*, *ERG 11*), oxidative stress genes (*TRR 1*), nucleolus stress genes (*PRL 11*), and apoptosis-related genes (*CaMCA 1*) were overexpressed, indicating that D-limonene can induce apoptosis in *C. albicans* cells through multiple pathways [85,93].

4.2. Antibiofilm Mechanism of D-Limonene

4.2.1. The Effects of D-Limonene on EPS Secretion and Gene Regulation

Curli is recognized as a key factor in biofilm formation and D-limonene concentrations at 12.5 μL/mL and 25 μL/mL inhibited *E. coli* biofilm formation by 55% and 92%, respectively, EPS production was reduced by 35% and 60%, and no curli were observed after 25 μL/mL D-limonene treatment, which is probably due to inhibition of the transcription of *E. coli* curli production genes (*csgA, csgB, csgC,* and *csgD*) [74]. The MIC of D-limonene against *C. albicans* was reported to be 300 μg/mL, at which concentration the secretion of proteinases and phospholipases, adhesion ability, and biofilm formation were significantly reduced by 73%, 53%, 91%, and 87%, respectively, and, furthermore, a good docking score was obtained in the molecular docking analysis with virulence-associated proteins (Plb1 and Tec1), indicating that D-limonene may inhibit the adhesion ability, biofilm-forming ability, and morphological transition of *Candida* by associating with key *Candida* pathogenicity proteins [84].

4.2.2. The Inhibition of D-Limonene on Quorum Sensing and Efflux Pump Systems

The quorum sensing and efflux pump systems are important for biofilm formation and virulence expression [120,121]. The QS system is a process of microbial communication through small, diffuse chemical signaling molecules (i.e., QS molecules), which can be involved in the coordination of certain behaviors, such as biofilm formation, virulence, and antibiotic resistance [122,123], and the EP system is responsible for secreting toxins, proteins, and polysaccharides formed by the cell, as well as the efflux of toxic compounds found in the microbial context, such as antibiotics [124]; D-limonene has an inhibitory effect on both systems (Figure 3).

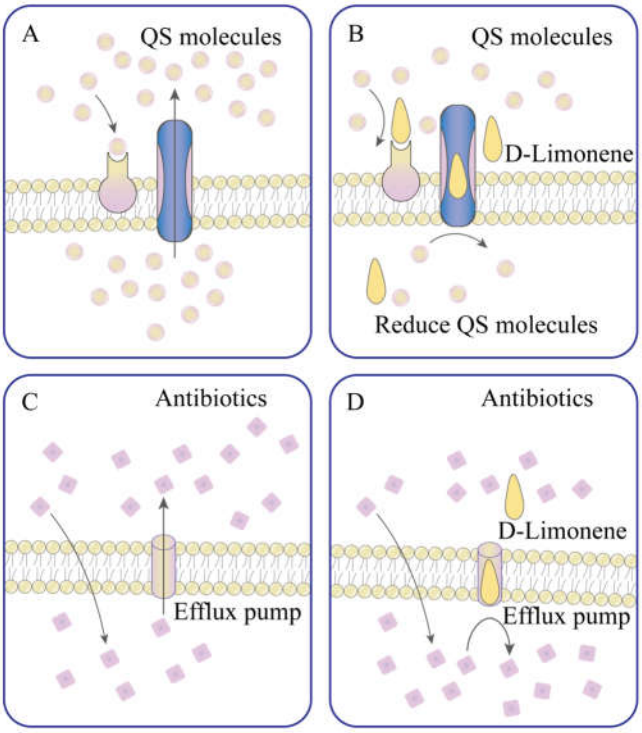

Figure 3. (**A**) Active quorum sensing; (**B**) Inhibited quorum sensing (Inhibited QS molecule synthesis, transport, and competition for receptors); (**C**) Active efflux pump; (**D**) Inhibited efflux pump (Inhibited substance transport in the EP system).

Autoinducer-2 (AI-2) is a QS signaling molecule commonly shared by gram-positive and gram-negative bacteria that is synthesized by the enzyme LuxS [125] and D-limonene may inhibit *E. coli* QS by interfering with AI-2 communication; the expression of AI-2-related genes (*lsrA*, *lsrB*, *lsrC,* and *lsrF*) was decreased [74]. Similarly, Luciardi et al. [126] also reported the inhibitory effect of D-limonene in the production of an autoinducer (AI) in *P. aeruginosa*, whereby D-limonene at 0.8–4 mg/mL reduced the AI production by 17%–30%. *Pseudomonas psychrophila* is one of the main causes of the spoilage of frozen foods [127] and another study treated *P. aeruginosa* with 135, 65, and 35 μL/mL of D-limonene and showed that bacterial biofilm formation was inhibited and that proteolytic activity and exopolysaccharide synthesis were reduced by 35%, 29%, and 28%, and 58%, 32%, and 41%, respectively. Additionally, the synthesis of QS autoinducers (AHL and alkyl quinolone molecules) was also reduced below detectable levels, indicating that D-limonene effectively inhibited the normal process of QS, and it was found that D-limonene binds to QS receptor proteins (LasR, RhlR, TraR, and PqsR), which may result in inhibition of the normal functioning of the QS system through competitive or non-competitive binding [128]. Inhibition of the EP system significantly inhibited microbial biofilm formation, indicating that the EP system is important for microbial biofilm formation [129]. In the study, it was found that D-limonene suppresses the expression of the EP system-related genes *MrsA* and *TetK* of *S. aureus* [130], D-limonene also binds to EP proteins (MuxB, MexB, and Mfs) on the *P. psychrophila* cell membrane, and it inhibits the expression of the EP system transcriptional regulatory genes *MarR* and *TetR* [128].

5. Anthelmintic Activity and Insecticidal Activity of D-Limonene

Pesticides have caused extremely serious harm to the environment due to the unregulated use of pesticides in agricultural production over a long period of time and, with deeper research, it has also been found that pesticides not only contaminate the local soil but also spread to the world with the atmospheric cycle and enter the human body along with the food chain, which threatens public safety in many ways. In order to cope with this serious problem, researchers are searching for safe degradation of pesticides and safe and reliable alternatives to pesticides [131–133]. In addition to its antibacterial and antifungal properties, D-limonene has anthelmintic and insecticidal activities [134,135] and D-limonene has been the most used botanical insecticide in California in the past decade (averaging >20,000 kg per year) [136]. Research has shown that D-limonene is cytotoxic to some harmful insects and can have a repellent and toxic effect [137,138].

5.1. Anthelmintic and Insecticidal Activity

It is reported that low concentrations of D-limonene can kill *Aonidiella aurantii* [139], the LC_{50} for adult *Sitophilus oryzae* was 36.85 μL/L [140], and the percentage of death in *Rhipicephalus sanguineus* treated with D-limonene at 0.1 μL/L was 82.6% [141]. The use of oil-in-water nanoemulsions made of D-limonene (8.9% *w*/*w*), water (30.2% *w*/*w*), Tween 20 (36.9% *w*/*w*), propylene glycol (15.1% *w*/*w*), and ethanol (8.9% *w*/*w*) were highly toxic to larvae of *Culex pipiens molestus* and *Aedes albopictus* and the toxicity effect was stronger than that of the unencapsulated D-limonene solution; this is probably due to the increased surface to volume ratio of nanoencapsulated D-limonene, which is beneficial to penetration, making it easier to pass through the insect's exoskeleton and protect the active substances within it from inactivation and degradation. After treatment, the larvae have a fragile appearance, with a wrinkled body surface and changes to the head, thorax, siphon, and abdominal cuticle, indicating potential for application in integrated pest control [142], and for *Aedes aegypti* and *Aedes albopictus* eggs, D-limonene causes morphological damage to the outer villous cuticle and blocks stomata, leading to respiratory distress [143]. Of note, D-limonene exhibited low toxicity to the natural enemies of this mosquito, *Poecilia latipinna* and *Poecilia reticulata*, suggesting that it has potential for biological control.

Showler et al. [144] showed that D-limonene directly affected the development of the adults, larvae, and pupae of *Haematobia irritans irritans* and that D-limonene at a concentration of 5.8% rendered *H. irritans irritans* immobile and significantly interfered with the fecundity and egg hatchability of the insect, but the mechanism was not clear. Interestingly, D-limonene was present in salivary gland extracts of *Ceratitis capitata* [145] and D-limonene had an attractive effect on *H. irritans irritans* at concentrations below 0.1%, indicating that D-limonene has potential application in trapping these insects [144]. In addition, D-limonene not only inhibited the fecundity activity of *Bactrocera dorsalis* but also showed a significant toxic effect on adults and pupae and exhibited a dose-dependent killing effect on larvae [146]. However, Papanastasiou et al. [147] found that D-limonene exhibited acute toxicity to the insect at high concentrations but promoted its survival and reproduction at low concentrations, probably due to the hormetic-like effect of D-limonene.

5.2. Antiparastic Activity

D-limonene has also been used to treat parasitic infections [135]. Researchers have discovered that D-limonene exhibits cytotoxicity against parasites, such as *Leishmania*, causing increased plasma membrane fluidity and cell lysis, thus killing the parasite and acting as a treatment for leishmaniasis caused by the parasite [148,149]. In addition, D-limonene reduces the isoprenylation of Ras- and Rap-related proteins, thereby causing developmental arrest in *Plasmodium falciparum* [150], possibly due to the inhibition of dolichol and ubiquinone synthesis by D-limonene [151]. In a study, D-limonene was found to have an LC_{50} of 245 μL/mL against *Haemonchus contortus* and exhibited extremely strong repellent activity (97.5%), probably because D-limonene has acetylcholinesterase inhibitory activity [152], and Moreno et al. [153] found that D-limonene was cytotoxic to *Trypanosoma cruzi*, causing altered cell morphology, impaired membrane potential, reduced cytoplasmic volume, absence of flagella, phosphatidylserine externalization, nuclear chromosome condensation, and DNA fragmentation, and it induced apoptosis by inhibiting the PIP3/Akt pathway, oxidative stress stimulation, and caspase activation.

6. Pharmacological Activity of D-Limonene: A Potential Natural Medicine

6.1. Antioxidant Activity

D-limonene is a potential antioxidant natural active substance that has been applied to counteract endoplasmic reticulum stress and reactive oxygen species release caused by methylglyoxal, etc. [154,155]. The ferric-reducing antioxidant power test showed that *C. sinensis* essential oil, which is rich in D-limonene (88.9%), has excellent antioxidant activity [156]. By in vitro assay, D-limonene at 16–64 mg/mL had significant ABTS radical scavenging ability, but the DPPH scavenging activity was weak [71]. In addition, in the same vitro assay, D-limonene inhibited low reactive oxygen species (ROS) production and accumulation induced by $A\beta_{1-42}$ oligomers [157], as well as inhibiting the activity of NADPH oxidase subunits and increasing the levels of antioxidant enzymes superoxide dismutase and heme oxygenase-1 [158]. *In vivo* tests of rats by AlSaffar et al. [159] showed that D-limonene prevented lipid oxidation and reduced catalase, superoxide dismutase, and glutathione peroxidase activities induced by carbon tetrachloride.

6.2. Anti-Inflammatory Activity

A number of studies have reported that D-limonene exerts anti-inflammatory and analgesic effects [160,161] because it blocks the release of inflammatory mediators, inhibits vascular permeability, and reduces neutrophil migration [20]. Huang et al. [162] found that D-limonene significantly inhibited formalin-injection-induced paw swelling and oxidative-stress-induced pain in mice and it inhibited RAW265.7 cell migration, suggesting that D-limonene has potential anti-inflammatory activity. In animal trials, D-limonene was shown to exert anti-inflammatory effects by reducing the production of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and myeloperoxidase, thereby increasing the concentration of antioxidant substances, such as glutathione peroxidase and superoxide dismutase, and maintaining the integrity of the inflammation site [17,163]. In addition, D-limonene can inhibit inflammation induced by exogenous substances [158], such as inhibition of the increased activity of inflammatory markers triggered by carbon tetrachloride, including high-sensitivity corticotropin-releasing factor, IL-6, and TNF-α [159].

Moreover, D-limonene is cardioprotective and gastroprotective [20,164], in addition to inhibiting the activity of cardiotoxicity biomarkers, such as alanine aminotransferase, lactate dehydrogenase, creatine kinase, creatine kinase MB, and the MAPK/NF-κB pathway; to reduce the damage of myocardial infarction, it also prevents cardiac histopathological changes [159,165]. Furthermore, oral D-limonene can increase local gastric mucosal defense mechanisms, such as mucus secretion, regulation of oxidative stress and inflammatory responses, and inhibition of the NF-κB pathway, to exert gastroprotective effects [17]. Aside from inhibiting oxazolone-induced colitis and histopathological changes, it also reduces pain caused by oxidative stress and prevents gastric ulcers caused by ethanol [166].

It has been demonstrated that D-limonene plays an active role in inhibiting the spread of cancer cells, acting on molecules such as Bcl-2, Bax, and caspases involved in various pathways, such as apoptosis pathways, PI3K/Akt signaling, autophagy, and vascular endothelial growth factor activity against cancer [167]. In addition, D-limonene has the ability to inhibit cancer cell growth; its combination with docetaxel induced more ROS production, thereby significantly enhancing the ability of docetaxel to induce apoptosis in cancer cells [168]; and D-limonene can induce apoptosis in cancer cells by inducing the mitochondrial death pathway and by inhibiting the PI3K/Akt pathway [169]. Other researchers have experimentally demonstrated that D-limonene has antifibrosis activity [170], prevents ischemia-induced brain injury, and alleviates acute kidney injury owing to its antioxidant and anti-inflammatory activities [171,172].

6.3. Neuroprotective Activity

Neuroprotective effects are other non-negligible biological activities of D-limonene, which can be used against neurodegenerative diseases [20]. D-limonene has been reported to inhibit acetylcholinesterase activity and protect neurons from cellular damage by blocking the decrease in mitochondrial dehydrogenase activity, ROS production, and KV3.4 channel hyperfunction triggered by $A\beta_{1-42}$ oligomers, thereby delaying the development of Alzheimer's disease [157]. Tang et al. [158] showed that corticosterone triggers oxidative stress and inflammatory responses, ultimately leading to apoptosis and neural cell damage, but D-limonene was able to reduce the damage caused by corticosterone by activating the AMPKα signaling pathway. In addition, D-limonene reduced hyperalgesia and astrocytosis and improved the neuronal regeneration and recovery of sensorimotor function in peripheral nerve injury mice by reducing the inflammatory response and upregulating neurotrophic processes [173]. In another study, D-limonene acts as an antidepressant by inhibiting neuroinflammation and nitrite levels in the hippocampus and relieves anxiety through A2A receptor-mediated DAergic and GABAergic neuronal activity, both of which have been demonstrated in animal studies [174,175].

Although D-limonene has a variety of biological activities, some researchers have pointed out that while D-limonene has been shown to have low toxicity in humans [168], it still exhibits various adverse side effects at high concentrations, most commonly skin sensitization [176]. Therefore, its medical application needs to be further evaluated for safety.

6.4. Antiviral Activity

The antiviral efficacy of plant essential oils and their constituents has attracted the interest of researchers due to their safety and reliability. Dozens of herbs and hundreds of natural compounds have been reported to exhibit antiviral effects by modifying the immune system and inhibiting viral replication [177,178].

D-limonene has been considered to have antiviral properties. Nagy et al. [179] speculated that the antiviral activity of D-limonene may be attributed to the presence of cyclohexenyl. According to the paper, D-limonene has an inhibitory effect on the replication of herpes simplex virus type I; treatment with the maximum non-cytotoxic concentration of D-limonene before infection reduced the infection rate by 100%, but the treatment only slightly reduced plaque formation after the virus penetrated the cells, suggesting that D-limonene primarily targets the free herpes simplex virus type I. This result indicates the potential medicinal value of D-limonene in treating recurrent herpes labialis [180].

In addition, the influenza A virus H1N1 inhibition assay demonstrated that D-limonene achieved a virucidal activity log reduction that was 4.32 and 3.94 after 250 and 125 μg/mL (0.025% and 0.0125%), respectively, effectively killing 99.99% of the virus. This efficacy is comparable to that of household disinfectant sodium hypochlorite used at 0.21% [46]. Minari et al. [181] utilized molecular docking analysis to show that the inhibitory effect of D-limonene on Lassa virus L polymerase, an enzyme essential for viral transcription and replication, was comparable to ribavirin, which is currently the most effective drug for treating Lassa virus fever.

COVID-19, caused by SARS-CoV-2, remains a significant public health concern. ACE_2 is the human host factor or cell entry receptor for SARS-CoV-2 [182]. Molecular docking revealed that D-limonene has structural similarity to thymine in the SARS-CoV-2 viral genome and can potentially inhibit the receptor binding domain of the SARS-CoV-2 spike protein from fusing with the ACE2 protein. This could reduce SARS-CoV-2 host cell binding, cellular internalization, and pathogen release [53,183]. Moreover, cytokine storm is a major cause of death in COVID-19 patients. D-limonene, by mediating multiple inflammatory pathways and mediators, might inhibit cytokine storm [27] and regulate the expression of various signaling pathways, such as PI3K/Akt/IKK-α/NF-κB P65, making it a potential candidate for preventing or treating COVID-19-related pulmonary fibrosis [184].

Current research shows the potential of D-limonene in the development of novel antiviral drugs. However, as different viruses cause varied infection symptoms, further in-depth studies are necessary to understand the mechanisms and efficacy of D-limonene against different viral infections.

7. Application: Nanotechnology and D-Limonene

Although D-limonene has great potential in the fight against bacteria and fungi, its large-scale application is limited because of its highly hydrophobic and oxidative degradation properties [185]; volatilization under light, air, moisture, and high temperature; and sensitivity to oxidation and chemical transformation [186]. To develop D-limonene products with high stability, controlled release, and long-term effectiveness, D-limonene is currently loaded using polymer encapsulation technology and the possibility of its practical application is being investigated (Figure 4) [22].

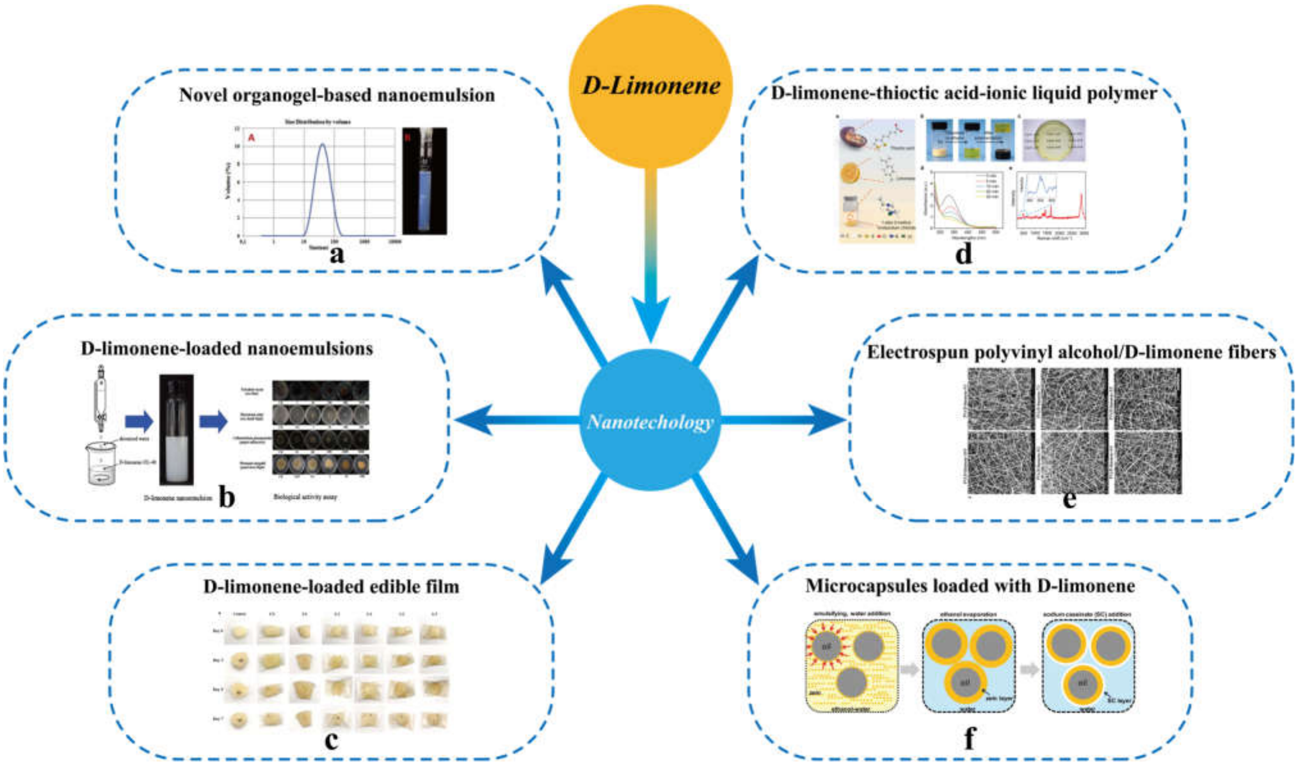

Figure 4. The application of D-limonene: (**a**) D-limonene using a novel organogel-based nanoemulsion (Reprinted from Zahi et al. [187]). (**b**) D-limonene-loaded nanoemulsions (Reprinted from Feng et al. [188]). (**c**) D-limonene-loaded edible film (Reprinted from Luo et al. [189]). (**d**) D-limonene-thioctic acid-ionic liquid polymer (Reprinted from Sun et al. [190]). (**e**) Electrospun polyvinyl alcohol/D-limonene fibers (Reprinted from Lan et al. [191]). (**f**) Microcapsules loaded with D-limonene (Reprinted from Chen et al. [192]).

7.1. Nanotechnology: Improving Properties and Enhancing Bioactivity

Different encapsulation techniques, such as spray drying, thin-layer drying, freeze-drying, emulsification, coalescence, and ionic polymerization, have been used to improve the physicochemical properties and bioactivity of D-limonene to form polymeric materials, such as nanoemulsions, nanoparticles, nanogels, and microcapsules, whereas gum arabic, chitosan, alginate, and maltodextrins are common loading materials [25,186,193–198].

Castel et al. [186] used brea gum as an encapsulating wall material to produce D-limonene microcapsules and they found that brea gum allowed good encapsulation and protection of D-limonene. Microcapsules made from 20% *w*/*w* brea gum solution had the best stability and there was no significant difference in the average particle size after 7 days of storage at room temperature. In addition, using high-viscosity sodium alginate and gelatin (type A) as wall materials and fabricated composite coalescent microcapsules, we encapsulated D-limonene by a spray drying and in situ composite coalescence method, which had 75% ± 6% of the degree of reconsolidation and retained up to 82.7% of the D-limonene during drying and 80% of the D-limonene when stored at room temperature for more than 72 days [194]. In a study, D-limonene, lipoic acid, and 1-ethyl-3-methylimidazole sulfate were used to prepare a D-limonene-lipoic acid-ionic liquid polymer that exhibited long-term stability and moderate strain, high bond strength to various substrates, good self-healing ability due to the presence of disulfide and hydrogen bonds, and excellent antibacterial ability [190] and the electrostatic spinning technology can be used to prepare a new antibacterial active packaging fiber of polyvinyl alcohol/D-limonene with excellent tensile strength and elongation at break, which exhibited optimal degradability, antibacterial properties, and the lowest oxygen permeability at a polyvinyl alcohol:D-limonene ratio of 7:3 [191]. In another study, zein-based microcapsules loaded with D-limonene were prepared using an antisolvent method, which resulted in good stability and lower initial release compared to whey protein isolate (WPI)-stabilized emulsions, and it exhibited better retention as the duration phase tended to be progressive [192].

This shows that nanotechnology can not only improve the physicochemical properties of D-limonene and make it applicable to more fields but can also enhance its biological activity, which is valuable for in-depth research.

7.2. Applications

7.2.1. Food

As a natural compound with excellent antimicrobial activity, D-limonene has the potential to be used in food preservation but, if it is added directly, it will affect the quality of the food itself; nanoencapsulation is one of the feasible ways to overcome this problem. Nanoencapsulation not only improves the physicochemical properties of the active substance and prevents them from interacting with the food matrix but also increases the passive cellular absorption mechanism, reducing mass transfer resistance and improving antimicrobial activity, possibly due to its subcellular size. [199].

Nanoencapsulated D-limonene can improve the shelf life of food. For example, the nanoemulsion coating prepared using deionized water, propylene glycol, D-limonene, and sodium alginate had good particle size uniformity (3–5 nm) and resulted in better inhibition of *L. monocytogenes*, *S. enterica,* and *E. coli* than unencapsulated D-limonene, with 50%, 90%, and 87.5% reductions in the MBCs, respectively, and it reduced the rate of water and weight loss during storage of bananas, inhibited pectinase activity, and extended shelf life [200] and Umagiliyage et al. [201] found the materials made from D-limonene encapsulated in liposomes exhibited good inhibitory activity against both bacteria and fungi and it significantly extended the shelf life of blueberries.

In addition, the biobased composites made of D-limonene and β-cyclodextrin have excellent heat resistance, which could prevent the loss of D-limonene during high-temperature processing and have potential applications in the preparation of reactive food packaging films [202]. Edible biopolymer (pullulan/carrageenan) functional composite films prepared by Roy et al. [203], with the addition of copper sulfide nanoparticles and D-limonene, exhibited enhanced tensile strength and UV-blocking function, as well as a degree of antibacterial activity. The new fragrant starch-based films prepared with D-limonene exhibited significantly lower hygroscopicity and water solubility, as well as significantly higher tensile strength and, because of the addition of D-limonene, they exhibited effective antimicrobial activity and a pleasant aromatic odor, thus favoring their use for the preservation of some foods with special odors [204]; Lan et al. [205] prepared a composite film made of polyvinyl alcohol/chitosan combined with D-limonene that had good biodegradability and light transmission and the addition of D-limonene (5% *w*/*w*) enhanced the barrier capacity and mechanical properties of polyvinyl alcohol/chitosan films and improved their antibacterial activity against *E. coli* and *S. aureus*, which prolonged the shelf life of mangoes at room temperature. In addition, fish-gelatin–chitosan-edible films supplemented with D-limonene exhibited better antimicrobial activity and D-limonene addition effectively improved their ductility, as well as their water vapor and light barrier properties [206].

Although the above-mentioned D-limonene-loaded nanocarriers overcome the defects in the physicochemical properties of D-limonene, there is still a lack of research on the possible modes and mechanisms of their antimicrobial action.

7.2.2. Agriculture

Along with the increasing concern for environmental protection, the search for a non-hazardous natural compound to replace chemical pesticides has attracted the interest of researchers. As a potential alternative to chemical pesticides, a large number of studies have demonstrated D-limonene's ability to combat a wide range of pathogenic bacteria and pests, but its use has been challenged by properties such as high volatility, low solubility, and thermal instability. It has been found that nanoencapsulation can overcome these issues, providing better stability, protection, release control, and bioavailability [207].

Feng et al. [188] reported greater antifungal activity of D-limonene nanoemulsions against *Pyricularia oryzae*, *Rhizoctonia solani*, *Colletortrichum gloeosporiodes*, and *Phomopsis amygdali* compared to free D-limonene at the concentration of EC_{50}s, with an increase in inhibition from 22.2%, 30.4%, 24.4%, and 32.5% to 48.7%, 50.9%, 47.4%, and 51.7%, respectively, which could be attributed to the increased permeability and water solubility of the nanoemulsions.

Anopheles stephensi and *Culex quinquefasciatus* are vectors of several diseases. Alireza et al. [208] found that, compared to D-limonene, nanoliposomes of D-limonene had a stronger larvicidal effect on these two mosquitoes, with the LC_{50}s decreasing from 20.12 and 16.36 μg/mL to 13.6 and 6.41 μg/mL, respectively, and the LC_{90}s decreasing from 80.05 and 31.29 μg/mL to 25.08 and 12.71 μg/mL, respectively, and the D-limonene nanoemulsions prepared by Ioanna et al. [142] showed larvicidal properties against the third- to fourth-instar larvae of *Aedes albopictus* and *Culex pipiens molestus*, with LC_{50}s and LC_{90}s showing the same decreasing trend compared to D-limonene; this may be due to the fact that nanoencapsulation enhances the physical stabilization, permeation, and propagation of D-limonene.

Columbicola columbae is the main cause of ectoparasitic infections in pigeons, which can lead to symptoms such as anemia, dermatitis, decreased egg production, and slow weight gain, and the general method of counteracting this is the use of deltamethrin but this not only leads to environmental contamination but also negatively affects the pigeons and their products. Therefore, Gadelhaq et al. [24] proposed the use of D-limonene instead of deltamethrin and showed that 30 mg/mL of D-limonene and its nanoemulsion exhibited equivalent lousicidal activity to 0.025 mg/mL of deltamethrin without affecting pigeons, both through the neuromuscular inhibition of AchE and contact distortion of the body wall, with the difference that D-limonene and its nanoemulsion did not affect the pigeons and, remarkably, the D-limonene nanoemulsion remained stable after 50 days of storage and exhibited significant insecticidal activity.

Although studies have shown that nanoencapsulated D-limonene has enhanced physical stability and bioactivity, there is a need for more extensive research and evaluation as nanoencapsulated D-limonene has been studied to control fewer pest species and has not been validated in practical applications.

7.2.3. Medicine

A large number of experimental results have shown that D-limonene has excellent clinical pharmacological activity and antimicrobial activity against many clinically pathogenic microorganisms, but its use and efficacy are hampered by reasons such as its solubility and stability so the use of nanoencapsulation technology to improve its properties for clinical application is the direction of the investigation.

Doxycycline is an important antineoplastic anthracycline chemotherapeutic drug, but it has cumulative cardiotoxicity. In a study, nanodelivery systems (nanoemulsion, niosomes, and polylactic nanoparticles) of doxycycline and D-limonene were prepared with a maximum loading rate of up to 75.8%, which had desirable stability and antioxidant properties, and exhibited enhanced anticancer activity against liver cancer cells as well as lower cytotoxicity against normal liver cells [209].

In the study, D-limonene was found to have anticancer activity against both melanoma cell line A-375 and breast cancer cell line MDA-MB-468 with IC_{50}s of 246.05 and 2118.94 μg/mL, respectively, which was significantly improved by chitosan nanoencapsulation, with IC_{50}s reduced to 30.24 and 650.7 μg/mL, respectively, which may be attributed to the nanoencapsulation improving the hydrophobicity of D-limonene or possibly of the use of its lipophilicity to improve permeability [210,211].

Researchers believe that D-limonene can act as a permeation enhancer, fluidizing or disrupting the integrity of the stratum corneum of the skin for the purpose of transdermal drug delivery, decreasing systemic adverse effects or increasing bioavailability [212]. The study showed that benzocaine-loaded poly(D,L-lactide-co-glycolide) nanoparticles with added D-limonene significantly enhanced permeation rate and prolonged anesthetic efficacy and reduced cytotoxicity [211], whereas another study showed that D-limonene-containing nanovesicles showed higher encapsulation efficiency and transdermal delivery of asenapine maleate compared to cineole and hydromiscible cosolvent (transcutol®). In addition, this was probably due to the effect of structural activity, which allowed better transdermal delivery of lipophilic molecules of hydrocarbon terpenes (D-limonene) than ketone terpenes (cineole), and a significant increase in the bioavailability of transdermal administration compared to oral administration of 3% to 54.5% [213].

Through nanoencapsulation, the physicochemical properties of D-limonene can be effectively improved and the available range can be expanded, but the current research mainly stays focused on in vitro cellular experiments or animal experiments and putting into application in the clinic needs more review studies.

8. Necessity of a Security Assessment

Exposure to D-limonene is very common because it is a volatile flavor component widely present in various fruits or plants. Food is considered the main source, accounting for 96% of exposure, followed by ambient air at 4% [214].

Previous reports have identified D-limonene peroxide as a serious skin contact allergen. The widespread use of D-limonene in food, detergents, and cosmetics significantly increases the risk of skin exposure for consumers, leading to reported cases of skin allergies in multiple regions [215]. According to one study, dermal exposure to high concentrations of D-limonene resulted in irritation or a purpuric rash, which was related to the degree of oxidation of D-limonene [216]. To mitigate this risk, some researchers suggest producing and transporting D-limonene at low temperatures or adding antioxidants ensuring the peroxide content remains less than 20 mmol/L [215,216].

In addition, clinical trials have shown that non-peroxidized D-limonene did not exhibit genotoxicity, neurotoxicity, and reproductive toxicity in humans but did exhibit skin irritation [217]. In animal experiments, D-limonene showed carcinogenicity, respiratory sensitization, and nephrotoxicity in rats [214]. However, this finding is not applicable to humans due to the absence of the related protein α_{2u}-globulin in humans [217].

It is worth noting that there have been some reports of sensitization or other adverse reactions to products containing D-limonene, such as perfumes, cosmetics, and household products, but none of these reports have conclusively identified D-limonene as the direct cause [218–220].

Currently, the daily intake of D-limonene is set at "not specified", but Ravichandran et al. point out that the metabolic pathway, safe levels, and risk assessment of D-limonene are necessary; as the consumption of citrus juices increases, the risk of consumers' exposure rises, potentially leading to toxicity under prolonged exposure [214].

9. Conclusions and Outlook

In this review, we present the preparation of D-limonene and its antimicrobial, anthelmintic, and medicinal potentials at cellular and molecular levels. However, the properties of volatility, high hydrophobicity, and oxidative degradation have limited its expansion in many application scenarios. With the development of nanoencapsulation technology, making D-limonene into novel materials, such as nanoemulsions and microcapsules, not only improves the undesired physicochemical properties but also effectively enhances its biological activity.

Although D-limonene as a natural active substance has promising applications in many fields, the current research on it is mainly in the laboratory environment and the feasibility of extending its application in real-life production still needs to be verified in practice. Moreover, D-limonene peroxide is a well-known skin-contact allergen that has been shown to cause allergic reactions at high concentrations in clinical trials. It has also demonstrated carcinogenic and other effects in animal studies; although some of the results may not apply to humans, a more detailed re-examination of the safety of D-limonene is necessary.

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References

1. Fang, S.; Yu, W.S.; Li, C.L.; Liu, Y.D.; Qiu, J.; Kong, F.Y. Adsorption behavior of three triazole fungicides on polystyrene microplastics. *Sci. Total Environ.* **2019**, *691*, 1119–1126. https://doi.org/10.1016/j.scitotenv.2019.07.176.
2. Feng, C.; Ouyang, X.; Deng, Y.; Wang, J.; Tang, L. A novel g-C_3N_4/g-C_3N_{4-x} homojunction with efficient interfacial charge transfer for photocatalytic degradation of atrazine and tetracycline. *J. Hazard. Mater.* **2023**, *441*, 129845. https://doi.org/10.1016/j.jhazmat.2022.129845.
3. Sharma, A.; Pant, K.; Brar, D.S.; Thakur, A.; Nanda, V. A review on Api-products: Current scenario of potential contaminants and their food safety concerns. *Food Control* **2023**, *145*, 109499. https://doi.org/10.1016/j.foodcont.2022.109499.
4. Sun, C.; Cheng, X.; Yuan, C.; Xia, X.; Zhou, Y.; Zhu, X. Carboxymethyl cellulose/Tween 80/Litsea cubeba essential oil nanoemulsion inhibits the growth of Penicillium digitatum and extends the shelf-life of 'Shatangju' mandarin. *Food Control* **2024**, *160*, 110323. https://doi.org/10.1016/j.foodcont.2024.110323.

5. Wang, H.; Yang, Z.; Ying, G.; Yang, M.; Nian, Y.; Wei, F.; Kong, W. Antifungal evaluation of plant essential oils and their major components against toxigenic fungi. *Ind. Crops Prod.* **2018**, *120*, 180–186. https://doi.org/10.1016/j.indcrop.2018.04.053.
6. Kakouri, E.; Daferera, D.; Kanakis, C.; Revelou, P.-K.; Kaparakou, E.H.; Dervisoglou, S.; Perdikis, D.; Tarantilis, P.A. Origanum majorana Essential Oil—A Review of Its Chemical Profile and Pesticide Activity. *Life* **2022**, *12*, 1982. https://doi.org/10.3390/life12121982.
7. Soleimani, M.; Arzani, A.; Arzani, V.; Roberts, T.H. Phenolic compounds and antimicrobial properties of mint and thyme. *J. Herb. Med.* **2022**, *36*, 100604. https://doi.org/10.1016/j.hermed.2022.100604.
8. Kowalczyk, T.; Merecz-Sadowska, A.; Ghorbanpour, M.; Szemraj, J.; Piekarski, J.; Bijak, M.; Śliwiński, T.; Zajdel, R.; Sitarek, P. Enhanced Natural Strength: Lamiaceae Essential Oils and Nanotechnology in In Vitro and In Vivo Medical Research. *Int. J. Mol. Sci.* **2023**, *24*, 5279. https://doi.org/10.3390/ijms242015279.
9. Visakh, N.U.; Pathrose, B.; Chellappan, M.; Ranjith, M.T.; Sindhu, P.V.; Mathew, D. Chemical characterisation, insecticidal and antioxidant activities of essential oils from four Citrus spp. fruit peel waste. *Food Biosci.* **2022**, *50*, 102163. https://doi.org/10.1016/j.fbio.2022.102163.
10. Ardakani, A.S.; Hosseininejad, S.A. Identification of chemical components from essential oils and aqueous extracts of some medicinal plants and their nematicidal effects on Meloidogyne incognita. *J. Basic Appl. Zool.* **2022**, *83*, 14. https://doi.org/10.1186/s41936-022-00279-6.
11. Pathirana, H.N.K.S.; Wimalasena, S.H.M.P.; De Silva, B.C.J.; Hossain, S.; Heo, G.-J. Antibacterial activity of lime (*Citrus aurantifolia*) essential oil and limonene against fish pathogenic bacteria isolated from cultured olive flounder (*Paralichthys olivaceus*). *Arch. Pol. Fish.* **2018**, *26*, 131–139. https://doi.org/10.2478/aopf-2018-0014.
12. Samba, N.; Aitfella-Lahlou, R.; Nelo, M.; Silva, L.; Coca, R.; Rocha, P.; Lopez Rodilla, J.M. Chemical Composition and Antibacterial Activity of *Lippia multiflora* Moldenke Essential Oil from Different Regions of Angola. *Molecules* **2020**, *26*, 155. https://doi.org/10.3390/molecules26010155.
13. Vieira, A.J.; Beserra, F.P.; Souza, M.C.; Totti, B.M.; Rozza, A.L. Limonene: Aroma of innovation in health and disease. *Chem. Biol. Interact.* **2018**, *283*, 97–106. https://doi.org/10.1016/j.cbi.2018.02.007.
14. Di, S.; Xie, Y.; Cang, T.; Liu, Z.; Chu, Y.; Zhao, H.; Qi, P.; Wang, Z.; Wang, X. Comprehensive evaluation of chiral sedaxane with four stereoisomers for risk reduction: Bioactivity, toxicity, and stereoselective dissipation in crop planting systems. *Food Chem.* **2023**, *434*, 137375. https://doi.org/10.1016/j.foodchem.2023.137375.
15. Chen, B.; Liu, C.; Shang, L.; Guo, H.; Qin, J.; Ge, L.; Jing, C.J.; Feng, C.; Hayashi, K. Electric-field enhancement of molecularly imprinted sol–gel-coated Au nano-urchin sensors for vapor detection of plant biomarkers. *J. Mater. Chem. C* **2020**, *8*, 262–269. https://doi.org/10.1039/c9tc05522c.
16. Kvittingen, L.; Sjursnes, B.J.; Schmid, R. Limonene in Citrus: A String of Unchecked Literature Citings? *J. Chem. Educ.* **2021**, *98*, 3600–3607. https://doi.org/10.1021/acs.jchemed.1c00363.
17. de Souza, M.C.; Vieira, A.J.; Beserra, F.P.; Pellizzon, C.H.; Nobrega, R.H.; Rozza, A.L. Gastroprotective effect of limonene in rats: Influence on oxidative stress, inflammation and gene expression. *Phytomedicine* **2019**, *53*, 37–42. https://doi.org/10.1016/j.phymed.2018.09.027.
18. Sousa, C.; Leitao, A.J.; Neves, B.M.; Judas, F.; Cavaleiro, C.; Mendes, A.F. Standardised comparison of limonene-derived monoterpenes identifies structural determinants of anti-inflammatory activity. *Sci. Rep.* **2020**, *10*, 7199. https://doi.org/10.1038/s41598-020-64032-1.
19. Shao, Q.; Zhang, Q.; Fang, S.; Huang, W.; Li, Z.; Fang, X.; Bao, X.; Lin, L.; Cao, J.; Luo, J. Upgrading volatile fatty acids production from anaerobic co-fermentation of orange peel waste and sewage sludge: Critical roles of limonene on functional consortia and microbial metabolic traits. *Bioresour. Technol.* **2022**, *362*, 127773. https://doi.org/10.1016/j.biortech.2022.127773.
20. Eddin, L.B.; Jha, N.K.; Meeran, M.F.N.; Kesari, K.K.; Beiram, R.; Ojha, S. Neuroprotective Potential of Limonene and Limonene Containing Natural Products. *Molecules* **2021**, *26*, 4535. https://doi.org/10.3390/molecules26154535.
21. da Silva, E.G.; Bandeira Junior, G.; Cargnelutti, J.F.; Santos, R.C.V.; Gündel, A.; Baldisserotto, B. In Vitro Antimicrobial and Antibiofilm Activity of S-(-)-Limonene and R-(+)-Limonene against Fish Bacteria. *Fishes* **2021**, *6*, 32. https://doi.org/10.3390/fishes6030032.
22. Akhavan-Mahdavi, S.; Sadeghi, R.; Faridi Esfanjani, A.; Hedayati, S.; Shaddel, R.; Dima, C.; Malekjani, N.; Boostani, S.; Jafari, S.M. Nanodelivery systems for d-limonene; techniques and applications. *Food Chem.* **2022**, *384*, 132479. https://doi.org/10.1016/j.foodchem.2022.132479.
23. Qi, H.; Chen, S.; Zhang, J.; Liang, H. Robust stability and antimicrobial activity of d-limonene nanoemulsion by sodium caseinate and high pressure homogenization. *J. Food Eng.* **2022**, *334*, 111159. https://doi.org/10.1016/j.jfoodeng.2022.111159.
24. Gadelhaq, S.M.; Aboelhadid, S.M.; Abdel-Baki, A.S.; Hassan, K.M.; Arafa, W.M.; Ibrahium, S.M.; Al-Quraishy, S.; Hassan, A.O.; Abd El-Kareem, S.G. D-limonene nanoemulsion: Lousicidal activity, stability, and effect on the cuticle of Columbicola columbae. *Med. Vet. Entomol.* **2023**, *37*, 63–75. https://doi.org/10.1111/mve.12607.
25. Sohan, M.S.R.; Elshamy, S.; Lara-Valderrama, G.; Changwatchai, T.; Khadizatul, K.; Kobayashi, I.; Nakajima, M.; Neves, M.A. Encapsulation of D-Limonene into O/W Nanoemulsions for Enhanced Stability. *Polymers* **2023**, *15*, 471. https://doi.org/10.3390/polym15020471.
26. Shao, P.; Zhang, H.; Niu, B.; Jiang, L. Antibacterial activities of R-(+)-Limonene emulsion stabilized by *Ulva fasciata* polysaccharide for fruit preservation. *Int. J. Biol. Macromol.* **2018**, *111*, 1273–1280. https://doi.org/10.1016/j.ijbiomac.2018.01.126.

27. Nagoor Meeran, M.F.; Seenipandi, A.; Javed, H.; Sharma, C.; Hashiesh, H.M.; Goyal, S.N.; Jha, N.K.; Ojha, S. Can limonene be a possible candidate for evaluation as an agent or adjuvant against infection, immunity, and inflammation in COVID-19? *Heliyon* **2021**, *7*, e05703. https://doi.org/10.1016/j.heliyon.2020.e05703.
28. Ren, Q.; Zhang, J.; Hu, S.; Ma, S.; Huang, R.; Su, S.; Wang, Y.; Jiang, L.; Xu, J.; Xiang, J. Novel photothermal pyrolysis on waste tire to generate high-yield limonene. *Fuel* **2022**, *329*, 125482. https://doi.org/10.1016/j.fuel.2022.125482.
29. Munoz-Fernandez, G.; Martinez-Buey, R.; Revuelta, J.L.; Jimenez, A. Metabolic engineering of Ashbya gossypii for limonene production from xylose. *Biotechnol. Biofuels Bioprod.* **2022**, *15*, 79. https://doi.org/10.1186/s13068-022-02176-0.
30. Kumar, H.; Bhardwaj, K.; Sharma, R.; Nepovimova, E.; Kuca, K.; Dhanjal, D.S.; Verma, R.; Bhardwaj, P.; Sharma, S.; Kumar, D. Fruit and Vegetable Peels: Utilization of High Value Horticultural Waste in Novel Industrial Applications. *Molecules* **2020**, *25*, 2812. https://doi.org/10.3390/molecules25122812.
31. Banerjee, J.; Singh, R.; Vijayaraghavan, R.; MacFarlane, D.; Patti, A.F.; Arora, A. Bioactives from fruit processing wastes: Green approaches to valuable chemicals. *Food Chem.* **2017**, *225*, 10–22. https://doi.org/10.1016/j.foodchem.2016.12.093.
32. Jo, Y.; Ameer, K.; Kang, Y.-H.; Ahn, D.U.; Kwon, J.-H. Calibrated Photo-Stimulated Luminescence and E-Sensing Analyses Discriminate Korean Citrus Fruits Treated with Electron Beam. *Food Anal. Methods* **2018**, *11*, 3190–3200. https://doi.org/10.1007/s12161-018-1291-1.
33. Deng, X.X. Citrus Breeding and Genetic Improvement Programme in China. *Acta Hortic.* **2008**, *773*, 17–23. https://doi.org/10.17660/ActaHortic.2008.773.1.
34. Cozzolino, R.; Câmara, J.S.; Malorni, L.; Amato, G.; Cannavacciuolo, C.; Masullo, M.; Piacente, S. Comparative Volatilomic Profile of Three Finger Lime (*Citrus australasica*) Cultivars Based on Chemometrics Analysis of HS-SPME/GC–MS Data. *Molecules* **2022**, *27*, 7846. https://doi.org/10.3390/molecules27227846.
35. Hassan, E.M.; El Gendy, A.E.-N.G.; Abd-ElGawad, A.M.; Elshamy, A.I.; Farag, M.A.; Alamery, S.F.; Omer, E.A. Comparative Chemical Profiles of the Essential Oils from Different Varieties of *Psidium guajava* L. *Molecules* **2020**, *26*, 119. https://doi.org/10.3390/molecules26010119.
36. Ozturk, B.; Winterburn, J.; Gonzalez-Miquel, M. Orange peel waste valorisation through limonene extraction using bio-based solvents. *Biochem. Eng. J.* **2019**, *151*, 107298. https://doi.org/10.1016/j.bej.2019.107298.
37. Dai, Y.; Verpoorte, R.; Choi, Y.H. Natural deep eutectic solvents providing enhanced stability of natural colorants from safflower (*Carthamus tinctorius*). *Food Chem.* **2014**, *159*, 116–121. https://doi.org/10.1016/j.foodchem.2014.02.155.
38. Wikandari, R.; Nguyen, H.; Millati, R.; Niklasson, C.; Taherzadeh, M.J. Improvement of biogas production from orange peel waste by leaching of limonene. *Biomed. Res. Int.* **2015**, *2015*, 494182. https://doi.org/10.1155/2015/494182.
39. Khandare, R.D.; Tomke, P.D.; Rathod, V.K. Kinetic modeling and process intensification of ultrasound-assisted extraction of d-limonene using citrus industry waste. *Chem. Eng. Process.—Process Intensif.* **2021**, *159*, 108181. https://doi.org/10.1016/j.cep.2020.108181.
40. Rizzioli, F.; Benedetti, V.; Patuzzi, F.; Baratieri, M.; Bolzonella, D.; Battista, F. Valorization of orange peels in a biorefinery loop: Recovery of limonene and production of volatile fatty acids and activated carbon. *Biomass Convers. Biorefinery* **2023**, *14*, 9793–9803. https://doi.org/10.1007/s13399-023-03738-4.
41. Khalil, N.; El-Jalel, L.; Yousif, M.; Gonaid, M. Altitude impact on the chemical profile and biological activities of Satureja thymbra L. essential oil. *BMC Complement. Med. Ther.* **2020**, *20*, 186. https://doi.org/10.1186/s12906-020-02982-9.
42. Phuyal, N.; Jha, P.K.; Raturi, P.P.; Rajbhandary, S. Comparison between essential oil compositions of Zanthoxylum armatum DC. fruits grown at different altitudes and populations in Nepal. *Int. J. Food Prop.* **2020**, *23*, 1971–1978. https://doi.org/10.1080/10942912.2020.1833032.
43. Santos, S.M.d.; Cardoso, C.A.L.; de Oliveira Junior, P.C.; da Silva, M.E.; Pereira, Z.V.; Silva, R.M.M.F.; Formagio, A.S.N. Seasonal and geographical variation in the chemical composition of essential oil from Allophylus edulis leaves. *South Afr. J. Bot.* **2023**, *154*, 41–45. https://doi.org/10.1016/j.sajb.2022.12.013.
44. Kabdal, T.; Himani; Kumar, R.; Prakash, O.; Nagarkoti, K.; Rawat, D.S.; Srivastava, R.M.; Kumar, S.; Dubey, S.K. Seasonal variation in the essential oil composition and biological activities of Thymus linearis Benth. Collected from the Kumaun region of Uttarakhand, India. *Biochem. Syst. Ecol.* **2022**, *103*, 104449. https://doi.org/10.1016/j.bse.2022.104449.
45. Dias, A.L.B.; Sousa, W.C.; Batista, H.R.F.; Alves, C.C.F.; Souchie, E.L.; Silva, F.G.; Pereira, P.S.; Sperandio, E.M.; Cazal, C.M.; Forim, M.R.; et al. Chemical composition and in vitro inhibitory effects of essential oils from fruit peel of three Citrus species and limonene on mycelial growth of *Sclerotinia sclerotiorum*. *Braz. J. Biol.* **2020**, *80*, 460–464. https://doi.org/10.1590/1519-6984.216848.
46. Fadilah, N.Q.; Jittmittraphap, A.; Leaungwutiwong, P.; Pripdeevech, P.; Dhanushka, D.; Mahidol, C.; Ruchirawat, S.; Kittakoop, P. Virucidal Activity of Essential Oils from *Citrus × aurantium* L. against Influenza A Virus H1N1:Limonene as a Potential Household Disinfectant against Virus. *Nat. Prod. Commun.* **2022**, *17*. https://doi.org/10.1177/1934578 × 211072713.
47. Yang, J.; Wang, Q.; Li, L.; Li, P.; Yin, M.; Xu, S.; Chen, Y.; Feng, X.; Wang, B. Chemical Composition and Antifungal Activity of *Zanthoxylum armatum* Fruit Essential Oil against *Phytophthora capsici. Molecules* **2022**, *27*, 8636. https://doi.org/10.3390/molecules27238636.
48. Lima, A.S.; Fernandes, Y.M.L.; Silva, C.R.; Costa-Junior, L.M.; Figueiredo, P.L.B.; Monteiro, O.S.; Maia, J.G.S.; da Rocha, C.Q. Anthelmintic evaluation and essential oils composition of *Hyptis dilatata* Benth. and *Mesosphaerum suaveolens* Kuntze from the Brazilian Amazon. *Acta Trop.* **2022**, *228*, 106321. https://doi.org/10.1016/j.actatropica.2022.106321.

49. Kgang, I.E.; Klein, A.; Mohamed, G.G.; Mathabe, P.M.K.; Belay, Z.A.; Caleb, O.J. Enzymatic and proteomic exploration into the inhibitory activities of lemongrass and lemon essential oils against *Botrytis cinerea* (causative pathogen of gray mold). *Front. Microbiol.* **2023**, *13*, 1101539. https://doi.org/10.3389/fmicb.2022.1101539.
50. Zhong, W.; Chen, K.; Yang, L.; Tang, T.; Jiang, S.; Guo, J.; Gao, Z. Essential Oils From Citrus unshiu Marc. Effectively Kill Aeromonas hydrophila by Destroying Cell Membrane Integrity, Influencing Cell Potential, and Leaking Intracellular Substances. *Front. Microbiol.* **2022**, *13*, 869953. https://doi.org/10.3389/fmicb.2022.869953.
51. Chandra Das, S.; Hossain, M.; Hossain, M.Z.; Jahan, N.; Uddin, M.A. Chemical analysis of essential oil extracted from pomelo sourced from Bangladesh. *Heliyon* **2022**, *8*, e11843. https://doi.org/10.1016/j.heliyon.2022.e11843.
52. Gao, Z.; Yu, Z.; Qiao, Y.; Bai, L.; Song, X.; Shi, Y.; Li, X.; Pang, B.; Ayiguli, M.; Yang, X. Chemical profiles and enzyme-targeting acaricidal properties of essential oils from *Syzygium aromaticum*, *Ilex chinensis* and *Citrus limon* against *Haemaphysalis longicornis* (Acari: Ixodidae). *Ind. Crops Prod.* **2022**, *188*, 115697. https://doi.org/10.1016/j.indcrop.2022.115697.
53. Correa, A.N.R.; Weimer, P.; Rossi, R.C.; Hoffmann, J.F.; Koester, L.S.; Suyenaga, E.S.; Ferreira, C.D. Lime and orange essential oils and d-limonene as a potential COVID-19 inhibitor: Computational, in chemico, and cytotoxicity analysis. *Food Biosci.* **2023**, *51*, 102348. https://doi.org/10.1016/j.fbio.2022.102348.
54. Jumbo, L.O.V.; Corrêa, M.J.M.; Gomes, J.M.; Armijos, M.J.G.; Valarezo, E.; Mantilla-Afanador, J.G.; Machado, F.P.; Rocha, L.; Aguiar, R.W.S.; Oliveira, E.E. Potential of Bursera graveolens essential oil for controlling bean weevil infestations: Toxicity, repellence, and action targets. *Ind. Crops Prod.* **2022**, *178*, 114611. https://doi.org/10.1016/j.indcrop.2022.114611.
55. Alam, A.; Jawaid, T.; Alsanad, S.M.; Kamal, M.; Balaha, M.F. Composition, Antibacterial Efficacy, and Anticancer Activity of Essential Oil Extracted from *Psidium guajava* (L.) Leaves. *Plants* **2023**, *12*, 246. https://doi.org/10.3390/plants12020246.
56. Noshad, M.; Alizadeh Behbahani, B.; Nikfarjam, Z. Chemical composition, antibacterial activity and antioxidant activity of Citrus bergamia essential oil: Molecular docking simulations. *Food Biosci.* **2022**, *50*, 2123. https://doi.org/10.1016/j.fbio.2022.102123.
57. Liao, S.; Yang, G.; Huang, S.; Li, B.; Li, A.; Kan, J. Chemical composition of *Zanthoxylum schinifolium* Siebold & Zucc. essential oil and evaluation of its antifungal activity and potential modes of action on *Malassezia restricta*. *Ind. Crops Prod.* **2022**, *180*, 114698. https://doi.org/10.1016/j.indcrop.2022.114698.
58. Borotova, P.; Galovicova, L.; Vukovic, N.L.; Vukic, M.; Kunova, S.; Hanus, P.; Kowalczewski, P.L.; Bakay, L.; Kacaniova, M. Role of Litsea cubeba Essential Oil in Agricultural Products Safety: Antioxidant and Antimicrobial Applications. *Plants* **2022**, *11*, 1504. https://doi.org/10.3390/plants11111504.
59. Ren, Y.; Liu, S.; Jin, G.; Yang, X.; Zhou, Y.J. Microbial production of limonene and its derivatives: Achievements and perspectives. *Biotechnol. Adv.* **2020**, *44*, 107628. https://doi.org/10.1016/j.biotechadv.2020.107628.
60. Leferink, N.G.H.; Jervis, A.J.; Zebec, Z.; Toogood, H.S.; Hay, S.; Takano, E.; Scrutton, N.S. A 'Plug and Play' Platform for the Production of Diverse Monoterpene Hydrocarbon Scaffolds in *Escherichia coli*. *ChemistrySelect* **2016**, *1*, 1893–1896. https://doi.org/10.1002/slct.201600563.
61. Rolf, J.; Julsing, M.K.; Rosenthal, K.; Lutz, S. A Gram-Scale Limonene Production Process with Engineered *Escherichia coli*. *Molecules* **2020**, *25*, 1881. https://doi.org/10.3390/molecules25081881.
62. Yao, F.; Liu, S.C.; Wang, D.N.; Liu, Z.J.; Hua, Q.; Wei, L.J. Engineering oleaginous yeast *Yarrowia lipolytica* for enhanced limonene production from xylose and lignocellulosic hydrolysate. *FEMS Yeast Res.* **2020**, *20*, foaa046. https://doi.org/10.1093/femsyr/foaa046.
63. Zhao, M.L.; Cai, W.S.; Zheng, S.Q.; Zhao, J.L.; Zhang, J.L.; Huang, Y.; Hu, Z.L.; Jia, B. Metabolic Engineering of the Isopentenol Utilization Pathway Enhanced the Production of Terpenoids in *Chlamydomonas reinhardtii*. *Mar. Drugs* **2022**, *20*, 577. https://doi.org/10.3390/md20090577.
64. Pan, Q.; Ma, X.; Liang, H.; Liu, Y.; Zhou, Y.; Stephanopoulos, G.; Zhou, K. Biosynthesis of geranate via isopentenol utilization pathway in *Escherichia coli*. *Biotechnol. Bioeng.* **2023**, *120*, 230–238. https://doi.org/10.1002/bit.28255.
65. Luo, Z.; Liu, N.; Lazar, Z.; Chatzivasileiou, A.; Ward, V.; Chen, J.; Zhou, J.; Stephanopoulos, G. Enhancing isoprenoid synthesis in *Yarrowia lipolytica* by expressing the isopentenol utilization pathway and modulating intracellular hydrophobicity. *Metab. Eng.* **2020**, *61*, 344–351. https://doi.org/10.1016/j.ymben.2020.07.010.
66. Clomburg, J.M.; Qian, S.; Tan, Z.; Cheong, S.; Gonzalez, R. The isoprenoid alcohol pathway, a synthetic route for isoprenoid biosynthesis. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 12810–12815. https://doi.org/10.1073/pnas.1821004116.
67. Aguilera, J.; Gomes, A.R.; Olaru, I. Principles for the risk assessment of genetically modified microorganisms and their food products in the European Union. *Int. J. Food Microbiol.* **2013**, *167*, 2–7. https://doi.org/10.1016/j.ijfoodmicro.2013.03.013.
68. Saravanan, A.; Kumar, P.S.; Ramesh, B.; Srinivasan, S. Removal of toxic heavy metals using genetically engineered microbes: Molecular tools, risk assessment and management strategies. *Chemosphere* **2022**, *298*, 134341. https://doi.org/10.1016/j.chemosphere.2022.134341.
69. Mate, J.; Periago, P.M.; Ros-Chumillas, M.; Grullon, C.; Huertas, J.P.; Palop, A. Fat and fibre interfere with the dramatic effect that nanoemulsified d-limonene has on the heat resistance of Listeria monocytogenes. *Food Microbiol.* **2017**, *62*, 270–274. https://doi.org/10.1016/j.fm.2016.10.031.
70. Gupta, A.; Jeyakumar, E.; Lawrence, R. Strategic approach of multifaceted antibacterial mechanism of limonene traced in Escherichia coli. *Sci. Rep.* **2021**, *11*, 13816. https://doi.org/10.1038/s41598-021-92843-3.
71. Li, Y.; Liu, S.; Zhao, C.; Zhang, Z.; Nie, D.; Tang, W.; Li, Y. The Chemical Composition and Antibacterial and Antioxidant Activities of Five Citrus Essential Oils. *Molecules* **2022**, *27*, 7044. https://doi.org/10.3390/molecules27207044.

72. Zhang, Z.; Vriesekoop, F.; Yuan, Q.; Liang, H. Effects of nisin on the antimicrobial activity of d-limonene and its nanoemulsion. *Food Chem.* **2014**, *150*, 307–312. https://doi.org/10.1016/j.foodchem.2013.10.160.
73. Khelissa, S.; El Fannassi, Y.; Mechmechani, S.; Alhuthali, S.; El Amrani, M.A.; Gharsallaoui, A.; Barras, A.; Chihib, N.E. Water-Soluble Ruthenium (II) Complex Derived From Optically Pure Limonene and Its Microencapsulation Are Efficient Tools Against Bacterial Food Pathogen Biofilms: *Escherichia coli, Staphylococcus aureus, Enteroccocus faecalis*, and *Listeria monocytogenes*. *Front. Microbiol.* **2021**, *12*, 711326. https://doi.org/10.3389/fmicb.2021.711326.
74. Wang, R.; Vega, P.; Xu, Y.; Chen, C.Y.; Irudayaraj, J. Exploring the anti-quorum sensing activity of a d-limonene nanoemulsion for *Escherichia coli* O157:H7. *J. Biomed. Mater. Res. A* **2018**, *106*, 1979–1986. https://doi.org/10.1002/jbm.a.36404.
75. Sreepian, A.; Popruk, S.; Nutalai, D.; Phutthanu, C.; Sreepian, P.M. Antibacterial Activities and Synergistic Interaction of Citrus Essential Oils and Limonene with Gentamicin against Clinically Isolated Methicillin-Resistant *Staphylococcus aureus*. *Sci. World J.* **2022**, *2022*, 8418287. https://doi.org/10.1155/2022/8418287.
76. Salinas, C.; Florentin, G.; Rodriguez, F.; Alvarenga, N.; Guillen, R. Terpenes Combinations Inhibit Biofilm Formation in *Staphyloccocus aureus* by Interfering with Initial Adhesion. *Microorganisms* **2022**, *10*, 1527. https://doi.org/10.3390/microorganisms10081527.
77. Sieniawska, E.; Swatko-Ossor, M.; Sawicki, R.; Ginalska, G. Morphological Changes in the Overall *Mycobacterium tuberculosis* H37Ra Cell Shape and Cytoplasm Homogeneity due to *Mutellina purpurea* L. Essential Oil and Its Main Constituents. *Med. Princ. Pract.* **2015**, *24*, 527–532. https://doi.org/10.1159/000439351.
78. Sieniawska, E.; Sawicki, R.; Swatko-Ossor, M.; Napiorkowska, A.; Przekora, A.; Ginalska, G.; Augustynowicz-Kopec, E. The Effect of Combining Natural Terpenes and Antituberculous Agents against Reference and Clinical Mycobacterium tuberculosis Strains. *Molecules* **2018**, *23*, 176. https://doi.org/10.3390/molecules23010176.
79. Han, Y.; Sun, Z.; Chen, W. Antimicrobial Susceptibility and Antibacterial Mechanism of Limonene against Listeria monocytogenes. *Molecules* **2019**, *25*, 33. https://doi.org/10.3390/molecules25010033.
80. Montironi, I.D.; Cariddi, L.N.; Reinoso, E.B. Evaluation of the antimicrobial efficacy of *Minthostachys verticillata* essential oil and limonene against *Streptococcus uberis* strains isolated from bovine mastitis. *Rev. Argent Microbiol.* **2016**, *48*, 210–216. https://doi.org/10.1016/j.ram.2016.04.005.
81. Sun, Y.; Chen, S.; Zhang, C.; Liu, Y.; Ma, L.; Zhang, X. Effects of sub-minimum inhibitory concentrations of lemon essential oil on the acid tolerance and biofilm formation of *Streptococcus mutans*. *Arch. Oral Biol.* **2018**, *87*, 235–241. https://doi.org/10.1016/j.archoralbio.2017.12.028.
82. Morcia, C.; Tumino, G.; Ghizzoni, R.; Bara, A.; Salhi, N.; Terzi, V. In Vitro Evaluation of Sub-Lethal Concentrations of Plant-Derived Antifungal Compounds on FUSARIA Growth and Mycotoxin Production. *Molecules* **2017**, *22*, 1271. https://doi.org/10.3390/molecules22081271.
83. Hamdi, A.; Majouli, K.; Flamini, G.; Marzouk, B.; Marzouk, Z.; Heyden, Y.V. Antioxidant and anticandidal activities of the Tunisian *Haplophyllum tuberculatum* (Forssk.) A. Juss. essential oils. *South Afr. J. Bot.* **2017**, *112*, 210–214. https://doi.org/10.1016/j.sajb.2017.05.026.
84. Ahmedi, S.; Pant, P.; Raj, N.; Manzoor, N. Limonene inhibits virulence associated traits in Candida albicans: In-vitro and in-silico studies. *Phytomedicine Plus* **2022**, *2*, 100285. https://doi.org/10.1016/j.phyplu.2022.100285.
85. Leite-Andrade, M.C.; de Araujo Neto, L.N.; Buonafina-Paz, M.D.S.; de Assis Graciano Dos Santos, F.; da Silva Alves, A.I.; de Castro, M.; Mori, E.; de Lacerda, B.; Araujo, I.M.; Coutinho, H.D.M.; et al. Antifungal Effect and Inhibition of the Virulence Mechanism of D-Limonene against Candida parapsilosis. *Molecules* **2022**, *27*, 8884. https://doi.org/10.3390/molecules27248884.
86. Yu, H.; Lin, Z.-X.; Xiang, W.-L.; Huang, M.; Tang, J.; Lu, Y.; Zhao, Q.-H.; Zhang, Q.; Rao, Y.; Liu, L. Antifungal activity and mechanism of d-limonene against foodborne opportunistic pathogen *Candida tropicalis*. *LWT* **2022**, *159*, 113144. https://doi.org/10.1016/j.lwt.2022.113144.
87. Bertuso, P.C.; Mayer, D.M.D.; Nitschke, M. Combining Celery Oleoresin, Limonene and Rhamnolipid as New Strategy to Control Endospore-Forming *Bacillus cereus*. *Foods* **2021**, *10*, 455. https://doi.org/10.3390/foods10020455.
88. Wang, B.; Li, P.; Yang, J.; Yong, X.; Yin, M.; Chen, Y.; Feng, X.; Wang, Q. Inhibition efficacy of *Tetradium glabrifolium* fruit essential oil against *Phytophthora capsici* and potential mechanism. *Ind. Crops Prod.* **2022**, *176*, 114310. https://doi.org/10.1016/j.indcrop.2021.114310.
89. Chee, H.Y.; Kim, H.; Lee, M.H. In vitro Antifungal Activity of Limonene against *Trichophyton rubrum*. *Mycobiology* **2009**, *37*, 243–246. https://doi.org/10.4489/MYCO.2009.37.3.243.
90. Padhan, D.; Pattnaik, S.; Behera, A.K. Growth-arresting Activity of Acmella Essential Oil and its Isolated Component D-Limonene (1, 8 P-Mentha Diene) against *Trichophyton rubrum* (Microbial Type Culture Collection 296). *Pharmacogn. Mag.* **2017**, *13*, S555–S560. https://doi.org/10.4103/pm.pm_65_17.
91. Costa, M.D.S.; Rocha, J.E.; Campina, F.F.; Silva, A.R.P.; Da Cruz, R.P.; Pereira, R.L.S.; Quintans-Junior, L.J.; De Menezes, I.R.A.; De, S.A.A.A.; De Freitas, T.S.; et al. Comparative analysis of the antibacterial and drug-modulatory effect of d-limonene alone and complexed with beta-cyclodextrin. *Eur. J. Pharm. Sci.* **2019**, *128*, 158–161. https://doi.org/10.1016/j.ejps.2018.11.036.
92. Zapata-Zapata, C.; Loaiza-Oliva, M.; Martinez-Pabon, M.C.; Stashenko, E.E.; Mesa-Arango, A.C. In Vitro Activity of Essential Oils Distilled from Colombian Plants against Candidaauris and Other Candida Species with Different Antifungal Susceptibility Profiles. *Molecules* **2022**, *27*, 6837. https://doi.org/10.3390/molecules27206837.

93. Thakre, A.; Zore, G.; Kodgire, S.; Kazi, R.; Mulange, S.; Patil, R.; Shelar, A.; Santhakumari, B.; Kulkarni, M.; Kharat, K.; et al. Limonene inhibits Candida albicans growth by inducing apoptosis. *Med. Mycol.* **2018**, *56*, 565–578. https://doi.org/10.1093/mmy/myx074.
94. Justino de Araujo, A.C.; Freitas, P.R.; Rodrigues Dos Santos Barbosa, C.; Muniz, D.F.; Rocha, J.E.; Albuquerque da Silva, A.C.; Datiane de Morais Oliveira-Tintino, C.; Ribeiro-Filho, J.; Everson da Silva, L.; Confortin, C.; et al. GC-MS-FID characterization and antibacterial activity of the Mikania cordifolia essential oil and limonene against MDR strains. *Food Chem. Toxicol.* **2020**, *136*, 111023. https://doi.org/10.1016/j.fct.2019.111023.
95. Lee, Y.; Puumala, E.; Robbins, N.; Cowen, L.E. Antifungal Drug Resistance: Molecular Mechanisms in *Candida albicans* and Beyond. *Chem. Rev.* **2021**, *121*, 3390–3411. https://doi.org/10.1021/acs.chemrev.0c00199.
96. Huang, L.; Wu, C.; Gao, H.; Xu, C.; Dai, M.; Huang, L.; Hao, H.; Wang, X.; Cheng, G. Bacterial Multidrug Efflux Pumps at the Frontline of Antimicrobial Resistance: An Overview. *Antibiotics* **2022**, *11*, 520. https://doi.org/10.3390/antibiotics11040520.
97. Kumar, S.; Mukherjee, M.M.; Varela, M.F. Modulation of Bacterial Multidrug Resistance Efflux Pumps of the Major Facilitator Superfamily. *Int. J. Bacteriol.* **2013**, *2013*, 204141. https://doi.org/10.1155/2013/204141.
98. Freitas, P.R.; de Araujo, A.C.J.; Dos Santos Barbosa, C.R.; Muniz, D.F.; de Almeida, R.S.; de Menezes, I.R.A.; da Costa, J.G.M.; Rodrigues, F.F.G.; Rocha, J.E.; Pereira-Junior, F.N.; et al. Inhibition of the MepA efflux pump by limonene demonstrated by in vitro and in silico methods. *Folia Microbiol.* **2022**, *67*, 15–20. https://doi.org/10.1007/s12223-021-00909-6.
99. Caballero Gomez, N.; Manetsberger, J.; Benomar, N.; Castillo Gutierrez, S.; Abriouel, H. Antibacterial and antibiofilm effects of essential oil components, EDTA and HLE disinfectant solution on Enterococcus, Pseudomonas and Staphylococcus sp. multiresistant strains isolated along the meat production chain. *Front. Microbiol.* **2022**, *13*, 1014169. https://doi.org/10.3389/fmicb.2022.1014169.
100. Oliveira, F.S.; Freitas, T.S.; Cruz, R.P.D.; Costa, M.D.S.; Pereira, R.L.S.; Quintans-Junior, L.J.; Andrade, T.A.; Menezes, P.D.P.; Sousa, B.M.H.; Nunes, P.S.; et al. Evaluation of the antibacterial and modulatory potential of alpha-bisabolol, beta-cyclodextrin and alpha-bisabolol/beta-cyclodextrin complex. *Biomed. Pharmacother.* **2017**, *92*, 1111–1118. https://doi.org/10.1016/j.biopha.2017.06.020.
101. Manoharan, R.K.; Lee, J.H.; Lee, J. Efficacy of 7-benzyloxyindole and other halogenated indoles to inhibit Candida albicans biofilm and hyphal formation. *Microb. Biotechnol.* **2018**, *11*, 1060–1069. https://doi.org/10.1111/1751-7915.13268.
102. Galié, S.; García-Gutiérrez, C.; Miguélez, E.M.; Villar, C.J.; Lombó, F. Biofilms in the Food Industry: Health Aspects and Control Methods. *Front. Microbiol.* **2018**, *9*, 898. https://doi.org/10.3389/fmicb.2018.00898.
103. Liu, J.; Wu, S.; Feng, L.; Wu, Y.; Zhu, J. Extracellular matrix affects mature biofilm and stress resistance of psychrotrophic spoilage Pseudomonas at cold temperature. *Food Microbiol.* **2023**, *112*, 104214. https://doi.org/10.1016/j.fm.2023.104214.
104. Mulya, E.; Waturangi, D.E. Screening and quantification of anti-quorum sensing and antibiofilm activity of Actinomycetes isolates against food spoilage biofilm-forming bacteria. *BMC Microbiol.* **2021**, *21*, 1. https://doi.org/10.1186/s12866-020-02060-7.
105. Cheah, Y.T.; Chan, D.J.C. A methodological review on the characterization of microalgal biofilm and its extracellular polymeric substances. *J. Appl. Microbiol.* **2022**, *132*, 3490–3514. https://doi.org/10.1111/jam.15455.
106. Sharan, M.; Vijay, D.; Dhaka, P.; Bedi, J.S.; Gill, J.P.S. Biofilms as a microbial hazard in the food industry: A scoping review. *J. Appl. Microbiol.* **2022**, *133*, 2210–2234. https://doi.org/10.1111/jam.15766.
107. Amankwah, S.; Abdella, K.; Kassa, T. Bacterial Biofilm Destruction: A Focused Review On The Recent Use of Phage-Based Strategies With Other Antibiofilm Agents. *Nanotechnol. Sci. Appl.* **2021**, *14*, 161–177. https://doi.org/10.2147/NSA.S325594.
108. Jamal, M.; Ahmad, W.; Andleeb, S.; Jalil, F.; Imran, M.; Nawaz, M.A.; Hussain, T.; Ali, M.; Rafiq, M.; Kamil, M.A. Bacterial biofilm and associated infections. *J. Chin. Med. Assoc.* **2018**, *81*, 7–11. https://doi.org/10.1016/j.jcma.2017.07.012.
109. Subramenium, G.A.; Vijayakumar, K.; Pandian, S.K. Limonene inhibits streptococcal biofilm formation by targeting surface-associated virulence factors. *J. Med. Microbiol.* **2015**, *64*, 879–890. https://doi.org/10.1099/jmm.0.000105.
110. Melkina, O.E.; Plyuta, V.A.; Khmel, I.A.; Zavilgelsky, G.B. The Mode of Action of Cyclic Monoterpenes (-)-Limoneneand (+)-alpha-Pinene on Bacterial Cells. *Biomolecules* **2021**, *11*, 806. https://doi.org/10.3390/biom11060806.
111. Hac-Wydro, K.; Flasinski, M.; Romanczuk, K. Essential oils as food eco-preservatives: Model system studies on the effect of temperature on limonene antibacterial activity. *Food Chem.* **2017**, *235*, 127–135. https://doi.org/10.1016/j.foodchem.2017.05.051.
112. Park, K.M.; Lee, S.J.; Yu, H.; Park, J.Y.; Jung, H.S.; Kim, K.; Lee, C.J.; Chang, P.S. Hydrophilic and lipophilic characteristics of non-fatty acid moieties: Significant factors affecting antibacterial activity of lauric acid esters. *Food Sci. Biotechnol.* **2018**, *27*, 401–409. https://doi.org/10.1007/s10068-018-0353-x.
113. Han, Y.; Chen, W.; Sun, Z. Antimicrobial activity and mechanism of limonene against Staphylococcus aureus. *J. Food Saf.* **2021**, *41*, 12918. https://doi.org/10.1111/jfs.12918.
114. Vázquez-López, N.A.; Cruz-Jiménez, G.; Obregón-Herrera, A.; Ruiz-Baca, E.; Pedraza-Reyes, M.; López-Romero, E.; Cuéllar-Cruz, M.; Gutiérrez-Grijalva, E. Identification of Secondary Metabolites from Mexican Plants with Antifungal Activity against Pathogenic Candida Species. *J. Chem.* **2022**, *2022*, 8631284. https://doi.org/10.1155/2022/8631284.
115. Monk, B.C.; Goffeau, A. Outwitting multidrug resistance to antifungals. *Science* **2008**, *321*, 367–369. https://doi.org/10.1126/science.1159746.
116. Brennan, T.C.; Kromer, J.O.; Nielsen, L.K. Physiological and transcriptional responses of Saccharomyces cerevisiae to d-limonene show changes to the cell wall but not to the plasma membrane. *Appl. Environ. Microbiol.* **2013**, *79*, 3590–3600. https://doi.org/10.1128/AEM.00463-13.

117. Liu, J.; Zhu, Y.; Du, G.; Zhou, J.; Chen, J. Exogenous ergosterol protects Saccharomyces cerevisiae from D-limonene stress. *J. Appl. Microbiol.* **2013**, *114*, 482–491. https://doi.org/10.1111/jam.12046.
118. Xiong, H.-B.; Zhou, X.-H.; Xiang, W.-L.; Huang, M.; Lin, Z.-X.; Tang, J.; Cai, T.; Zhang, Q. Integrated transcriptome reveals that d-limonene inhibits Candida tropicalis by disrupting metabolism. *LWT* **2023**, *176*, 114535. https://doi.org/10.1016/j.lwt.2023.114535.
119. Sawicki, R.; Sieniawska, E.; Swatko-Ossor, M.; Golus, J.; Ginalska, G. The frequently occurring components of essential oils beta elemene and R-limonene alter expression of dprE1 and clgR genes of *Mycobacterium tuberculosis* H37Ra. *Food Chem. Toxicol.* **2018**, *112*, 145–149. https://doi.org/10.1016/j.fct.2017.12.052.
120. Nove, M.; Kincses, A.; Szalontai, B.; Racz, B.; Blair, J.M.A.; Gonzalez-Pradena, A.; Benito-Lama, M.; Dominguez-Alvarez, E.; Spengler, G. Biofilm Eradication by Symmetrical Selenoesters for Food-Borne Pathogens. *Microorganisms* **2020**, *8*, 566. https://doi.org/10.3390/microorganisms8040566.
121. Moreira, J.; Duraes, F.; Freitas-Silva, J.; Szemeredi, N.; Resende, D.; Pinto, E.; da Costa, P.M.; Pinto, M.; Spengler, G.; Cidade, H.; et al. New diarylpentanoids and chalcones as potential antimicrobial adjuvants. *Bioorg. Med. Chem. Lett.* **2022**, *67*, 128743. https://doi.org/10.1016/j.bmcl.2022.128743.
122. Wang, W.Q.; Feng, X.C.; Shi, H.T.; Wang, Y.M.; Jiang, C.Y.; Xiao, Z.J.; Xu, Y.J.; Zhang, X.; Yuan, Y.; Ren, N.Q. Biofilm inhibition based on controlling the transmembrane transport and extracellular accumulation of quorum sensing signals. *Environ. Res.* **2023**, *221*, 115218. https://doi.org/10.1016/j.envres.2023.115218.
123. Li, S.; Leung, P.H.M.; Xu, X.; Wu, C. Homogentisic acid γ-lactone suppresses the virulence factors of Pseudomonas aeruginosa by quenching its quorum sensing signal molecules. *Chin. Chem. Lett.* **2018**, *29*, 313–316. https://doi.org/10.1016/j.cclet.2017.09.052.
124. Hajiagha, M.N.; Kafil, H.S. Efflux pumps and microbial biofilm formation. *Infect. Genet. Evol.* **2023**, *112*, 105459. https://doi.org/10.1016/j.meegid.2023.105459.
125. Hardie, K.R.; Heurlier, K. Establishing bacterial communities by 'word of mouth': LuxS and autoinducer 2 in biofilm development. *Nat. Rev. Microbiol.* **2008**, *6*, 635–643. https://doi.org/10.1038/nrmicro1916.
126. Luciardi, M.C.; Blazquez, M.A.; Alberto, M.R.; Cartagena, E.; Arena, M.E. Lemon Oils Attenuate the Pathogenicity of Pseudomonas aeruginosa by Quorum Sensing Inhibition. *Molecules* **2021**, *26*, 2863. https://doi.org/10.3390/molecules26102863.
127. Yan, M.; Luo, L.; Li, D.; Liu, Z.; Wei, R.; Yi, J.; Qiao, L.; You, C. Biofilm formation risk assessment for psychrotrophic pseudomonas in raw milk by MALDI-TOF mass spectrometry. *LWT* **2023**, *176*, 114508. https://doi.org/10.1016/j.lwt.2023.114508.
128. Tomaś, N.; Myszka, K.; Wolko, Ł.; Nuc, K.; Szwengiel, A.; Grygier, A.; Majcher, M. Effect of black pepper essential oil on quorum sensing and efflux pump systems in the fish-borne spoiler Pseudomonas psychrophila KM02 identified by RNA-seq, RT-qPCR and molecular docking analyses. *Food Control* **2021**, *130*, 108284. https://doi.org/10.1016/j.foodcont.2021.108284.
129. Alav, I.; Sutton, J.M.; Rahman, K.M. Role of bacterial efflux pumps in biofilm formation. *J. Antimicrob. Chemother.* **2018**, *73*, 2003–2020. https://doi.org/10.1093/jac/dky042.
130. de Araújo, A.C.J.; Freitas, P.R.; dos Santos Barbosa, C.R.; Muniz, D.F.; de Almeida, R.S.; Alencar de Menezes, I.R.; Ribeiro-Filho, J.; Tintino, S.R.; Coutinho, H.D.M. In Vitro and In Silico Inhibition of *Staphylococcus aureus* Efflux Pump NorA by α-Pinene and Limonene. *Curr. Microbiol.* **2021**, *78*, 3388–3393. https://doi.org/10.1007/s00284-021-02611-9.
131. Kaur, R.; Choudhary, D.; Bali, S.; Bandral, S.S.; Singh, V.; Ahmad, M.A.; Rani, N.; Singh, T.G.; Chandrasekaran, B. Pesticides: An alarming detrimental to health and environment. *Sci. Total Environ.* **2024**, *915*, 170113. https://doi.org/10.1016/j.scitotenv.2024.170113.
132. Maggi, F.; la Cecilia, D.; Tang, F.H.M.; McBratney, A. The global environmental hazard of glyphosate use. *Sci. Total Environ.* **2020**, *717*, 137167. https://doi.org/10.1016/j.scitotenv.2020.137167.
133. Zhang, Y.; Tang, J.; Wang, S.; Zhou, X.; Peng, C.; Zhou, H.; Wang, D.; Lin, H.; Xiang, W.; Zhang, Q.; et al. Mechanism of deltamethrin biodegradation by Brevibacillus parabrevis BCP-09 with proteomic methods. *Chemosphere* **2024**, *350*, 141100. https://doi.org/10.1016/j.chemosphere.2023.141100.
134. Zhang, W.; Yu, L.; Han, B.; Liu, K.; Shao, X. Mycorrhizal Inoculation Enhances Nutrient Absorption and Induces Insect-Resistant Defense of Elymus nutans. *Front. Plant Sci.* **2022**, *13*, 898969. https://doi.org/10.3389/fpls.2022.898969.
135. Lam, N.S.; Long, X.; Su, X.Z.; Lu, F. *Melaleuca alternifolia* (tea tree) oil and its monoterpene constituents in treating protozoan and helminthic infections. *Biomed. Pharmacother.* **2020**, *130*, 110624. https://doi.org/10.1016/j.biopha.2020.110624.
136. Isman, M.B. Botanical Insecticides in the Twenty-First Century-Fulfilling Their Promise? *Annu. Rev. Entomol.* **2020**, *65*, 233–249. https://doi.org/10.1146/annurev-ento-011019-025010.
137. Zeni, V.; Benelli, G.; Campolo, O.; Giunti, G.; Palmeri, V.; Maggi, F.; Rizzo, R.; Lo Verde, G.; Lucchi, A.; Canale, A. Toxics or Lures? Biological and Behavioral Effects of Plant Essential Oils on Tephritidae Fruit Flies. *Molecules* **2021**, *26*, 5898. https://doi.org/10.3390/molecules26195898.
138. Caballero-Gallardo, K.; Fuentes-Lopez, K.; Stashenko, E.E.; Olivero-Verbel, J. Chemical Composition, Repellent Action, and Toxicity of Essential Oils from *Lippia origanoide, Lippia. alba* Chemotypes, and Pogostemon cablin on Adults of *Ulomoides dermestoides* (Coleoptera: Tenebrionidae). *Insects* **2022**, *14*, 41. https://doi.org/10.3390/insects14010041.
139. Mohammed, K.; Agarwal, M.; Li, B.; Newman, J.; Liu, T.; Ren, Y. Evaluation of d-Limonene and beta-Ocimene as Attractants of *Aphytis melinus* (Hymenoptera: Aphelinidae), a Parasitoid of *Aonidiella aurantii* (Hemiptera: Diaspididae) on *Citrus* spp. *Insects* **2020**, *11*, 44. https://doi.org/10.3390/insects11010044.
140. Fouad, H.A.; de Souza Tavares, W.; Zanuncio, J.C. Toxicity and repellent activity of monoterpene enantiomers to rice weevils (Sitophilus oryzae). *Pest Manag. Sci.* **2021**, *77*, 3500–3507. https://doi.org/10.1002/ps.6403.

141. Prado-Rebolledo, O.F.; Molina-Ochoa, J.; Lezama-Gutiérrez, R.; García-Márquez, L.J.; Minchaca-Llerenas, Y.B.; Morales-Barrera, E.; Tellez, G.; Hargis, B.; Skoda, S.R.; Foster, J.E. Effect of Metarhizium anisopliae (Ascomycete), Cypermethrin, and D-Limonene, Alone and Combined, on Larval Mortality of Rhipicephalus sanguineus (Acari: Ixodidae). *J. Med. Entomol.* **2017**, *54*, 1323–1327. https://doi.org/10.1093/jme/tjx092.
142. Theochari, I.; Giatropoulos, A.; Papadimitriou, V.; Karras, V.; Balatsos, G.; Papachristos, D.; Michaelakis, A. Physicochemical Characteristics of Four Limonene-Based Nanoemulsions and Their Larvicidal Properties against Two Mosquito Species, Aedes albopictus and Culex pipiens molestus. *Insects* **2020**, *11*, 740. https://doi.org/10.3390/insects11110740.
143. Moungthipmalai, T.; Puwanard, C.; Aungtikun, J.; Sittichok, S.; Soonwera, M. Ovicidal toxicity of plant essential oils and their major constituents against two mosquito vectors and their non-target aquatic predators. *Sci. Rep.* **2023**, *13*, 2119. https://doi.org/10.1038/s41598-023-29421-2.
144. Showler, A.T.; Harlien, J.L.; Perez de Leon, A.A. Effects of Laboratory Grade Limonene and a Commercial Limonene-Based Insecticide on *Haematobia irritans irritans* (Muscidae: Diptera): Deterrence, Mortality, and Reproduction. *J. Med. Entomol.* **2019**, *56*, 1064–1070. https://doi.org/10.1093/jme/tjz020.
145. Gonçalves, G.B.; Silva, C.E.; Dos Santos, J.C.G.; Dos Santos, E.S.; Do Nascimento, R.R.; Da Silva, E.L.; De Lima Mendonça, A.; Do Rosário Tenório De Freitas, M.; Sant'Ana, A.E.G. Comparison of the Volatile Components Released by Calling Males of Ceratitis Capitata (Diptera: Tephritidae) with Those Extractable from the Salivary Glands. *Fla. Entomol.* **2006**, *89*, 375–379. https://doi.org/10.1653/0015-4040(2006)89[375:Cotvcr]2.0.Co;2.
146. Jaffar, S.; Lu, Y. Toxicity of Some Essential Oils Constituents against Oriental Fruit Fly, *Bactrocera dorsalis* (Hendel) (Diptera: Tephritidae). *Insects* **2022**, *13*, 954. https://doi.org/10.3390/insects13100954.
147. Papanastasiou, S.A.; Bali, E.D.; Ioannou, C.S.; Papachristos, D.P.; Zarpas, K.D.; Papadopoulos, N.T. Toxic and hormetic-like effects of three components of citrus essential oils on adult Mediterranean fruit flies (Ceratitis capitata). *PLoS ONE* **2017**, *12*, e0177837. https://doi.org/10.1371/journal.pone.0177837.
148. Arruda, D.C.; Miguel, D.C.; Yokoyama-Yasunaka, J.K.; Katzin, A.M.; Uliana, S.R. Inhibitory activity of limonene against Leishmania parasites in vitro and in vivo. *Biomed. Pharmacother.* **2009**, *63*, 643–649. https://doi.org/10.1016/j.biopha.2009.02.004.
149. Camargos, H.S.; Moreira, R.A.; Mendanha, S.A.; Fernandes, K.S.; Dorta, M.L.; Alonso, A. Terpenes increase the lipid dynamics in the Leishmania plasma membrane at concentrations similar to their IC50 values. *PLoS ONE* **2014**, *9*, e104429. https://doi.org/10.1371/journal.pone.0104429.
150. Moura, I.C.; Wunderlich, G.; Uhrig, M.L.; Couto, A.S.; Peres, V.J.; Katzin, A.M.; Kimura, E.A. Limonene arrests parasite development and inhibits isoprenylation of proteins in *Plasmodium falciparum*. *Antimicrob. Agents Chemother.* **2001**, *45*, 2553–2558. https://doi.org/10.1128/AAC.45.9.2553-2558.2001.
151. Rodrigues Goulart, H.; Kimura, E.A.; Peres, V.J.; Couto, A.S.; Aquino Duarte, F.A.; Katzin, A.M. Terpenes arrest parasite development and inhibit biosynthesis of isoprenoids in *Plasmodium falciparum*. *Antimicrob. Agents Chemother.* **2004**, *48*, 2502–2509. https://doi.org/10.1128/AAC.48.7.2502-2509.2004.
152. Katiki, L.M.; Barbieri, A.M.E.; Araujo, R.C.; Verissimo, C.J.; Louvandini, H.; Ferreira, J.F.S. Synergistic interaction of ten essential oils against *Haemonchus contortus* in vitro. *Vet. Parasitol.* **2017**, *243*, 47–51. https://doi.org/10.1016/j.vetpar.2017.06.008.
153. Moreno, E.M.; Leal, S.M.; Stashenko, E.E.; Garcia, L.T. Induction of programmed cell death in Trypanosoma cruzi by *Lippia alba* essential oils and their major and synergistic terpenes (citral, limonene and caryophyllene oxide). *BMC Complement. Altern. Med.* **2018**, *18*, 225. https://doi.org/10.1186/s12906-018-2293-7.
154. Suh, K.S.; Chon, S.; Choi, E.M. Limonene attenuates methylglyoxal-induced dysfunction in MC3T3-E1 osteoblastic cells. *Food Agric. Immunol.* **2017**, *28*, 1256–1268. https://doi.org/10.1080/09540105.2017.1337082.
155. Barbosa, M.H.R.; Gonçalves, S.d.Á.; Marangoni Júnior, L.; Alves, R.M.V.; Vieira, R.P. Physicochemical properties of chitosan-based films incorporated with limonene. *J. Food Meas. Charact.* **2022**, *16*, 2011–2023. https://doi.org/10.1007/s11694-022-01337-x.
156. Al Kamaly, O.; Numan, O.; Almrfadi, O.M.A.; Alanazi, A.S.; Conte, R. Separation and evaluation of potential antioxidant, analgesic, and anti-inflammatory activities of limonene-rich essential oils from *Citrus sinensis* (L.). *Open Chem.* **2022**, *20*, 1517–1530. https://doi.org/10.1515/chem-2022-0254.
157. Piccialli, I.; Tedeschi, V.; Caputo, L.; Amato, G.; De Martino, L.; De Feo, V.; Secondo, A.; Pannaccione, A. The Antioxidant Activity of Limonene Counteracts Neurotoxicity Triggered byAbeta(1-42) Oligomers in Primary Cortical Neurons. *Antioxidants* **2021**, *10*, 937. https://doi.org/10.3390/antiox10060937.
158. Tang, X.P.; Guo, X.H.; Geng, D.; Weng, L.J. d-Limonene protects PC12 cells against corticosterone-induced neurotoxicity by activating the AMPK pathway. *Environ. Toxicol. Pharmacol.* **2019**, *70*, 103192. https://doi.org/10.1016/j.etap.2019.05.001.
159. AlSaffar, R.M.; Rashid, S.; Ahmad, S.B.; Rehman, M.U.; Hussain, I.; Parvaiz Ahmad, S.; Ganaie, M.A. D-limonene (5 (one-methyl-four-[1-methylethenyl]) cyclohexane) diminishes CCl(4)-induced cardiac toxicity by alleviating oxidative stress, inflammatory and cardiac markers. *Redox Rep.* **2022**, *27*, 92–99. https://doi.org/10.1080/13510002.2022.2062947.
160. Amorim, J.L.; Simas, D.L.; Pinheiro, M.M.; Moreno, D.S.; Alviano, C.S.; da Silva, A.J.; Fernandes, P.D. Anti-Inflammatory Properties and Chemical Characterization of the Essential Oils of Four Citrus Species. *PLoS ONE* **2016**, *11*, e0153643. https://doi.org/10.1371/journal.pone.0153643.
161. Blevins, L.K.; Bach, A.P.; Crawford, R.B.; Zhou, J.; Henriquez, J.E.; Rizzo, M.D.; Sermet, S.; Khan, D.; Turner, H.; Small-Howard, A.L.; et al. Evaluation of the anti-inflammatory effects of selected cannabinoids and terpenes from Cannabis Sativa employing human primary leukocytes. *Food Chem. Toxicol.* **2022**, *170*, 113458. https://doi.org/10.1016/j.fct.2022.113458.

162. Huang, X.L.; Li, X.J.; Qin, Q.F.; Li, Y.S.; Zhang, W.K.; Tang, H.B. Anti-inflammatory and antinociceptive effects of active ingredients in the essential oils from *Gynura procumbens*, a traditional medicine and a new and popular food material. *J. Ethnopharmacol.* **2019**, *239*, 111916. https://doi.org/10.1016/j.jep.2019.111916.
163. Pereira, E.W.M.; Heimfarth, L.; Santos, T.K.; Passos, F.R.S.; Siqueira-Lima, P.; Scotti, L.; Scotti, M.T.; Almeida, J.; Campos, A.R.; Coutinho, H.D.M.; et al. Limonene, a citrus monoterpene, non-complexed and complexed with hydroxypropyl-beta-cyclodextrin attenuates acute and chronic orofacial nociception in rodents: Evidence for involvement of the PKA and PKC pathway. *Phytomedicine* **2022**, *96*, 153893. https://doi.org/10.1016/j.phymed.2021.153893.
164. Espinel-Mesa, D.X.; Gonzalez Rugeles, C.I.; Mantilla Hernandez, J.C.; Stashenko, E.E.; Villegas-Lanau, C.A.; Quimbaya Ramirez, J.J.; Garcia Sanchez, L.T. Immunomodulation and Antioxidant Activities as Possible Trypanocidal and Cardioprotective Mechanisms of Major Terpenes from *Lippia alba* Essential Oils in an Experimental Model of Chronic Chagas Disease. *Antioxidants* **2021**, *10*, 1851. https://doi.org/10.3390/antiox10111851.
165. Younis, N.S. D-Limonene mitigate myocardial injury in rats through MAPK/ERK/NF-κB pathway inhibition. *Korean J. Physiol. Pharmacol.* **2020**, *24*, 259–266. https://doi.org/10.4196/kjpp.2020.24.3.259.
166. Adriana Estrella, G.R.; Maria Eva, G.T.; Alberto, H.L.; Maria Guadalupe, V.D.; Azucena, C.V.; Sandra, O.S.; Noe, A.V.; Francisco Javier, L.M. Limonene from *Agastache mexicana* essential oil produces antinociceptive effects, gastrointestinal protection and improves experimental ulcerative colitis. *J. Ethnopharmacol.* **2021**, *280*, 114462. https://doi.org/10.1016/j.jep.2021.114462.
167. Araujo-Filho, H.G.; Dos Santos, J.F.; Carvalho, M.T.B.; Picot, L.; Fruitier-Arnaudin, I.; Groult, H.; Quintans-Junior, L.J.; Quintans, J.S.S. Anticancer activity of limonene: A systematic review of target signaling pathways. *Phytother. Res.* **2021**, *35*, 4957–4970. https://doi.org/10.1002/ptr.7125.
168. Rabi, T.; Bishayee, A. d -Limonene sensitizes docetaxel-induced cytotoxicity in human prostate cancer cells: Generation of reactive oxygen species and induction of apoptosis. *J. Carcinog* **2009**, *8*, 9. https://doi.org/10.4103/1477-3163.51368.
169. Jia, S.S.; Xi, G.P.; Zhang, M.; Chen, Y.B.; Lei, B.; Dong, X.S.; Yang, Y.M. Induction of apoptosis by D-limonene is mediated by inactivation of Akt in LS174T human colon cancer cells. *Oncol. Rep.* **2013**, *29*, 349–354. https://doi.org/10.3892/or.2012.2093.
170. Ahmad, S.B.; Rehman, M.U.; Fatima, B.; Ahmad, B.; Hussain, I.; Ahmad, S.P.; Farooq, A.; Muzamil, S.; Razzaq, R.; Rashid, S.M.; et al. Antifibrotic effects of D-limonene (5(1-methyl-4-[1-methylethenyl]) cyclohexane) in CCl(4) induced liver toxicity in Wistar rats. *Environ. Toxicol.* **2018**, *33*, 361–369. https://doi.org/10.1002/tox.22523.
171. Wang, X.; Li, G.; Shen, W. Protective effects of D-Limonene against transient cerebral ischemia in stroke-prone spontaneously hypertensive rats. *Exp. Ther. Med.* **2018**, *15*, 699–706. https://doi.org/10.3892/etm.2017.5509.
172. Babaeenezhad, E.; Hadipour Moradi, F.; Rahimi Monfared, S.; Fattahi, M.D.; Nasri, M.; Amini, A.; Dezfoulian, O.; Ahmadvand, H. D-Limonene Alleviates Acute Kidney Injury Following Gentamicin Administration in Rats: Role of NF-kappaB Pathway, Mitochondrial Apoptosis, Oxidative Stress, and PCNA. *Oxid. Med. Cell Longev.* **2021**, *2021*, 6670007. https://doi.org/10.1155/2021/6670007.
173. Araujo-Filho, H.G.; Pereira, E.W.M.; Heimfarth, L.; Souza Monteiro, B.; Santos Passos, F.R.; Siqueira-Lima, P.; Gandhi, S.R.; Viana Dos Santos, M.R.; Guedes da Silva Almeida, J.R.; Picot, L.; et al. Limonene, a food additive, and its active metabolite perillyl alcohol improve regeneration and attenuate neuropathic pain after peripheral nerve injury: Evidence for IL-1beta, TNF-alpha, GAP, NGF and ERK involvement. *Int. Immunopharmacol.* **2020**, *86*, 106766. https://doi.org/10.1016/j.intimp.2020.106766.
174. Lorigooini, Z.; Boroujeni, S.N.; Sayyadi-Shahraki, M.; Rahimi-Madiseh, M.; Bijad, E.; Amini-Khoei, H. Limonene through Attenuation of Neuroinflammation and Nitrite Level Exerts Antidepressant-Like Effect on Mouse Model of Maternal Separation Stress. *Behav. Neurol.* **2021**, *2021*, 8817309. https://doi.org/10.1155/2021/8817309.
175. Song, Y.; Seo, S.; Lamichhane, S.; Seo, J.; Hong, J.T.; Cha, H.J.; Yun, J. Limonene has anti-anxiety activity via adenosine A2A receptor-mediated regulation of dopaminergic and GABAergic neuronal function in the striatum. *Phytomedicine* **2021**, *83*, 153474. https://doi.org/10.1016/j.phymed.2021.153474.
176. Wojtunik-Kulesza, K.A. Toxicity of Selected Monoterpenes and Essential Oils Rich in These Compounds. *Molecules* **2022**, *27*, 1716. https://doi.org/10.3390/molecules27051716.
177. Bizzoca, M.E.; Leuci, S.; Mignogna, M.D.; Muzio, E.L.; Caponio, V.C.A.; Muzio, L.L. Natural compounds may contribute in preventing SARS-CoV-2 infection: A narrative review. *Food Sci. Hum. Wellness* **2022**, *11*, 1134–1142. https://doi.org/10.1016/j.fshw.2022.04.005.
178. Xian, Y.; Zhang, J.; Bian, Z.; Zhou, H.; Zhang, Z.; Lin, Z.; Xu, H. Bioactive natural compounds against human coronaviruses: A review and perspective. *Acta Pharm. Sin. B* **2020**, *10*, 1163–1174. https://doi.org/10.1016/j.apsb.2020.06.002.
179. Nagy, M.M.; Al-Mahdy, D.A.; Abd El Aziz, O.M.; Kandil, A.M.; Tantawy, M.A.; El Alfy, T.S.M. Chemical Composition and Antiviral Activity of Essential Oils from Citrus reshni hort. ex Tanaka (*Cleopatra mandarin*) Cultivated in Egypt. *J. Essent. Oil Bear. Plants* **2018**, *21*, 264–272. https://doi.org/10.1080/0972060x.2018.1436986.
180. Astani, A.; Schnitzler, P. Antiviral activity of monoterpenes beta-pinene and limonene against herpes simplex virus in vitro. *Iran J. Microbiol.* **2014**, *6*, 149–155.
181. Minari, J.B.; Agho, E.E.; Adebiyi, F.D.; Rotimi, O.O.; Sholaja, B.O.; Adejumo, J. Molecular Docking and Identification of Candidate Blockers for Endonuclease Domain of Lassa Virus Polymerase as Potential Drugs. *J. Appl. Sci. Environ. Manag.* **2022**, *25*, 1899–1907. https://doi.org/10.4314/jasem.v25i11.8.
182. Senthil Kumar, K.J.; Gokila Vani, M.; Wang, C.-S.; Chen, C.-C.; Chen, Y.-C.; Lu, L.-P.; Huang, C.-H.; Lai, C.-S.; Wang, S.-Y. Geranium and Lemon Essential Oils and Their Active Compounds Downregulate Angiotensin-Converting Enzyme 2 (ACE2), a SARS-CoV-2 Spike Receptor-Binding Domain, in Epithelial Cells. *Plants* **2020**, *9*, 770. https://doi.org/10.3390/plants9060770.

183. Roviello, V.; Roviello, G.N. Less COVID-19 deaths in southern and insular Italy explained by forest bathing, Mediterranean environment, and antiviral plant volatile organic compounds. *Environ. Chem. Lett.* **2021**, *20*, 7–17. https://doi.org/10.1007/s10311-021-01309-5.
184. Yang, F.; Chen, R.; Li, W.Y.; Zhu, H.Y.; Chen, X.X.; Hou, Z.F.; Cao, R.S.; Zang, G.; Li, Y.X.; Zhang, W. D-Limonene Is a Potential Monoterpene to Inhibit PI3K/Akt/IKK-alpha/NF-kappaB p65 Signaling Pathway in Coronavirus Disease 2019 Pulmonary Fibrosis. *Front. Med.* **2021**, *8*, 591830. https://doi.org/10.3389/fmed.2021.591830.
185. Bei, W.; Zhou, Y.; Xing, X.; Zahi, M.R.; Li, Y.; Yuan, Q.; Liang, H. Organogel-nanoemulsion containing nisin and D-limonene and its antimicrobial activity. *Front. Microbiol.* **2015**, *6*, 1010. https://doi.org/10.3389/fmicb.2015.01010.
186. Castel, V.; Rubiolo, A.C.; Carrara, C.R. Powdered D-limonene microcapsules obtained by spray drying using native and thermal-treated Brea gum as wall materials. *Powder Technol.* **2023**, *417*, 118263. https://doi.org/10.1016/j.powtec.2023.118263.
187. Zahi, M.R.; Liang, H.; Yuan, Q. Improving the antimicrobial activity of d-limonene using a novel organogel-based nanoemulsion. *Food Control* **2015**, *50*, 554–559. https://doi.org/10.1016/j.foodcont.2014.10.001.
188. Feng, J.; Wang, R.; Chen, Z.; Zhang, S.; Yuan, S.; Cao, H.; Jafari, S.M.; Yang, W. Formulation optimization of D-limonene-loaded nanoemulsions as a natural and efficient biopesticide. *Colloids Surf. A Physicochem. Eng. Asp.* **2020**, *596*, 124746. https://doi.org/10.1016/j.colsurfa.2020.124746.
189. Luo, S.; Chen, J.; He, J.; Li, H.; Jia, Q.; Hossen, M.A.; Dai, J.; Qin, W.; Liu, Y. Preparation of corn starch/rock bean protein edible film loaded with d-limonene particles and their application in glutinous rice cake preservation. *Int. J. Biol. Macromol.* **2022**, *206*, 313–324. https://doi.org/10.1016/j.ijbiomac.2022.02.139.
190. Sun, P.; Wang, Y.; Huang, Z.; Yang, X.; Dong, F.; Xu, X.; Liu, H. Limonene-thioctic acid-ionic liquid polymer: A self-healing and antibacterial material for movement detection sensor. *Ind. Crops Prod.* **2022**, *189*, 115802. https://doi.org/10.1016/j.indcrop.2022.115802.
191. Lan, W.; Liang, X.; Lan, W.; Ahmed, S.; Liu, Y.; Qin, W. Electrospun Polyvinyl Alcohol/d-Limonene Fibers Prepared by Ultrasonic Processing for Antibacterial Active Packaging Material. *Molecules* **2019**, *24*, 767. https://doi.org/10.3390/molecules24040767.
192. Chen, Y.; Shu, M.; Yao, X.; Wu, K.; Zhang, K.; He, Y.; Nishinari, K.; Phillips, G.O.; Yao, X.; Jiang, F. Effect of zein-based microencapsules on the release and oxidation of loaded limonene. *Food Hydrocoll.* **2018**, *84*, 330–336. https://doi.org/10.1016/j.foodhyd.2018.05.049.
193. Masood, A.; Ahmed, N.; Razip Wee, M.F.M.; Patra, A.; Mahmoudi, E.; Siow, K.S. Atmospheric Pressure Plasma Polymerisation of D-Limonene and Its Antimicrobial Activity. *Polymers* **2023**, *15*, 307. https://doi.org/10.3390/polym15020307.
194. Tang, Y.; Scher, H.B.; Jeoh, T. Industrially scalable complex coacervation process to microencapsulate food ingredients. *Innov. Food Sci. Emerg. Technol.* **2020**, *59*, 102257. https://doi.org/10.1016/j.ifset.2019.102257.
195. Türkoğlu, G.C.; Sarıışık, A.M.; Erkan, G.; Yıkılmaz, M.S.; Kontart, O. Micro- and nano-encapsulation of limonene and permethrin for mosquito repellent finishing of cotton textiles. *Iran. Polym. J.* **2020**, *29*, 321–329. https://doi.org/10.1007/s13726-020-00799-4.
196. Baiocco, D.; Zhang, Z. Microplastic-Free Microcapsules to Encapsulate Health-Promoting Limonene Oil. *Molecules* **2022**, *27*, 7215. https://doi.org/10.3390/molecules27217215.
197. Sözbir, M.; Simsek, E.B.; Mert, H.H.; Kekevi, B.; Mert, M.S.; Mert, E.H. Renewable terpene-based highly porous polymer monoliths for the effective removal of persistent pharmaceuticals of tetracycline and ibuprofen. *Microporous Mesoporous Mater.* **2023**, *354*, 112509. https://doi.org/10.1016/j.micromeso.2023.112509.
198. Campra, N.A.; Reinoso, E.B.; Montironi, I.D.; Moliva, M.V.; Raviolo, J.; Ruiz Moreno, F.; Marin, C.; Camacho, N.M.; Paredes, A.J.; Moran, M.C.; et al. Spray-drying-microencapsulated Minthostachys verticillata essential oil and limonene as innovative adjuvant strategy to bovine mastitis vaccines. *Res. Vet. Sci.* **2022**, *149*, 136–150. https://doi.org/10.1016/j.rvsc.2022.04.014.
199. Donsì, F.; Annunziata, M.; Sessa, M.; Ferrari, G. Nanoencapsulation of essential oils to enhance their antimicrobial activity in foods. *LWT—Food Sci. Technol.* **2011**, *44*, 1908–1914. https://doi.org/10.1016/j.lwt.2011.03.003.
200. Hou, C.Y.; Hazeena, S.H.; Hsieh, S.L.; Li, B.H.; Chen, M.H.; Wang, P.Y.; Zheng, B.Q.; Liang, Y.S. Effect of D-Limonene Nanoemulsion Edible Film on Banana (*Musa sapientum* Linn.) Post-Harvest Preservation. *Molecules* **2022**, *27*, 6157. https://doi.org/10.3390/molecules27196157.
201. Umagiliyage, A.L.; Becerra-Mora, N.; Kohli, P.; Fisher, D.J.; Choudhary, R. Antimicrobial efficacy of liposomes containing d-limonene and its effect on the storage life of blueberries. *Postharvest Biol. Technol.* **2017**, *128*, 130–137. https://doi.org/10.1016/j.postharvbio.2017.02.007.
202. Dobrzynska-Mizera, M.; Knitter, M.; Mallardo, S.; Del Barone, M.C.; Santagata, G.; Di Lorenzo, M.L. Thermal and Thermo-Mechanical Properties of Poly(L-lactic Acid) Biocomposites Containing beta-Cyclodextrin/d-Limonene Inclusion Complex. *Materials* **2021**, *14*, 2569. https://doi.org/10.3390/ma14102569.
203. Roy, S.; Rhim, J.W. Fabrication of Copper Sulfide Nanoparticles and Limonene Incorporated Pullulan/Carrageenan-Based Film with Improved Mechanical and Antibacterial Properties. *Polymers* **2020**, *12*, 2665. https://doi.org/10.3390/polym12112665.
204. Antosik, A.K.; Wilpiszewska, K.; Wróblewska, A.; Markowska-Szczupak, A.; Malko, M.W. Fragrant starch-based films with limonene. *Curr. Chem. Lett.* **2017**, *6*, 41–48. https://doi.org/10.5267/j.ccl.2017.2.002.
205. Lan, W.; Wang, S.; Chen, M.; Sameen, D.E.; Lee, K.; Liu, Y. Developing poly(vinyl alcohol)/chitosan films incorporate with d-limonene: Study of structural, antibacterial, and fruit preservation properties. *Int. J. Biol. Macromol.* **2020**, *145*, 722–732. https://doi.org/10.1016/j.ijbiomac.2019.12.230.

206. Yao, Y.; Ding, D.; Shao, H.; Peng, Q.; Huang, Y. Antibacterial Activity and Physical Properties of Fish Gelatin-Chitosan Edible Films Supplemented with D-Limonene. *Int. J. Polym. Sci.* **2017**, *2017*, 1–9. https://doi.org/10.1155/2017/1837171.
207. Nunes, M.R.; Agostinetto, L.; da Rosa, C.G.; Sganzerla, W.G.; Pires, M.F.; Munaretto, G.A.; Rosar, C.R.; Bertoldi, F.C.; Barreto, P.L.M.; Veeck, A.P.d.L.; et al. Application of nanoparticles entrapped orange essential oil to inhibit the incidence of phytopathogenic fungi during storage of agroecological maize seeds. *Food Res. Int.* **2024**, *175*, 113738. https://doi.org/10.1016/j.foodres.2023.113738.
208. Sanei-Dehkordi, A.; Moemenbellah-Fard, M.D.; Saffari, M.; Zarenezhad, E.; Osanloo, M. Nanoliposomes containing limonene and limonene-rich essential oils as novel larvicides against malaria and filariasis mosquito vectors. *BMC Complement. Med. Ther.* **2022**, *22*, 140. https://doi.org/10.1186/s12906-022-03624-y.
209. Assali, M.; Jaradat, N.; Maqboul, L. The Formation of Self-Assembled Nanoparticles Loaded with Doxorubicin and d-Limonene for Cancer Therapy. *ACS Omega* **2022**, *7*, 42096–42104. https://doi.org/10.1021/acsomega.2c04238.
210. Alipanah, H.; Farjam, M.; Zarenezhad, E.; Roozitalab, G.; Osanloo, M. Chitosan nanoparticles containing limonene and limonene-rich essential oils: Potential phytotherapy agents for the treatment of melanoma and breast cancers. *BMC Complement. Med. Ther.* **2021**, *21*, 186. https://doi.org/10.1186/s12906-021-03362-7.
211. Campos, E.V.R.; Proença, P.L.F.; da Costa, T.G.; de Lima, R.; Fraceto, L.F.; de Araujo, D.R.; Lehto, V.-P. Using Chitosan-Coated Polymeric Nanoparticles-Thermosensitive Hydrogels in association with Limonene as Skin Drug Delivery Strategy. *BioMed. Res. Int.* **2022**, *2022*, 9165443. https://doi.org/10.1155/2022/9165443.
212. Rani, V.; Venkatesan, J.; Prabhu, A. d-limonene-loaded liposomes target malignant glioma cells via the downregulation of angiogenic growth factors. *J. Drug Deliv. Sci. Technol.* **2023**, *82*, 104358. https://doi.org/10.1016/j.jddst.2023.104358.
213. El-Tokhy, F.S.e.; Abdel-Mottaleb, M.M.A.; El-Ghany, E.A.; Geneidi, A.S. Design of long acting invasomal nanovesicles for improved transdermal permeation and bioavailability of asenapine maleate for the chronic treatment of schizophrenia. *Int. J. Pharm.* **2021**, *608*, 121080. https://doi.org/10.1016/j.ijpharm.2021.121080.
214. Ravichandran, C.; Badgujar, P.C.; Gundev, P.; Upadhyay, A. Review of toxicological assessment of d-limonene, a food and cosmetics additive. *Food Chem. Toxicol.* **2018**, *120*, 668–680. https://doi.org/10.1016/j.fct.2018.07.052.
215. Matura, M.; Goossens, A.; Bordalo, O.; Garcia-Bravo, B.; Magnussona, K.; Wrangsj, K.; Karlberg, A.-T. Oxidized citrus oil (R-limonene): A frequent skin sensitizer in Europe. *J. Am. Acad. Dermatol.* **2002**, *47*, 709–714. https://doi.org/10.1067/mjd.2002.124817.
216. Api, A.M.; Belsito, D.; Botelho, D.; Bruze, M.; Burton, G.A.; Buschmann, J.; Cancellieri, M.A.; Dagli, M.L.; Date, M.; Dekant, W.; et al. RIFM fragrance ingredient safety assessment, dl-limonene (racemic), CAS Registry Number 138-86-3. *Food Chem. Toxicol.* **2022**, *161*, 112764. https://doi.org/10.1016/j.fct.2021.112764.
217. Kim, Y.W.; Kim, M.J.; Chung, B.Y.; Bang, D.Y.; Lim, S.K.; Choi, S.M.; Lim, D.S.; Cho, M.C.; Yoon, K.; Kim, H.S.; et al. Safety Evaluation And Risk Assessment Of d-Limonene. *J. Toxicol. Environ. Health-Part B-Crit. Rev.* **2013**, *16*, 17–38. https://doi.org/10.1080/10937404.2013.769418.
218. Eriksson, T.B.J.; Isaksson, M.; Engfeldt, M.; Dahlin, J.; Tegner, Y.; Ofenloch, R.; Bruze, M. Contact allergy in Swedish professional ice hockey players. *Contact Dermat.* **2024**, *90*, 574–584. https://doi.org/10.1111/cod.14529.
219. Hennighausen, I.; Muhlenbein, S.; Pfutzner, W. Immediate-type allergy to d-limonene and anethole in toothpaste. *Contact Dermat.* **2024**, *early view*. https://doi.org/10.1111/cod.14570.
220. Newton, J.; Ogunremi, O.; Paulsen, R.T.; Lien, M.; Sievers, M.; Greenway Bietz, M. A cross-sectional review of contact allergens in popular self-tanning products. *Int. J. Women's Dermatol.* **2024**, *10*, e134. https://doi.org/10.1097/jw9.0000000000000134.