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Toxicity and therapeutic applications of citrus essential oils (CEOs): a review

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ABSTRACT

Citrus essential oil (CEO) is obtained from the fruit of Genus *Citrus*, a flowering plant shrub in the family of the Rutaceae (*Eremocitrus* or *Microcitrus*) and extensively used in food, chemical industry, and traditional medicinal treatment owing to its pleasant aroma, antioxidant, and antiseptic properties. This review presents a botanical description, distribution, traditional uses, chemical composition, bioactive components, and the therapeutic uses as well as toxicological effects of the CEO. The objective was achieved via a comprehensive literature search of electronic databases such as Science Direct, PubMed, Web of Science, Wiley, ACS, Springer, Taylor and Francis, Google Scholar, SCOPUS, conference proceedings, thesis, and books until 2022 for publications. Citrus essential oils and their constituents are extracted and isolated either from the fruit peels, seeds, leaves, or flowers of the citrus plants. A comparative study of the sources of CEO confirmed its origin, ethnopharmacological and therapeutic uses. Over 2000 secondary metabolites have been isolated, with the main active constituents: being terpenes, monoterpenes, sesquiterpenes, and diterpenes. A comprehensive literature review revealed vast therapeutic benefits of CEO. Incomplete data report on *in vitro* and *in vivo* trials especially, on dosage, positive and negative control groups, intervention time, toxicity studies, phytochemical profiling, and clinical trials seem to be a knowledge gap.

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Introduction

The genus citrus (Rutaceae) is among the oldest and most grown crops all over the world due to its numerous benefits. The earliest record of citrus cultivation can be traced back to 2100 BC.^[1–3] Though the origin of citrus is still uncertain, it has been reported to have its origin in Southeast Asia.^[4] The family Rutaceae consists of 155 genera with over 1600 species, with the genus *Citrus* consisting of 17 species, and the popularly cultivated ones being lemons (*Citrus lemon*), oranges (*C. sinensis*), limes (*C. aurantifolia*), and tangerines/mandarin (*C. reticulata*).^[5] The products of different species of citrus are used as food and their essential oil is used in the production of perfumes, soaps, and other skin products.^[6] Citrus essential oils contain secondary metabolites which protect the citrus plant against insects, herbivores, and microorganisms.^[7,8] These essential oils are formed specifically through two known biosynthetic pathways; Mevalonate and phenylpropanoid pathways.^[9] In recent times, citrus peel and leaf essential oils are used in the production of air fresheners, pharmaceuticals, cleaning agents, soft drinks, solvents, and fine perfumes.^[10] Citrus is the major source of essential oils which

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have been used from ancient times till date.^[11] The term “essential” was first coined by Paracelsus in the 16th century when he named the active constituent of a drug, “Quinta essential”.^[12] Citrus essential oils are aromatic volatile liquids obtained from various parts of the citrus plant including buds, leaves, flowers, seeds, twigs, peels, seeds, and roots.^[13,14] Essential oils from citrus have therapeutic uses including their ability to reduce anxiety and depression, relieve pain, heal wounds, and treat fungal and bacterial infections.^[15] They are easily extracted by steam distillation due to the volatile nature of the oil.

Essential oils are highly volatile and consist of a mixture of organic compounds such as natural terpenes, monoterpenes, sesquiterpenes, diterpenes, and others with characteristic odor or aroma resulting from the plant’s secondary metabolites (γ -terpinene, linalool, linalyl acetate, α -terpineol, geranyl acetate, terpinolene, and β -pinene) (Figure 1).^[7] These essential oils are usually extracted by steam distillation.^[16] Citrus essential oils consist of more than 2000 organic components with monoterpenes, and sesquiterpenes as well as their oxygenated derivatives, aliphatic aldehydes, alcohols, and esters constituting the major fractions.^[17] Despite the numerous benefits of citrus essential oils, some of them (*C. aurantifolia* essential oil) have been tagged with various toxic reactions like necrosis and injurious inflammatory response in rats.^[18] To fully maximize the health benefits of citrus essential oils, there is a need for an extensive and detailed review of the biological properties, therapeutic potentials, and toxicology, specifically those extracted from various species of the *Citrus* genus. A comprehensive review of the various CEOs will increase the scientific knowledge of the *Citrus* genus and highlight the prospects of CEOs production, application, and research. Therefore, this review brings to the fore the biological activities (medicinal uses and toxicity), and some recent discoveries in Citrus Essential Oils.

Methodology

In this review, we carefully searched, compiled, and reviewed articles on the composition, biological activities, and toxicity of various essential oils from different Citrus species published over the past 30 years (1998 to 2022). The review focused on the following citrus species, lime (*Citrus aurantifolia*), lemon (*Citrus × limon* L.), sweet orange (*Citrus sinensis*), bitter orange (*Citrus aurantium*), mandarin orange (*Citrus reticulata* Blanco cv. *clementine*), Bergamot orange (*Citrus bergamia*), Kumquat (*Citrus japonica/fortunella*), grapefruit (*Citrus ×paradisi*), and yuzu (*Citrus junos*). Articles indexed in electronic databases such as Google Scholar, PubMed, Science Direct, Web of Science, Wiley, ACS, Springer, Taylor and Francis, SCOPUS, conference proceedings, thesis, and books until 2022 were meticulously reviewed. The search keywords used were “citrus,” “citrus essential oils,” “biological activities,” “health benefits,” “antimicrobial,” “anti-inflammatory,” “antioxidant activity,” “histo-protective,” “larvicidal,” “insecticidal,” “aromatherapy,” “cytotoxic,” “phototoxicity,” “toxicity and safety.” Scientific publications were retrieved based on the above-listed search keywords and terms. The main focus was on Citrus essential oils (CEOs) and their major constituents isolated either from the fruit peels, leaves, flowers, and seeds of the various citrus species of the genus citrus listed above. All articles published on the application of citrus essential oils in human clinical studies, *in vitro* cell cultures, and *in vivo* animal experiments were included. Articles involving the use of extracts from different parts of citrus plants were excluded.

Composition of the citrus essential oil

Essential oils are a complex mixture of natural compounds with about 20 to 60 components existing in different concentrations. Essential oils mostly contain major constituents which give them their biological and chemical properties. These constituents are grouped into two biosynthetic origins. These are terpenes and terpenoids, with aliphatic constituents characterized by low molecular weight.^[16] Most citrus species produce essentials oils with major aromatic compounds like limonene, β -myrcene, α -pinene, p -cymene, β -pinene and terpinolene (Figure 1).^[19,20] Essential oils from the same

or different citrus fruits may have great differences in their compositions due to their origin, climate, age, and the type of extraction method used.^[21,22] D-limonene is a major component of monoterpenes which is present in sweet oranges, bitter oranges, mandarin, and grapefruit.^[23] Bitter orange leaf and flower essential oil contain linalyl acetate and linalool as major components (Figure 1).^[24] Mostly, similar constituents of citrus essential oil are found in different *citrus* spp. Forty-nine^[25] volatile organic compounds have been reported in 11 species: (*C. sinensis* (sweet orange), *C. reticulata* (mandarin), *C. paradisi* (grapefruit), *C. grandis* (pummelo), *C. limon* (lemon), *C. medica* (citron), *Citrus reshni* Hort. ex Tanaka, *C. aurantifolia* (lime), *C. aurantium* (bitter orange), *C. bergamia* (bergamot orange), and *C. junos* (yuzu)). Ninety percent (90%) of these compounds are terpenoids, even though about 50% of the volatile compounds found in citrus fruit peels are non-terpenoid.^[26] More than 400 volatiles of different chemical natures have been exclusively described in only one of these species as a result of geographical location. Some of these compounds have been useful as species biomarkers.^[26] The ethnopharmacological relevance of these phytochemicals is one of the reasons behind the compilation of this review which highlights their overwhelming therapeutic properties. A comprehensive review of the chemical composition of citrus essential oil obtained mainly from the rind, leaves or flowers reveals over one thousand volatile and semi-volatile compounds that have been documented during the last two decades.^[26] In this review, our main interest is in the therapeutic properties of these compounds.

Extraction of citrus essential oils (CEOs)

Most essential oils are produced as secondary metabolites which are normally stored in oil glands or sacs present in different parts of citrus plants such as the leaf, peels, and cuticles of fruits.^[27] Essential oils in different parts of plants are commonly obtained by different extraction methods. However, in commercial production, they are either obtained by cold-pressing or hydro-distillation process techniques. Over the years, different methods have been used in the extraction of CEOs and each method has presented its setbacks. This has led to the development of new methods and modification of the old ones to increase extraction yield, and minimize extraction time to preserve both volatile and nonvolatile compounds. One of the common methods is the hydro-distillation technique which involves boiling the leaves or peels to release the essential oil through evaporation. Moreover, steam distillation has also been used in the extraction of CEOs. In steam distillation, the leaves or fruit peels of citrus were exposed to steam and it released the essential oils in the form of vapor which was subsequently condensed and collected in vessels.^[27] Microwave hydro-diffusion and gravity methods are simple and new techniques used in extracting citrus essential oils in laboratories and industries.^[10] A bio-refinery method was also developed for orange peels by combining microwave and ultrasound which recycles the water of the peels resulting in the rapid attainment of high-value compounds.^[28] In a study, essential oil from *C. aurantifolia* fruit peels was extracted by hydro-distillation using the modified Clevenger apparatus.^[29] Also, microwave-assisted steam distillation (MASD) and steam distillation (SD) have been used to extract appreciable quantities of *C. sinensis*, *C. limon*, and *C. reticulata* essential oils.^[30]

Biological effects of citrus essential oils

Some of the isolated components of some citrus essential oils (CEOs) have been used individually and have shown numerous biological activities, notably, antimicrobial, anti-tumor, anti-inflammatory, antioxidant, insecticidal effects, and others.^[31] D-limonene, a major constituent of most CEOs has been reported to possess anti-inflammatory, antioxidant, and anti-carcinogenic activities.^[32,33] Despite the toxic reports about d-limonene, it has demonstrated anti-carcinogenic properties in lung cancer cells.^[34] For example, Benzopentaphene-induced cancer mice given d-limonene subcutaneously had delayed onset of lung tumor and therefore prolonged survival.^[35] Another study has corroborated the anti-cancer properties of D-limonene found in many citrus peel oils.^[36] D-limonene

has demonstrated that it could inhibit (MIC 0.31 $\mu\text{L.mL}^{-1}$) *Propionibacterium acnes*, which is the main pathogen in acne and is more potent than triclosan.^[37] Additionally, D-limonene and linalool derived from the peels of citrus fruits are reported to be specifically toxic in all the life stages of fleas.^[38] Again, linalool has shown good antifungal, anticancer, sedative, antidepressant, and pesticide activities.^[39,40] Also according to a study elsewhere, γ -Terpinene exhibits antioxidant activity, while α -terpineol exhibits anti-carcinogenic activity, and terpinolene possesses antioxidant properties.^[41,42] Studies elsewhere have reported that β -pinene possesses anti-proliferative and cytotoxic activities.^[43,44] Geranyl acetate also has anti-inflammatory and anti-fungal activities.^[45] The following subsections discuss details of the biological activities of various types of citrus essential oils. Carvone, which is a major constituent of citrus essential oil exhibits multiple pharmacological properties such as antibacterial, antifungal, antiparasitic, antineuraminidase, antioxidant, anti-inflammatory, and anticancer activities.^[46,47] Due to its remarkable biological effects in vitro and in vivo, the component being explored: for disinfection of food packaging, as poly(lactic acid) films, antibacterial coating (ppCar), could be an epochal candidate in drug development.^[47]

Antibacterial and antiviral

Treatments for most bacterial infections do exist but their efficacies over time have been compromised by antimicrobial resistance, thus, necessitating the search for new antimicrobial agents/drugs, especially those derived from plants and animal sources.^[46,47] Some Citrus essential oils over the years have exhibited antibacterial properties against different types of bacteria, and their antimicrobial activities have been comparatively analyzed and confirmed as an alternative to synthetic antimicrobials.^[48] Essential oil of *Citrus aurantifolia* (Lime) Swingle has shown significant antibacterial activity against *Escherichia coli*, *Bacillus subtilis*, *Enterococcus durans*, *Listeria monocytogenes*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Citrobacter* spp, *Klebsiella pneumoniae*, *Shigella flexnerii*, *Serratia marcescens* and *Salmonella typhi*.^[25,49,50] A recent study also reported the antibacterial effect of *C. aurantifolia* essential oil on four selected bacteria (*Azotobacter chroococcum*, *Micrococcus luteus*, *Serratia marcescens*, and *Priestia megaterium*) which are known to drive the decay of apples, pears, potatoes, and Kohlrabi.^[51] This promising result reveals the usefulness of CEOs in food preservation. Recently, a study reported that *C. aurantifolia* essential oil has shown a significant inhibitory effect on the growth of *Candida glabrata* and *Candida tropicalis* which are known to cause decay in fruits and plant products, specifically on apple, pear, potato, and Kohlrabi.^[51] In another interesting study, microcapsules were prepared using *C. aurantifolia* essential oil and alginate gelatin biopolymers cross-linked with calcium chloride (CaCl_2) using Tween 80 emulsifier. The *C. aurantifolia* essential oil microcapsules exhibited a marked growth inhibitory effect on *S. aureus*, *S. epidermidis*, *K. pneumoniae*, and *E. coli*.^[52] Also, crude extract of lemon peel essential oil inhibited the growth of some pathogenic bacteria.^[53] Another study reported the antimicrobial effect of the essential oil of lemon and attributed the activity to the presence of active terpenes, alcohols, aldehydes, and esters.^[54] Other studies have corroborated the anti-bacterial activity of lemon essential oil against *P. aeruginosa*, *Lactobacillus curvatus*, *E. amnigenus*, *Mycobacterium smegmatis*, *Micrococcus luteus*, *Proteus vulgaris*, *Enterobacter gergoviae*, *S. aureus*, *S. xylosus*, *S. carnosus*, *Listeria monocytogenes* and *L. sakei*.^[55,56] Like lemon, bergamot essential oil has shown effective antibacterial activity against *Campylobacter jejuni*, and *E. coli* O157 and linalool a major component of the bergamot essential oil confirmed its anti-bacterial activity by inhibiting the growth of *S. aureus* and *L. monocytogenes*.^[57] As expected, a different study has also reported that citrus orange essential oil can inhibit the growth of *E. coli* O457: H7 and *Salmonella* spp.^[58] Also, cold-pressed Valencia orange (*C. sinensis*) oil inhibited methicillin-resistant *Staphylococcus aureus* strains and vancomycin intermediate-resistant *S. aureus* on skin infected keratinocytes without any harmful effect on the keratinocytes.^[59] Additionally, *C. aurantium* leaf and flowers essential oils have displayed good antibacterial activity against six bacterial species namely, *Micrococcus luteus*, *Enterococcus faecium*, *E. coli*, *S. enterica*, *Listeria monocytogenes* and *Pseudomonas aeruginosa*.^[60] Essential oil from *Citrus aurantium* L. (Neroli) has

exhibited an antibacterial effect by inhibiting the growth of the following bacteria *Bacillus subtilis*, *B. cereus*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Micrococcus luteus*, *Listeria monocytogenes*, *Salmonella enteritidis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia* [22,61,62] further confirming its antimicrobial potency. In addition, studies elsewhere have touted the antimicrobial activity of bitter orange essential oil which inhibited the growth of *Penicillium digitatum* and *Penicillium italicum*. [61,63] Sweet orange essential oil has also been reported to inhibit the growth of some bacteria including *S. aureus*, *Listeria monocytogenes*, *Vibrio parahaemolyticus*, *Salmonella typhimurium*, *Escherichia coli* and *Pseudomonas aeruginosa*. [64–66] A different study also reported on the antibacterial activity of the fruit peels of *Citrus x sinensis* L. Osbeck ‘Tarocco’ essential oil against *S. aureus*, *E. coli*, and *B. subtilis*. [67]

Mandarin orange essential oil was able to inhibit the growth of certain bacteria which includes *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. [67–69]

Also, the mandarin orange (*C. reticulata*) and lime (*C. aurantifolia*) essential oils together with gentamicin showed robust antibacterial activity against clinical isolates of both methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA). [70] Moreover, Grape fruit (*Citrus paradisi* ‘toronja’) essential oil has also shown substantial antibacterial activity against *Bacillus cereus*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudococcus* sp., *Salmonella thyphimurium*, *Shigella flexneri*, and *Staphylococcus aureus* in other studies. [71,72]

The essential oil of Kumquat (*Fortunella crassifolia* Swingle) has also demonstrated strong antibacterial activity against *E. coli*, *Staphylococcus aureus*, *Bacillus cereus*, *Bacillus subtilis*, *Lactobacillus*

Table 1. Antibacterial activity of the essential oils of various citrus species.

Biological activity	Citrus species	Bacteria type	The activity of citrus spp	References
Anti-bacterial	<i>C. aurantifolia</i>	<i>Escherichia coli</i> , <i>Bacillus subtilis</i> , <i>Enterococcus durans</i> , <i>Listeria monocytogenes</i> , <i>Staphylococcus epidermidis</i> , <i>Staphylococcus aureus</i> , <i>Citrobacter</i> spp, <i>Klebsiella pneumoniae</i> , <i>Shigella flexnerii</i> , <i>Serratia marcescens</i> and <i>Salmonella typhi</i>	Growth inhibition Growth inhibition	[25, 25, 50, 52]
		<i>Azotobacter chroococcum</i> , <i>Micrococcus luteus</i> , <i>Serratia marcescens</i> , and <i>Priestia megaterium</i>		
		<i>S. aureus</i> , <i>S. epidermidis</i> K. pneumoniae and, <i>E. coli</i>		
	<i>C. sinensis</i>	<i>E. coli</i> O457:H7 and <i>Salmonella</i> spp	Growth inhibition	[58,5964–67]
		<i>S. aureus</i> , <i>Listeria monocytogenes</i> , <i>Vibrio parahaemolyticus</i> , <i>Salmonella typhimurium</i> , <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , and <i>Bacillus subtilis</i>		
	-Neroli	<i>Bacillus subtilis</i> , <i>B. cereus</i> , <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Enterococcus faecalis</i> , <i>Micrococcus luteus</i> , <i>Listeria monocytogenes</i> , <i>Salmonella enteritidis</i> , <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> and <i>Klebsiella pneumonia</i>	Growth inhibition	[22,61,62]
	<i>C. aurantium</i> (Bitter Orange)	<i>Micrococcus luteus</i> , <i>Enterococcus faecium</i> , <i>E. coli</i> , <i>S. enterica</i> , <i>Listeria monocytogenes</i> and <i>Pseudomonas aeruginosa</i>	Growth inhibition	[60]
	<i>C. paradisi</i> (Grapefruit)	<i>Bacillus cereus</i> , <i>Enterococcus faecalis</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumonia</i> , <i>Pseudococcus</i> sp., <i>Salmonella thyphimurium</i> , <i>Shigella flexneri</i> , and <i>Staphylococcus aureus</i>	Growth inhibition	[71,72]
	Kumquat (<i>Fortunella Crassifolia</i>)	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , <i>Bacillus cereus</i> , <i>Bacillus subtilis</i> , <i>Lactobacillus bulgaricus</i> , <i>Salmonella typhimurium</i> , <i>Bacillus laterosporus</i> .	Growth inhibition	[73]
	<i>C. bergamia</i>	<i>Campylobacter jejuni</i> , and <i>E. coli</i> O157	Growth inhibition	[57]
Antiviral Effect		<i>S. aureus</i> and <i>L. monocytogenes</i>		
	<i>C. reticulata</i> Blanco (mandarin)	<i>Escherichia coli</i> , <i>Bacillus subtilis</i> , <i>Pseudomonas aeruginosa</i> and <i>Staphylococcus aureus</i> .	Growth inhibition	[67,68,74]
	<i>C. lemon</i>	<i>P. aeruginosa</i> , <i>Lactobacillus curvatus</i> , <i>E. amnigenus</i> , <i>Mycobacterium smegmatis</i> , <i>Micrococcus luteus</i> , <i>Proteus vulgaris</i> , <i>Enterobacter gergoviae</i> , <i>S. aureus</i> , <i>S. xylosus</i> , <i>S. carnosus</i> , <i>Listeria monocytogenes</i> and <i>L. sakei</i>	Growth inhibition	[55,56,63]
	<i>C. reshni</i>	Avian influenza A (H5N1)	Growth inhibition	[75]

bulgaricus, *Salmonella typhimurium*, *Bacillus laterosporus*.^[73] These results as summarized in Table 1 demonstrates that the CEOs have exhibited strong detrimental effects on the growth and morphological structure of different bacteria and thus, could be used as natural food preservatives against bacteria or fungus. Interestingly, mandarin orange (*Citrus reshni Hort. ex Tanaka*) peels essential oil has also exhibited an antiviral effect against the avian influenza virus (H5N1 sub-type) as reported by Nagy and coworkers.^[2018,75] The application of CEOs might be vital in the treatment of infections of both susceptible and resistant bacteria while preventing bacterial resistance, and they can also be used with a low dose of already-known antibiotics such as gentamicin and vancomycin to produce a synergistic effect which will significantly reduce the menace of antimicrobial resistance (AMR). There is therefore enough data to support the long-held perception that essential oils from the genus citrus exhibit antimicrobial (antibacterial) activities, and can possibly serve as food preservation agents and as an alternative to the existing antibacterial therapies.

Antifungal and antihelminthic

Fungal diseases are difficult to diagnose due to nonspecific clinical features and are often difficult to treat because, unlike bacteria, fungi are eukaryotes and therefore agents that kill fungi may also be harmful to the individual.^[76] Therefore, treatment must be specific, and the need to develop new anti-fungal agents is of great interest to scientists. This is because there has been an increase in life-threatening systemic fungal infections over the past two decades with common ones being candidiasis, mycosis, aspergillosis, and others.^[77] Recent reports have shown that CEOs could potentially be novel anti-fungal agents. Some citrus essential oils have exhibited both anti-helminthic and anti-fungal properties, hence could be a promising agent for the treatment of various helminthic and fungal infections. Studies elsewhere have posited that *C. aurantifolia* essential oil significantly inhibits the growth of *Aspergillus flavus* (80% inhibition). Additionally, it inhibits the growth of other fungi including *Rhizopus stolonifera*, *Collectotrichum gloeosporioides*, *Aspergillus niger*, *Aspergillus parasiticus*, *Rhizoctonia solani*, *Candida albicans* and *Candida parapsilosis*.^[25,50]

Lemon (*C. limon*) essential oil has also been shown that it could significantly inhibit fungal growth ($\geq 1.25 \mu\text{L/mL}$) through the agar dilution method and vapor phase method against *Aspergillus parasiticus* and *Penicillium chrysogenum*.^[78] Bergamot essential oil in a chitosan-based film showed a significant dosed-dependent inhibitory effect on the growth of *Penicillium italicum*.^[79] Confirming the anti-fungal activity of Bergamot essential oil, other studies have reported its robust inhibitory activity against the growth of the following fungi *Hanseniaspora guilliermondii*, *Debaryomyces hansenii*, *Kluyveromyces fragile*, *Rhodotorula rubra*, *Candida albicans*, *Aspergillus Niger*, *A. flavus*, *Penicillium italicum*, *Fusarium solani*, *F. sporotrichioides*, *F. oxysporum*, *Culvularia lunata*, *Verticillium dahlia*, *Phomosis sp*, *Phoma sp*, and *myrothechium*.^[57,80–82] Furthermore, another study reported that the bergamot essential oil has an antifungal effect against dermatophytes belonging to genera *Trichophyton*, *Microsporum* and *Epidermophyton*, hence could serve as a potential agent for treating dermatophytosis in animals.^[83,84] Navel orange peel essential oil has been used to control the growth of mold in potatoes and also provided significant protection against *Aspergillus Niger*, *Penicillium funiculosum*, and *Rhizopus oryzae*.^[85] Additionally, the essential oils of the leaves of navel orange exhibited exceptional antifungal activity against *Trichoderma viride* ^[60] (Table 2). The bitter orange (*C. aurantium*) essential oil has also exhibited growth inhibition in *Penicillium digitatum* and *Penicillium italicum*.^[61,63] As reported by several studies, different species of fungi including *Aspergillus flavus*, *A. fumigatus*, *A. Niger*, *Alternaria alternata*, *cladosporium herbarum*, *curvularia lunata*, *Fusarium oxysporum*, *helminthosporum oryzae*, *Penicillium chrysogenum*, *penicillium overrucosum* and *trichoderma viride* were susceptible to *C. sinensis* essential oil.^[55,86,87] *Citrus aurantium L.* essential oil has reportedly shown significant inhibition against the growth of *Aspergillus Niger*, *A. flavus*, *A. nidulans*, *A. fusarium graminearum*, *F. oxyporum*, *C. albicans*, and *Alternaria alternata*.^[61,62,88,89] *C. reticulata* essential oil also showed antifungal properties by inhibiting the growth of *Aspergillus flavus* and it was found to cause 40% growth inhibition^[93] (Table 2). The mandarin

Table 2. Antifungal activity of the essential oils of various Citrus species.

Biological activity	Citrus species	Fungi Type	Activity	References
Antifungal	<i>C. sinensis</i> (Sweet Orange)	<i>Aspergillus flavus</i> , <i>A. fumigatus</i> , <i>A. niger</i> , <i>Alternaria alternata</i> , <i>cladosporium herbarum</i> , <i>curvularia lunata</i> , <i>Fusarium oxysporum</i> , <i>helminthosporium oryzae</i> , <i>Penicillium chrysogenum</i> , <i>penicillium overrucosum</i> and <i>trichoderma viride</i>	Growth inhibition	[55,86,87]
	Navel Orange	<i>Aspergillus Niger</i> , <i>Penicillium funiculosum</i> , and <i>Rhizopus oryzae</i>	Growth inhibition	[78,85]
	<i>C. aurantifolia</i>	<i>Rhizopus stolonifera</i> , <i>Collectotrichum gloeosporioides</i> ,	Growth Inhibition	[25,50,51]
		<i>Aspergillus niger</i> , <i>Aspergillus parasiticus</i> , <i>Rhizoctonia solani</i> , <i>Candida albicans</i> , and <i>Candida parapsilosis</i>	Growth inhibition	
		<i>Candida glabrata</i> and <i>Candida tropicalis</i>	Growth inhibition	
	<i>C. limon</i>	<i>Aspergillus parasiticus</i> and <i>Penicillium chrysogenum</i>	Growth inhibition	[61,63]
	<i>C. aurantium</i> (Bitter orange/ Neroli)	<i>Penicillium digitatum</i> and <i>Penicillium italicum</i> , <i>Alternaria, alternata</i> , <i>Candida albicans</i> , <i>Rhizoctonia solani</i> , <i>Curvularia lunata</i> , <i>Fusarium oxyporum</i> and <i>Helminthosporium oryzae</i>	Growth inhibition	[61,62,88,89]
	<i>C. reticulata</i>	<i>Aspergillus Niger</i> , <i>A. flavus</i> , <i>A. nidulans</i> , <i>A. Fusarium graminearum</i> , <i>F. oxyporum</i> , and <i>Alternaria alternata</i>	Growth inhibition	[68,90]
	<i>C. bergamia</i>	<i>Hanseniaspora guilliermondii</i> , <i>Debaryomyces hansenii</i> , <i>Kluyveromyces fragile</i> , <i>Rhodotorula rubra</i> , <i>Candida albicans</i> , <i>Aspergillus Niger</i> , <i>A. flavus</i> , <i>Penicillium italicum</i> , <i>Fusarium solani</i> , <i>F. sporotrichioides</i> , <i>F. oxysporum</i> , <i>Culvularia lunata</i> , <i>Verticillium dahlia</i> , <i>Phomosis sp</i> , <i>Phoma sp</i> , and <i>myrothecium</i>	Growth inhibition	[57,79–84]
	<i>C. paradisi</i> (Grape Fruit)	<i>Trichophyton</i> , <i>microsporum</i> , and <i>Epidermophyton</i>	Growth inhibition	[71,72]
		<i>Aspergillus Niger</i> , <i>Candida albicans</i> , <i>Cladosporium cucumerinum</i> , <i>Penicillium digitatum</i> , <i>P. italicum</i> , and <i>P. chrysogenum</i> <i>Candida albicans</i> genum		
Anti-helminthic	<i>C. sinensis</i>	<i>Haemonchus contortus</i> eggs	Growth inhibition	[91,92]
	<i>C. aurantifolia</i>	<i>Haemonchus contortus</i>	Growth Inhibition	

essential oils at the concentration of 0.1 ml/100 ml against the following plant pathogens: *Alternaria alternata*, *Rhizoctonia solani*, *Curvularia lunata*, *Fusarium oxyporum* and *Helminthosporium oryzae*. Percentage reductions in these fungal growths were 84%, 80%, 93%, 42%, and 54% respectively.^[90] Grapefruit essential oil also showed strong antifungal activity against *Aspergillus Niger*, *Candida albicans*, *Cladosporium cucumerinum*, *Penicillium digitatum*, *P. italicum*, and *P. chrysogenum*.^[71,72] (Table 2). *C. sinensis* essential oil exhibited anti-helminthic activity against gastrointestinal nematodes and was found to be five times more potent on *Haemonchus contortus* eggs compared to tea tree essential oil.^[91] Among the common methods or assays used, most of the works include mycelial growth inhibition, minimum inhibition concentration and minimum fungicidal concentration which worked either as a fungitoxic, fungicidal or fungistatic. These studies signify the diverse potential of various CEOs against fungal diseases either of humans, animals, or plants.

Anti-inflammatory and analgesic effects

Inflammation is known to be the underlying cause of most human diseases including hepatitis, wounds, rheumatoid arthritis, some carcinomas, and several other diseases.^[54] Among the discomforts that accompany inflammation is pain which is defined by^[94] as an uncomfortable sensory and emotional experience arising from actual or potential tissue injury and it is a key component of inflammation. Different citrus essential oils (CEOs) have been reported to have promising anti-inflammatory and analgesic properties. Essential oils from *C. limon*, *C. aurantifolia*, and *C. limonia* exhibited anti-inflammatory activity by lowering cytokine production, protein irruption, and cell

Table 3. Anti-inflammatory and analgesic activity of essential oil of various citrus species.

	Citrus species	Model	Mechanism of action	References
Anti-Inflammatory and Analgesic Effect	<i>C. aurantifolia</i>	Carrageenan-induced inflammatory model	Reduced cytokine production, protein extravasation, and cell migration	[95]
	<i>C. aurantium</i>	Acetic acid-induced writhing	Reduced the number of writhes in mice	[100]
	Bitter orange	Double-blind, placebo-controlled group study	Reduction in knee pain intensity and enhanced physical function	[101,102]
	<i>Citrus Limon</i>	Acetic acid-induced writhing	Reduction in the number of writhing	
	<i>Citrus sinensis</i>	formalin-induced nociception in ICR mice	Anti-nociception via dopamine-related activation of the anterior cingulate cortex of the brain and the descending pain inhibitory system	[103,104]
		Carrageenan-induced paw edema	Reduced paw edema volume significantly	
	<i>Citrus bergamia</i>	Carrageenan-induced paw edema	Inhibits IL-8 expression	[96,99]
	<i>Citrus junos</i> (Yuzu)	<i>In vitro</i> anti-inflammatory model using HL-clone 15 cells	Reduction in eosinophil migration Inhibits cytokine production	[105]

mobility in the carrageenan-induced inflammatory model.^[95] Pure limonene was also reported by the same group to exhibit the same effect suggesting the biologically active component of the oil.^[95] Bergamot essential oil *via* carrageenan-induced paw edema model in rats exhibited anti-inflammatory activity with ED₅₀ value of 0.079 mL/kg.^[96] Moreover, the same bergamot essential oil was used as a complementary medicine in managing chronic and neuropathic pain by reducing the perception of pain^[97,98] and this property can be attributed to the presence of bergapten and citropten found in this essential oil which is also known for inhibiting IL-8 expression^[99] (Figure 2, Table 3). Essential oil from *C. aurantium* also exhibited effective anti-inflammatory activity against both acute and chronic inflammation comparable to the standard drug, diclofenac sodium.^[100] The same oil was able to relieve severe knee pain through massaging^[101] and also moderately reduced initial labor pain in primiparous women^[106] (Table 3). The above results indicate that *C. aurantium* oil possesses both central and peripheral antinociceptive effects which support the ethnomedicinal claims of the use of the plant in the controlling of pain and inflammation.^[100] The essential oil extracted from the dried leaves and fruit peels of *Citrus sinensis* demonstrated significant suppression of inflammation-induced edema in rats' hind paws at an optimum dose of 200 mg/kg.^[104] The authors linked the anti-inflammatory activity to the rich stores of β -elemene and sabinene in the leaf and limonene in peels the essential oil.

Essential oil from the leaves of *Citrus limon* demonstrated analgesic activity in rats using acetic acid-induced writhing and the number of writhing was reduced significantly.^[102] Interestingly, the same lemon essential oil-induced analgesic effect *via* dopamine-related activation of the anterior cingulate cortex of the brain and the descending pain inhibitory system.^[103] In another development, essential oil from Yuzu was reported to possess anti-inflammatory properties by reducing eosinophil migration and inhibiting cytokine production, hence a potential agent for treating bronchial asthma.^[105] Most of the anti-inflammatory and anti-nociceptive activities mediated by the various CEOs listed above worked much more effectively on acute pain and inflammation but few works have assessed their efficacy in chronic pain and chronic inflammatory models.

Antioxidant and radical scavenging effect

The study of specific components of essential oils has revealed that different essential oils containing limonene possess radical scavenging and antioxidant activity.^[107] Sweet orange essential oil has been reported to have good radical scavenging activity.^[108] The *Citrus aurantifolia* leaf essential oil also

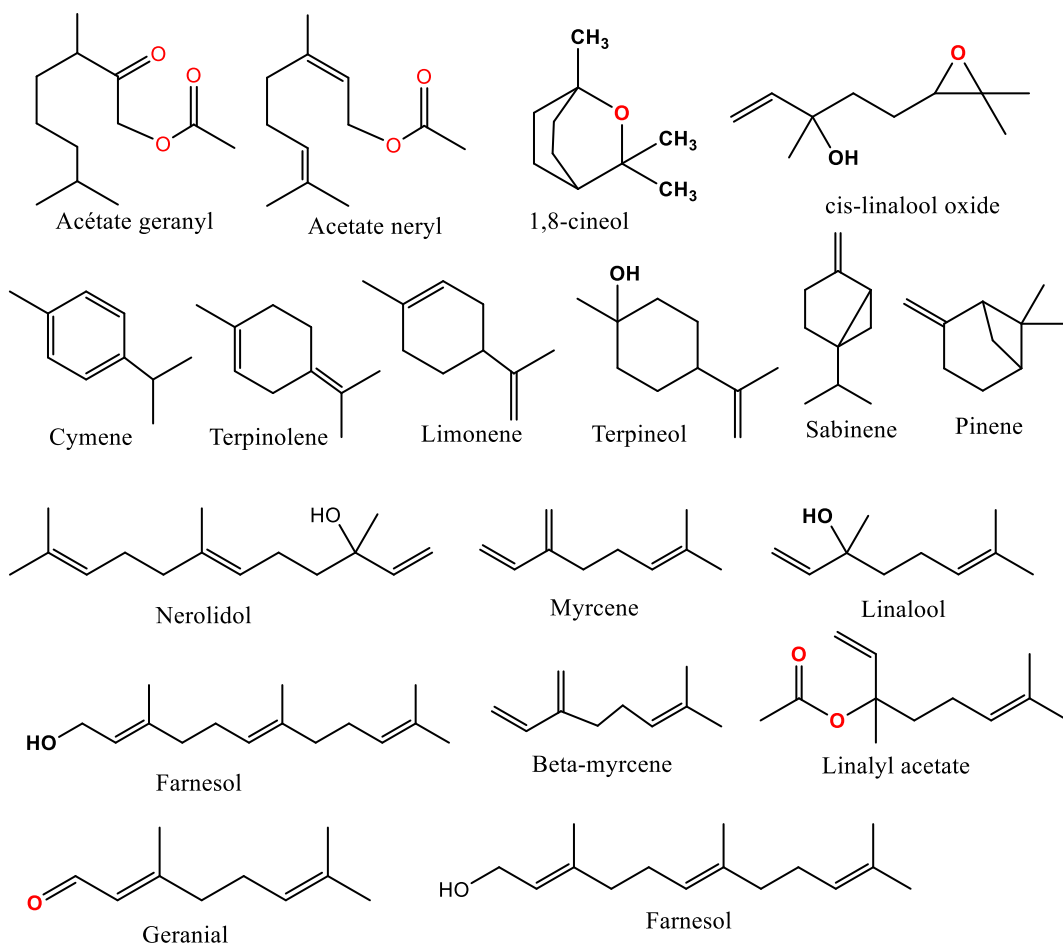


Figure 1. Chemical structures of some major components of citrus essential oil (CEO).

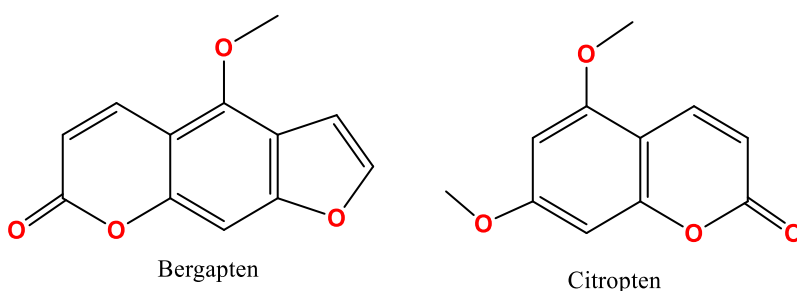


Figure 2. Chemical structure of perceived anti-inflammatory agent in Bergamot essential oil.

showed a significant antioxidant activity which was comparable to that of ascorbic acid.^[109] In another study, the antioxidant effect of citrus fruit peels essential oil was also found to be superior to Trolox in terms of activity.^[110] *C. reticulata* Essential Oil showed a moderate radical scavenging activity^[74] which was mainly attributed to the high d-limonene content^[32] (Table 4). Similarly, bitter orange (*C. aurantium*) essential oil demonstrated good radical scavenging activity and effectively reduced oxidative stress in acute otitis media in rats by increasing the activities of superoxide dismutase (SOD),

Table 4. Antioxidant activity of essential oil of various citrus species.

Biological Activity	Citrus species	The activity/Mechanism of action	Reference
Antioxidant Activity	<i>C. sinensis</i>	DPPH Radical Scavenging/inhibition activity	[108]
	<i>C. aurantium</i>	DPPH Radical scavenging activity Increased activities of SOD, CAT, and GSH	[61,111]
	<i>Citrus aurantifolia</i>	DPPH radical scavenging/inhibition activity	[109]
	<i>Citrus limon</i>	Increased Reduced-glutathione (GSH) levels, Nitric Oxide, and hydroxyl scavenging activity	[102]
	Kumquat	DPPH Radical-scavenging activity	[73,112]
	<i>Citrus reticulata</i>	DPPH/ABTS Radical-scavenging activity	[74]
	<i>Citrus junos</i> (Yuzu)	Inhibited the production of Radical Oxygen Species (ROS)	[105]

catalase (CAT) and reduced glutathione (GSH).^[61,111] Bitter orange essential oil rich in d-limonene also showed a good radical-scavenging activity^[22] (Table 4). Both the antioxidant and radical scavenging effect exhibited by the bitter orange essential oil were attributed to the substantial amount of d-limonene present in the oil.^[32]

The lemon essential oil also showed remarkable antioxidant activity by increasing reduced glutathione (GSH) levels as well as increased catalase, superoxide dismutase, and glutathione peroxidase activities in mouse hippocampus but reduced the levels of lipid peroxidase and nitrile content.^[102] In another development, evaluation *via* the 2,2-diphenyl-1-picrylhydrazyl (DPPH) test also demonstrated that Kumquat essential oil possesses considerable radical scavenging activity.^[73,112] Yuzu citrus fruit peels essential oil is also known to inhibit the production of radical oxygen species due to the presence of limonene^[105] (Table 4).

Anticancer and cytotoxicity

Strong *in vitro* evidence indicates that citrus essential oils (CEOs) have remarkable anti-cancer effects on the growth, invasion, angiogenesis, and metastasis of different tumor cells and thus could be a promising agent for cancer therapy. *C. aurantifolia* essential oil has exhibited a significant anticancer effect by stopping cancer cell mobility, blocking angiogenesis, and inducing tumor suppressor genes.^[113] The same oil inhibited purified isolates (SW480) cells by inducing apoptosis^[114] similar to the other *C. aurantifolia* essential oil found to exhibit an anti-carcinogenic effect by inducing apoptosis in human leucocyte antigen (HLA).^[115] The same essential oil demonstrated a potent anti-benign prostatic hyperplastic effect by reducing serum PSA levels significantly in testosterone-induced prostatic hyperplasia in rats.^[29] *Citrus sinensis* oil showed an anti-tumor effect by suppressing pre-neoplastic hepatic lesions in N-nitrosodiethylamine-induced hepatocarcinogenesis in rats via restoring normal phenotype and junctional complexes.^[116] In the *in vivo* models, the same *Citrus sinensis* essential oil injected into mice through a subcutaneous route 24 h before dibenzo-(α)-pyrene (DPB) considerably reduced tumor incidence to less than 50% after 30 weeks.^[35] Moreover, the anti-carcinogenic effect of *C. sinensis* oil was also confirmed as it induced apoptosis in HL-60 cells with the activity tagged with the presence of citral, decanal, and octanal compounds in the oil.^[115] Interestingly, Sweet Orange essential oil rich in limonene also showed an inhibitory effect on growth and also promoted the death of colon cancer cells in a culture.^[117] It's worth noting that, in another study, it was reported that this same *C. sinensis* essential oil inhibited the growth of lung and prostate cancer cell lines in culture *in vitro*.^[118] Bergamot essential oil was reported to exhibit a cytotoxic effect against SH-SY5Y human neuroblastoma cells and suppressed the rate of their growth by a mechanism quite like apoptotic and necrotic cell death.^[119,120] In a different study, bergamot essential oil stimulated autophagy in SH-SY5Y neuroblastoma cells in an autophagy reflux assay.^[121] Kumquat essential oil remarkably suppressed the proliferation of human prostate cancer (LNCaP) cells by inducing apoptosis.^[122] Grapefruit essential oil like Kumquat oil exhibited cytotoxic effect against human prostate and lung cancer cells *in vitro*.^[123] Moreover, the same grape fruit essential oil also showed a cytotoxic effect against PC-3 and A-549 cancer cells which are

Table 5. Anti-cancer activity of essential oil of various Citrus species.

Biological Activity	Citrus species	Cancer Type	Cancer cells used/Animal model	Activity/Mechanism of action	References
Anti-Cancer /Tumor Activity	<i>Citrus sinensis</i>	Hepatocellular carcinoma	Rats	Suppressed pre-neoplastic hepatic lesions.	[116,118,126]
		Lung and Prostate	Human lung cancer cell line A549 and Prostate cancer cell line 22RV-1	Suppressed the proliferation of A549 cells	
		Colon	SW480 and HT-29	Angiogenesis and metastasis inhibition	
	<i>Citrus aurantifolia</i>	Colon prostate	SW480 cells Rats (<i>in vivo</i>)	Induced apoptosis in SW480 cells	[29,114]
				Suppressed benign prostatic hyperplasia	
	Bergamot (<i>Citrus bergamia</i>)	Neuroblastoma	SH-SY5Y neuroblastoma cells	Inhibited the proliferation of SH-SY5Y Cells	[120,121]
			SH-SY5Y neuroblastoma cells	Modulation of autophagy	
	Kumquat	Neuroblastoma	SH-SY5Y human neuroblastoma cells	Exhibited cytotoxic effect on the cells	[119,122]
		Prostate	Human prostate cancer (LNCaP)	Exhibited antiproliferative and apoptotic	
	Grapefruit	Lungs	HL-60 cells	Induced apoptosis in HL-60 cells	[115,123]
		Prostate	PC-3 and A-549 cancer cells	Exhibited Cytotoxic effect	
	<i>C. reticulata</i>	Lymphoma	DLA cell lines	Inhibition of the growth DLA cells	[125]

prostate and lung cancer cells respectively.^[123] D-limonene which is commonly found in most citrus fruit peel oils also suppressed various cancer cell growths.^[124] *C. reticulata* fruit peels essential oil showed a significant anti-cancer activity against DLA (Dalton's Lymphoma Ascites) cell line in MMT assay^[125] (Table 5).

Aromatherapy, mood, and memory enhancer

Various CEOs have characteristic sweet scents hence playing a vital role in aromatherapy, especially in managing emotional, psychological, and memory disorders which include depression, anxiety, pain, and others.^[127] *Citrus sinensis* essential oil inhaled by chronic unpredictable mild stress model in mice reduced depressed-like behaviors.^[128] Female patients with dental problems who were exposed to sweet orange essential oil aroma before dental surgery showed reduced anxiety when compared to control patients exposed to just air.^[129] The citrus essential oil was found to reduce salivary cortisol and pulse rate in child anxiety.^[130] Moreover, the aroma of sweet orange essential oil reduced the symptoms of anxiety and enhanced the mood of people who were exposed to it.^[131] *Citrus sinensis* essential oil interestingly caused olfactory stimulation by sensations, comfort, and relaxation in humans.^[132] A result of a placebo-controlled double-blind trial revealed that bergamot essential oil inhalation provides good aromatherapy in children and young adolescents who were receiving stem cell infusion.^[133]

Clinical trial results demonstrate that the essential oil of citrus orange reduces anxiety in women during labor.^[134] *Citrus bergamia* essential oil also acted as a moderate sedative by calming and soothing the nervous system and also reduced stress-induced anxiety and depressive-like behaviors in rats.^[135] Lemon essential oil significantly improved memory, concentration, cognitive performance,

attention level, and mood in students during learning.^[136] Interestingly, the same lemon essential oil was reported to have delayed pain-induced increase in acetylcholine in formalin-induced nociception in rats.^[137] *C. aurantium* essential oil improved the mood and also reduced anxiety among chronic myeloid leukemia patients^[138] and also reduced anxiety among pregnant women during the initial stage of labor.^[139] Moreover, anti-anxiety activity through serotonin (5HT) receptor regulation in rats has also been reported.^[140] A recent study revealed interesting findings on the aromatherapy effect of three selected citrus essential oils in the exercise-induced fatigue model in rats. From the study, the aroma of *C. sinensis*, *C. bergamia*, and *C. limon* essential oils was able to reduce exhaustive exercise-induced fatigue in rats that inhaled the CEOs aroma after swimming training.^[141] The study further proved that the CEOs relieved fatigue through muscle protection, enhanced energy supply and glucose-metabolism, and prevention of oxidative stress. The findings from the various studies provide a novel insight into the usefulness of CEOs in aromatherapy and provide a direction for future studies in this area.

Anti-convulsant, hypnotic and anxiolytic action of CEOs

There is strong evidence that essential oils have proven ability to be used as anticonvulsants, anxiolytics, sedatives, and hypnotics agents.^[142] Intriguingly, essential oils of some citrus species also have shown anxiolytic, hypnotic, and anti-convulsive effects and thus could serve as an alternative approach to managing these nervous complications. Bitter orange (*C. aurantium*) essential oil was reported to have enhanced sleeping and hence could be used in managing insomnia and it also showed potent anxiolytic activity in rodents without motor impairment following 15 consecutive days of treatment^[143,144] (Table 6). The same oil has shown an anti-seizure and anti-convulsant effect, hence might also be a natural agent for managing epilepsy and seizures^[144] (Table 6). In this study, an increase in the latency period of tonic seizures in convulsing experimental models was observed at the dose of 0.5 g/kg CEOs but the effect was not dose-dependent. Moreover, the Neroli (*C. aurantium*) essential oil has exhibited anti-seizure and anti-convulsant effects via protection against clonic.^[146] It has been revealed in a different study that the *Citrus sinensis* essential oil had also demonstrated effective anxiolytic activity in Wistar rats^[147] (Table 6). In addition, bergamot essential oil has also demonstrated an anxiolytic effect similar to that of diazepam.^[145]

Anticholinesterase

Inhibition of acetyl cholinesterase and butyrylcholinesterase, which are the key enzymes facilitating the breakdown of acetylcholine, is known to be an inevitable strategy for the treatment and management of neurological disorders like Alzheimer’s disease, myasthenia gravis, ataxia and senile dementia.^[148,149] Some citrus essential oils have exhibited an anticholinesterase effect and hence could be a potential agent for the management of the above-mentioned diseases associated with the nervous system.^[150] Also, essential oils from *C. aurantium*, *C. aurantifolia* and *C. bergamia* exhibited anti-cholinesterase activity against acetylcholinesterase and butyrylcholinesterase.^[151] *Citrus aurantium* exhibited a strong anticholinesterase effect against Silverleaf white fly, *Bamisia tabaci*.^[152]

Table 6. Anti-convulsant, the hypnotic and anxiolytic activity of essential oils of various citrus species.

Biological activity	Citrus species	Activity	References
Anti-Convulsant, Hypnotic and Anxiolytic	<i>Citrus bergamia</i>	Anxiolytic	[145]
	Neroli (<i>C. aurantium</i>)	Antiseizures and anticonvulsant	[146]
	<i>C. aurantium</i>	Antiseizure and Anticonvulsant	[61,143,144]
	<i>C. sinensis</i>	Sedative and hypnotic Anxiolytic	[147]

Histoprotective, gastroprotective, and anti-aging

The exposure of body tissues to certain chemicals, excess of medication or biologically active compounds, radiations as well as the pathogenesis of certain diseases normally result in acute to severe tissue injuries which may lead to organ dysfunction.^[153] Some CEOs have shown tissue-protective (histo-protective) properties and may help in ameliorating certain injurious conditions in tissues. For instance, *C. aurantium* essential oil showed a nephroprotective effect on gentamicin-induced nephrotoxicity at a dose of 200 mg/kg/day for three weeks in rabbits.^[154] The lime essential oil was also reported to have minimized the enlargement of the prostate gland and also caused reversion in testosterone-induced histological changes.^[29] *Citrus reticulata* essential oil reduced bleomycin-induced pulmonary fibrosis in rats.^[155] The presence of d-limonene in *C. aurantium* essential oil gives it gastro-protective and ulcer-healing properties through the increased production of gastric mucus.^[156] Interestingly, a recent study reported that essential oil from the leaf of *C. aurantium* demonstrated a significant anti-collagenase and anti-elastase activities, this reveals its anti-aging potential which was linked to the abundance of major constituents such as linalool, α -terpineol, and linalyl acetate.^[157] This finding highlights the possible application of *C. aurantium* leaf essential oil in cosmetics since this activity together with its antioxidant properties have a direct connection with skin protection. These properties of the *C. aurantium* leaf essential oil can synergistically preserve elastin and collagen proteins from enzymatic degradation, thus rejuvenating the skin, since collagenase and elastase activities accelerate skin wrinkling, sagging and aging.^[158]

Anti-obese, antidiabetic and hypolipemic effect

Obesity and hyperlipidemia/hypercholesterolemia are major contributing factors to the development of diabetes mellitus in humans.^[159] Herbal medicine remains a major alternative therapy in some developing countries and different parts of herbal plants have been used in managing diabetes of which essential oils form a key component.^[160] CEOs have shown anti-obese, hypolipidemic, and anti-diabetic effects as revealed in different studies. Essential oil of *C. bergamia* was able to reduce total and low-density lipoprotein (LDL) cholesterol and triglyceride levels significantly, thus indirectly reducing blood glucose levels^[161] (Table 7). Lime essential oil has displayed a significant body weight reduction and food consumption in ketotifen-induced obese mice, hence it could be used for weight loss and also for the treatment of drug-induced obesity.^[163] The aroma of grape fruit essential oil was posited to have activated the sympathetic nerves which innervate the white adipose tissue (WAT) therefore facilitating lipolysis and subsequent suppression of weight gain.^[164] Furthermore, *C. sinensis* leaves essential oil showed a significant anti-hyperglycemic effect on diabetic rats by significantly reducing fasting blood glucose and hepatic glucose levels^[165] (Table 7). *C. aurantifolia* essential oil reduced fasting blood glucose and low-density lipoprotein but hepatic glycogen concentration and high-density lipoprotein were increased in hyperglycemic rats.^[166] Cold-pressed oil from *C. aurantifolia* inhibits the proliferation of vascular smooth muscle cells (VSMC) via the regulation of PI3K/MAPK signaling pathways.^[167] VSMC proliferation is a major cause of vascular disease and however, regulating and inhibiting signaling pathways may be a recipe for the development of a nature-based therapeutic agent for uncooperative vascular diseases such as hypertension and atherosclerosis.

Therapeutic potential of citrus essential oils on viruses

Viral diseases are exceedingly far-flung infections caused by viruses some of which are not curable such as Human immunodeficiency virus (HIV/AIDS), COVID-19 etc. The recent pandemic is COVID-19 which has lasted for approximately three years and has been tagged as the greatest global health crisis of the 21st century. As the number of cases and mortality continue to increase across the globe and the subsequent economic meltdown and increase in global anxiety have become a major concern worldwide.^[168] Currently, there is no conventional drug available for the treatment of

Table 7. Histoprotective and gastroprotective effects of essential oil of various citrus species.

Biological activity	Citrus species	Mechanism of action	Reference
Histoprotective and Gastroprotective	<i>C. aurantium</i>	Nephroprotective effect on gentamicin induced nephrotoxicity in rabbits gastro protective and ulcer healing through increased production of gastric mucus	[154,156]
Anti-aging	Lime (<i>Citrus aurantifolia</i>)	Restored the histology of testosterone-induced prostatic hyperplasia	[29]
	<i>Citrus reticulata</i>	Reduced bleomycin-induced pulmonary fibrosis in rats	[155,157]
	<i>C. aurantium</i>	Inhibition of collagenase and elastase activities	
Anticholinesterase	Lime (<i>C. aurantifolia</i>)	Strong selective acetylcholinesterase and butyrylcholinesterase inhibitor	[151]
	<i>Citrus aurantium</i>	Strong anticholinesterase effect against <i>Bamisia tabaci</i>	[152]
	<i>Citrus bergamia</i>	Strong selective acetylcholinesterase and butyrylcholinesterase inhibitor	[151]
Antibese, Antidiabetic and Hypolipemic Effect	Lemon balm (<i>C. limon</i>)	Glucose reduction and inhibition of lipid accumulation in <i>in vitro</i> 3T3-L1 adipocytes cells	[162]
	<i>C. bergamia</i>	Reduced total and low-density lipoprotein (LDL) cholesterol and triglyceride	[161]
	Lime	Reduced body weight and food consumption in ketotifen-induced obese mice.	[163]
	Grapefruit	Induced lipolysis and suppressed weight gain	[164]
	<i>C. sinensis</i>	Reduced fasting blood glucose and hepatic glucose levels diabetic in rats	[165]
	<i>C. aurantifolia</i>	Reduced fasting blood glucose and low-density lipoprotein in hyperglycemic rats. Inhibited vascular muscle cell proliferation via PI3K/MAPK pathway	[166,167]

COVID 19 infection, hence the search for therapeutic agents is still ongoing while more lives are lost daily as we wait for new drugs to be developed. However, the COVID-19 virus shares certain features with other viruses whose treatment agents are available, and it will be necessary to also focus on alternative treatments like the use of natural products from plant sources such as essential oils. Essential oils of *J. oxycedrus* spp. *Oxycedrus*, *L. nobilis*, and *T. orientalis* exhibited an inhibitory effect against the cytopathogenesis induced by SARS-COV. [169] Also, essential oil of the Citrus family has been reported to have effective antiviral activity for example *Citrus reshni* (Mandarin orange) exhibited inhibitory activity against the influenza virus (H5N1 sub type). [75] SARS-CoV which shares common features with COVID-19 has been reported to succumb to angiotensin-converting enzyme 2 (ACE 2) inhibitors. [167] Angiotensin-converting enzyme2 (ACE2) has been identified as an entry receptor for SARS-CoV. [170] The injection of SARS-CoV spike protein as well as elevated expression of ACE2 have been implicated in acute lung failure in mice models and this can be inhibited by blockade of the renin-angiotensin pathway. [171] Recent studies show that the COVID-19 spike proteins have a higher affinity for angiotensin-converting enzyme 2 (ACE2) than SARS-CoV on host cells. [172,173] Since the ACE2 receptor plays a vital role in the entry of COVID 19 virus into a host cell, thus ACE 2 receptors are a promising target for the treatment of viral diseases. [173] Interestingly, essential oils from lemon (*Citrus limon*) at the concentration of 12.5 µg/ml and 25 µg/ml showed a significant inhibitory effect on ACE 2 in HT-29 cells. The major components of lemon essential oil specifically, limonene, geraniol, neryl acetate, and citronellol showed significant activity against ACE2 induced by HT-29 cells. [168] These components are also present in appreciable quantities in other citrus species such as lime, bitter orange, and some others. The down regulation of angiotensin-converting enzyme 2 expression in epithelial cells, implies that lemon essential oil could be used to prevent the invasion of COVID-19 virus. [168] Recently, Citrus essential oils has been used to treat acute respiratory syndrome caused by coronavirus. [174,175] In an another development, lemon (*Citrus limon*), sweet orange (*Citrus sinensis*), grapefruit (*Citrus paradisi*), and rosemary cineole (*Rosmarinus officinalis* chemotype 1.8 cineole) essential oils reduced viral loads of hepatitis A virus (HAV) in soft fruits. [176] Recently, virucidal activity of *C. x aurantium* peels essential oil and both D and L-lemonene against

influenza A virus H1N1 exhibited about 99% reduction of virus demonstrating that the oil can be potentially be used as disinfectant against viruses.^[177]

Insecticidal, larvicidal, and biopesticide activities

Over the years, there has been an increased cost in controlling insect-based crop pest and their diseases as well as human diseases transmitting insect-vectors. Besides the transmission of various human, animal, and plant diseases, they also attack crop plants hence affecting their yield and the quality of plant products even when stored.^[178] The use of natural products for controlling pests has been touted as the sure modus operandi to tackle the problem due to its environmentally friendly nature. Different studies have confirmed the effectiveness of various CEOs on diverse species of adult insects, their larvae, and eggs either by being lethal or inhibiting their growth and development. For example, *Citrus sinensis* essential oil exhibited significant activity against the larvae and pupae of housefly (*Musca domestica*), a common vector of cholera, dysentery, and others. In this research, contact toxicity analysis furnished the percentage inhibition rate of oil against housefly pupae as 27.3–72.7% and 46.4–100% for fumigation assay.^[179] It has also been noted that essential oil from *C. aurantium* demonstrated a significant insecticidal effect against four selected storage grain-insects, *Cryptolestes ferrugineus*, *Liposcelis bostrychophila*, *tribolium castaneum* and *Sitophilus granarum*.^[62] The *C. aurantium* fruit peels essential oil also showed a remarkable toxicity effect against the survival of *Aphis punicae* at LC₅₀ of 0.37 µL/mL and *A. illinoisensis* at 0.82 µL/mL in 48 hours period.^[180] This finding provides hope for the effective management of these two pests affecting pomegranate and grapevine in an environmentally-friendly way. The lemon essential oil also exhibited insecticidal effects specifically against the *malaria vector* and *anopheles stephensi*.^[181] Grapefruit essential oil showed 95% lethality on the eggs and larvae of *Anastrepha fraterculus* and *Ceratitis capitata*.^[182] The same oil was able to completely inhibit the viability of *Aedes aegypti* eggs which were exposed at 400ppm and also inhibited the larval development at 100ppm.^[183] Moreover, it also exhibited a potent larvicidal effect on *Anopheles stephensi* at 80 ppm.^[184] *Citrus reticulata* (Mandarin orange) leaf and peels essential oil rich in terpenes, phenols, terpenoids, alkaloids, and flavonoids, showed a substantial larvicidal effect on *Anopheles stephensi* and *Culex quinquefasciatus*.^[185]

Citrus sinensis peels essential oil exhibited a toxic effect against the larvae of the yellow fever mosquito *Aedes aegypti* vector.^[186] *Citrus aurantium* and *Citrus sinensis* essential oils were effective larvicides of *Anopheles labranhiaie*.^[187] *Citrus limon* (lemon) essential oil is toxic to *Spodoptera littoralis*.^[188] *C. limon*, *C. aurantium* and *C. sinensis* essential oils have individually shown larvicidal effects against *Ceratitis capitata* (Diptera: Tephridae) larvae^[189] (Table 8). The citrus essential oils obtained from the peels of *C. limon*, *C. sinensis* and *C. paradisi* showed larvicidal activity against *Aedes albopictus* (Diptera: Culicidae)^[190] (Table 8). *Citrus sinensis* Osbeck displayed a promising toxic activity as a biopesticide against cereal leaf beetles (*Oulema melanopus*) and hence can be used as a pesticide among cereal crops.^[192] Interestingly, the biopesticidal effect of *Citrus sinensis* (L.) Osbeck and *Citrus paradisi* (Macfarlane) essential oils were also confirmed to have a remarkable inhibitory effect (mortality) on *Tribolium castaneum* Herbst (Coleoptera: Tenebrionidae).^[3] In this work, the oviposition deterrence activity of the essential oils significantly increased as concentrations of the oils were increased from 500 to 2500 ppm. Essential oils of *C. sinensis*, *C. aurantium* and *C. limon* (Sicilian lemon) rich in D-limonene showed significant pesticidal effects against *D. brevipes*, the Sicilian lemon oil exhibited the highest rate of mortality in the *D. brevipes* compared to the other citrus species^[193] (Table 8). Based on the above findings, *C. limon* was tested as larvicidal against the third-stage larvae of *Aedes aegypti* and molluscicide against the snail *Biomphalaria glabrata*. Lethal concentration (LC₅₀) of larvicidal activity and molluscicide, at 15.48, and 13.05 mg·L⁻¹ respectively.^[191] Moreover, a recent study reveals that essential oil from the leaves and peels of *C. limon* displayed a significant larvicidal effect on the larvae of *Culex quinquefasciatus* and *anopheles stephensi*.^[185] This attests to the fact that *C. limon* could be a potential larvicidal and molluscicidal agent and could be used to control malaria, leishmaniasis and cercaria insect vectors. The use of conventional pesticides and insecticides over time

Table 8. Insecticidal and larvicidal activity of essential oil of various citrus species.

Biological Activity	Citrus species	Type of insects	Biological Activity	References
Insecticidal and Larvicidal	<i>Citrus sinensis</i>	<i>Anopheles labranhiaie</i>	Larvicide	[186,187,189,190]
		<i>Aedes aegypti</i>	Larvicide	
		<i>Ceratitis capitata</i>	Larvicide	
		<i>Aedes albopictus</i>	Larvicide	
	Grape fruit	<i>Anastrepha fracterculus</i> and <i>Ceratitis capitata</i>	Shown 95% lethal to the eggs and larvae.	[182–184]
		<i>Aedes aegypti</i>	Inhibition of viability of eggs and larvicidal	
		<i>Anopheles stephensi</i>	larvicidal effect	
		<i>Aedes albopictus</i>	Insecticidal	
	<i>C. aurantium</i>	<i>Cryptolestes ferrugineus</i> , <i>Liposcelis bostrychophila</i> , <i>tribolium castaneum</i> and <i>Sitophilus graniarum</i> , <i>Aphis punicae</i> and <i>A. illinoisensis</i>	Insecticidal	[60,180,187,189]
		<i>Anopheles labranhiaie</i>	Insecticidal	
		<i>Ceratitis capitata</i>	Larvicidal	
		<i>malaria vector</i> and <i>anopheles stephensi</i>	Larvicidal	
	<i>Citrus limon</i>	<i>Spodoptera littoralis</i>	Larvicidal	[181, 185, 188, 188, 190, 191, 191]
		<i>Ceratitis capitata</i>	Larvicidal	
		<i>Aedes albopictus</i> , and <i>Aedes aegypti</i>	Larvicidal	
		<i>Biomphalaria glabrata</i>	Molluscicide effect	
		<i>Culex quinquefasciatus</i> and <i>anopheles stephensi</i>	Larvicidal	
		beetles (<i>Oulema melanopus</i>)	Pesticidal/Insecticidal	
Biopesticide	<i>C. sinensis</i>	<i>Tribolium castaneum</i>	Insecticidal/Pesticidal	[3,179,192,193]
		<i>D. brevipipes</i>	Pesticidal/Insecticidal	
		<i>Musca domestica</i>	Larvicidal/Insecticidal	
		<i>Tribolium castaneum</i>	Insecticidal	
	<i>C. paradisi</i>	<i>Culex quinquefasciatus</i> and <i>anopheles stephensi</i>	Larvicidal	[3]
	<i>C. reticulata</i>	<i>D.brevipes</i>	Pesticidal/Insecticidal	[185]
	<i>C. aurantium</i>	<i>D.brevipes</i>	Pesticidal/Insecticidal	[193]
	<i>C. limon</i> (Silician lemon)	<i>D.brevipes</i>	Pesticidal/Insecticidal	[193]

has led to resistance in some insect species coupled with a negative impact on the environment, especially on the ecosystem, and possibly poisoning of some food crops and their products.^[31] Thus, from the studies reviewed above, CEOs could be a potential insecticidal/ pesticidal agent with high efficacy, specificity, and yet friendly to the environment, specifically safe for humans, food crops, and the entire ecosystem.

Phototoxicity and toxicity of citrus essential oils

Predominantly, CEOs are reported to be nontoxic, non-carcinogenic, and non-mutagenic but few works revealed mild toxicity which was mainly phototoxic effects of some CEOs.^[33] Bergamot, lime, and bitter orange essential oils have been reported to have caused low to moderate phototoxicity and skin irritation or sensitizing in rabbits and mice.^[194] Bergapten and furocoumarins present in some CEOs are the main polycyclic molecules that absorb ultraviolet photons, store them for a while, and then release them in a burst onto the skin resulting in phototoxicity.^[33] Expressed bergamot essential oil triggered severe photo-dermatotoxic effects on hairless mice and pigs.^[195] The distilled oils are normally not phototoxic but the expressed oils always have a low to moderate risk of phototoxicity which could be attributed to the presence of furanocoumarins.^[195,196] Lemon essential oil exhibited phototoxic effects which could be due to the presence of oxypeucedanin which is a furocoumarin derivative and was able to cause photo pigmentation on the skin of colored-Guinea pigs.^[196] However, in plants, the phototoxic effects of some CEOs could inhibit the germination and elongation of the seeds of some selected weeds which may serve as a potential bioherbicide for weed control. Essential

oils from *Citrus aurantifolia* showed a significant reduction in the germination of three selected monocot weeds; *Avena fatua*, *Echinochloa crus-galli*, and *Phalaris minor* at concentrations ranging from 0.10–1.50 mg/mL.^[25] Also, *Citrus limon* essential oil showed effective inhibition in the radical elongation of *S. lycopersicum* and *L. sativum* germinating seeds at a concentration of 100 µg/mL while *C. myrtifolia* and *C. bergamia* essential oils showed significant inhibition against the germination of *P. oleracea* at initial concentrations of 100 and 10 µg/mL and final concentrations of 100, 10, and 1 µg/mL.^[197] It is worth noting that *Citrus aurantifolia* essential oil rich in citral has been reported to exhibit bone marrow suppression in rats and hence was deemed to be myelotoxic.^[92] Recently, our group reported mild toxicity of animals gavage with 100 and 500 mg/kg doses of unripe lime essential oil at the sub-chronic stage.^[18] The research revealed the ability of the unripe lime essential oil to affect cellular injury, specifically, necrosis and inflammatory response in tissues which could lead to organ malfunction, and it was suspected to have resulted from certain components such as β-pinene, trans-anethole, germacrene D and linalool. The data from this review demonstrate that, some citrus essential oils may lead to myelotoxic, mild haemato-toxic, nephrotoxic, and hepatotoxic effects *in vivo* at high concentration.

Conclusion

This review intended to throw more light on some of the extraction methods, therapeutic potentials, biological properties, and toxicity of various citrus essential oils. Additionally, the review also aimed at bringing the attention of the scientific community and researchers to the new developments and potential medicinal applications of citrus essential oils which could aid in the discovery and development of new drugs with specificity from citrus essential oils. Thus, the data presented gives a formidable basis to rekindle investigation into the medicinal uses of citrus essential oils based on their extraction and biological properties and to tap directly into the rich shores of the old art of 'essential oil therapy.

Abbreviations

5-HT- 5-Hydroxytryptamine; 5-MOP- 5-Methoxypsoralen; ABST- 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid); CAT-catalase; CEOs- citrus essential oils; DLA- Dalton's Lymphoma Ascites; DPB- Dibenzo-α-pyrene; DPPH- 2,2-Diphenyl-1-picrylhydrazyl; EOs- Essential oils; HL-60- Human Leukemia cells; H5N1-Hemagglutinin type 5 and Neuraminidase type 1; HD-Hydro distillation; GC-MS- Gas Chromatography-Mass Spectrometry; GSH-Reduced Glutathione; ICR-Institute of Cancer Research; LNCaP- Human prostate adenocarcinoma; LDL- Low-density lipoprotein; MASD-Microwave Assisted Steam Distillation; MIC- Minimum Inhibitory Concentration; PSA- Prostate Specific Antigen; ROS- Reactive Oxygen Species; SC-CO₂- Supercritical carbon dioxide; SD-Steam Distillation; SHSY5Y-Human neuroblastoma cells; SOD-Superoxide dismutase; UAE- Ultrasound-Assisted Extraction; WAT-White Adipose Tissue.

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Authors contributions

CKA, FAA, and CO conceptualized the study. CKA, ASB, and SAA reviewed the research proposal and conducted the ethnobotanical survey. ASB, SAA, and CO drafted the manuscript. All the authors participated in writing and giving feedback on the manuscript. All authors have read and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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