Review

Lemongrass essential oil components with antimicrobial and anticancer activities

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Abstract: The prominent cultivation of lemongrass relies on the pharmacological incentives of its essential oil. The lemongrass essential oil (LEO) has a significant amount of citral (mixture of geranial and neral), isoneral, isogeranial, geraniol, geranyl acetate, citronellal, citronellol, germacrene-D, and elemol in addition to numerous other bioactive compounds. These components confer various medicinal activities to LEO including antifungal, antibacterial, antiviral, anticancer, and antioxidant properties. These attributes are commercially exploited in pharmaceutical, cosmetics, and food preservations industries. Furthermore, the employment of LEO in the treatment of cancer opens a new vista in the field of therapeutics. Although different LEO components have shown promising anticancer activities in vitro, these effects have not been assessed yet in humans. Further studies on the anticancer mechanisms exerted by lemongrass components are required. The present review intends to provide a timely discussion on the relevance of lemongrass extracts in cancer and health, and in food industry applications.

Keywords: anticancer, antimicrobial, antioxidants, cancer signalling, citral, *Cymbopogon*, essential oil

1. Lemongrass

The lemongrass is a fast-growing C_4 perennial sedge from the grass family Poaceae and is commonly known as East Indian or Malabar grass. Lemongrass plants are primarily cultivated for the essential oils. These aromatic grasses are of great commercial interest due to their wide applications in different areas such as the food, pharmaceutical, and cosmetic industries. The plant propagates through seed and slips and has thin and lanceolate leaves that appear to emerge directly from the soil without any stem [1]. Although lemongrass cultivation is cosmopolitan, India has a monopoly over its production and export [2,3]. The lemongrass is also called Cochin grass since 90% of its global export is organised from Cochin port, India [4]. The lemongrass plant has extensive potential as food and fodder given its richness in vitamin A, C, E, folate, niacin, and riboflavin, protein, antioxidants, and mineral nutrients such as N (0.74%), P (0.07%), K (2.12%), S (0.19%), Mg (0.15%), Ca (0.36%), Zn (35.51 ppm), Mn (155.82%), Fe (126.73%),

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and Cu (56.64 ppm) [5,6]. Figure 1 illustrates the morphological attributes of lemongrass plants focusing on the characteristics of glandular trichomes and stomata.

Lemongrass cultivation is a rapidly growing economy. The major drive for lemongrass cultivation is its high industrial potential in the pharmaceutical, food, and cosmetics sectors. It is grown over an area of 16,000 ha on a global scale that produces about 1000 t of lemongrass essential oil (LEO) each year [7]. Out of this, India accounts for one-fourth of total production and area cropped worldwide [8]. Lemongrass cultivation can provide a net profit of about 300 USD per year per hectare [9]. A recent report by Profshare Market Research pins the global lemongrass oil market at 247 million dollars in 2019 and expects to grow to 421 million dollars in 2027 at a compound annual growth rate of 7%. Additionally, the lemongrass export of India has risen more than 1250% from 2001 to 2020 which solidifies its demand and importance (source: The Directorate General of Commercial Intelligence and Statistics). Moreover, the size of the essential oil market is estimated by numerous market research firms. One such study by Facts and Factors estimates its size to be 7 billion dollars which are expected to double by 2027. Given the growing consumer demand and global market for essential oil, few recent reports have suggested various sustainable approaches for enhancing lemongrass production even further [3].

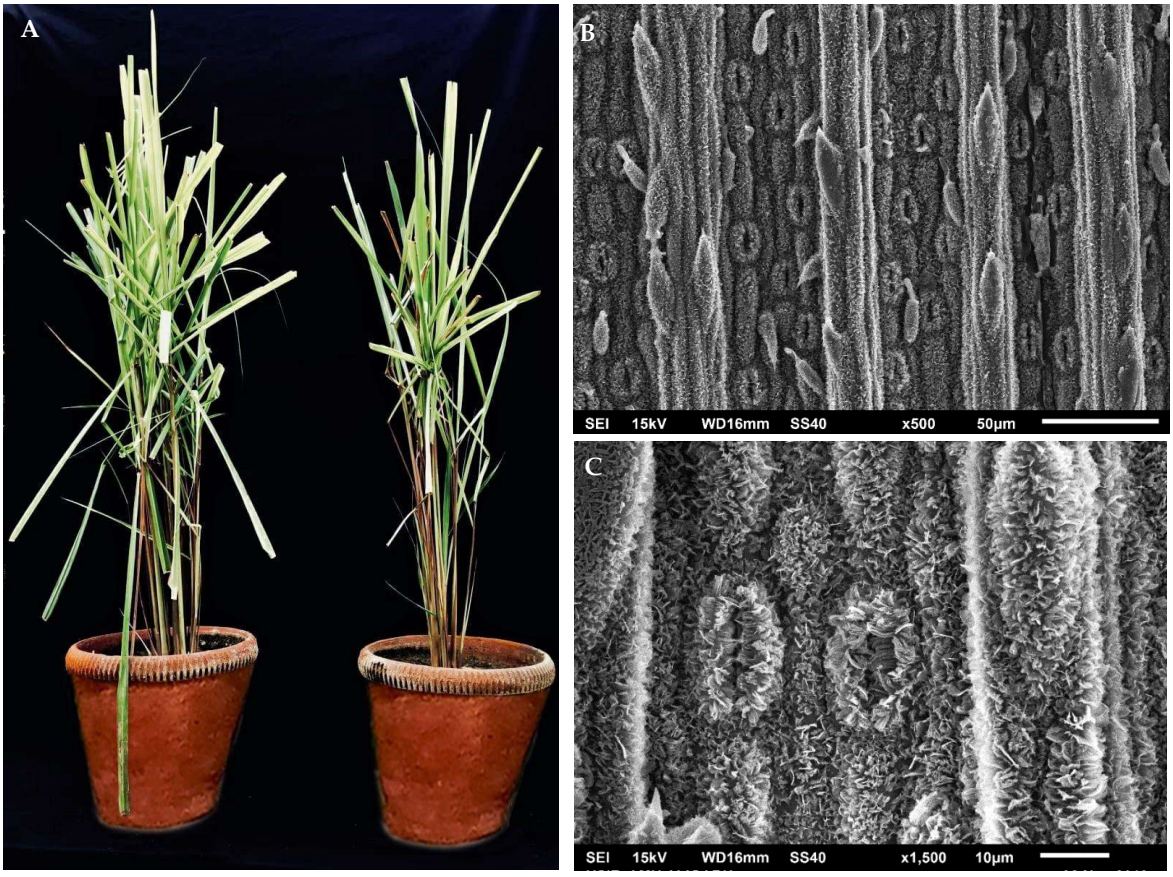

Figure 1. Morphological and anatomical profile of the lemongrass plants. *The morphological representation of 150-days-old healthy lemongrass plants (A). Scanning electron microscopy (SEM) analysis of lemongrass leaf visualising glandular trichomes at ×500 magnification (B) and stomatal characteristics at ×1500 magnification (C).*

2. LEO: Biosynthesis and chemical composition

Lemongrass oil is a cocktail of various terpenes and terpenoids, out of which the major components belong to cyclic and acyclic monoterpenes. The monoterpenes are

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derived from geranyl diphosphate (GPP). The GPP is a fusion component of isopentenyl diphosphate (IPP) and its allylic isomer dimethylallyl diphosphate (DMAPP). The IPP is a precursor of all the terpenes and terpenoids. Earlier it was widely accepted that plants produce IPP through a cytoplasmic mevalonate (MVA) pathway. However, empirical studies reveal that a newly discovered methylerythritol phosphate (MEP) pathway for monoterpenes biosynthesis is more dominant in lemongrass species [10]. The plastidic MEP pathway begins with the reaction of pyruvate with thiamine diphosphate (TPP) that yields hydroxyethyl-TPP. Hydroxyethyl-TPP upon reacting with glyceraldehyde 3-phosphate (GAP) releases 1-deoxy-D-xylulose 5-phosphate (DXP). Subsequently, DXP rearranges and reduces to MEP that is further phosphorylated and ultimately generates IPP.

On the other hand, the MVA pathway involves the condensation of three acetyl-CoA molecules into 3-hydroxymethylglutaryl-CoA (HMG-CoA). The HMG-CoA is reduced to MVA and the subsequent steps of MVA phosphorylation produce IPP. The IPP produced from MEP/MVA pathway reacts with DMAPP to yield GPP which subsequently forms geraniol in lemongrass. Geraniol through different reversible reactions produces all the major components of lemongrass oil [11]. (Figure 2)

LEO is produced only in young and rapidly growing lemongrass leaves and floral tops and is stored in specialized parenchymal oil cells between vascular bundles proximal to non-photosynthetic tissue [12]. The amount of lemongrass oil is about 1-2% of its total dry weight [13]. However, various drying methods can produce different content and quality of LEO [14]. The LEO components can be categorised into terpenes, terpenoids, flavonoids, phenols, phenolics, tannins, fatty alcohols, and steroids. The genus Cymbopogon comprises about 180 species differing in their essential oil content and composition. The most common lemongrass species are *C. citratus*, *C. flexuosus*, *C. winterianus*, *C. martinii*, *C. nardus*, and *C. refractus*. The content of oil constituents may also vary with the extraction method, developmental stage, and the solvent used for extraction [15]. The major components in most lemongrass species include neral, isoneral, geranial, isogeranial, geraniol, geranyl acetate, citronellal, citronellol, germacrene-D, and elemol and make up about 60-80% of LEO. The remaining components also called minor components, comprise camphene, pinene, limonene, linalool, citronellyl acetate, elemene, and caryophyllene oxide [11]. The isomeric mixture of geranial and neral is known as citral and its content can be used as a quality marker for LEO [16]. This aldehyde monoterpene is the key active constituent (<80%) of *Cymbopogon flexuosus* oil, making it an aldehyde-type grass. Alternatively, *Cymbopogon martinii* (Palmarosa) has more alcohol content (nerol and geraniol) than aldehydes (neral and geranial) and thus is called an alcohol type grass while *Cymbopogon winterianus* (Java citronella) is an intermediate type due to the moderate contents of aldehyde and alcohol in its essential oil [17]. (Figure 2)

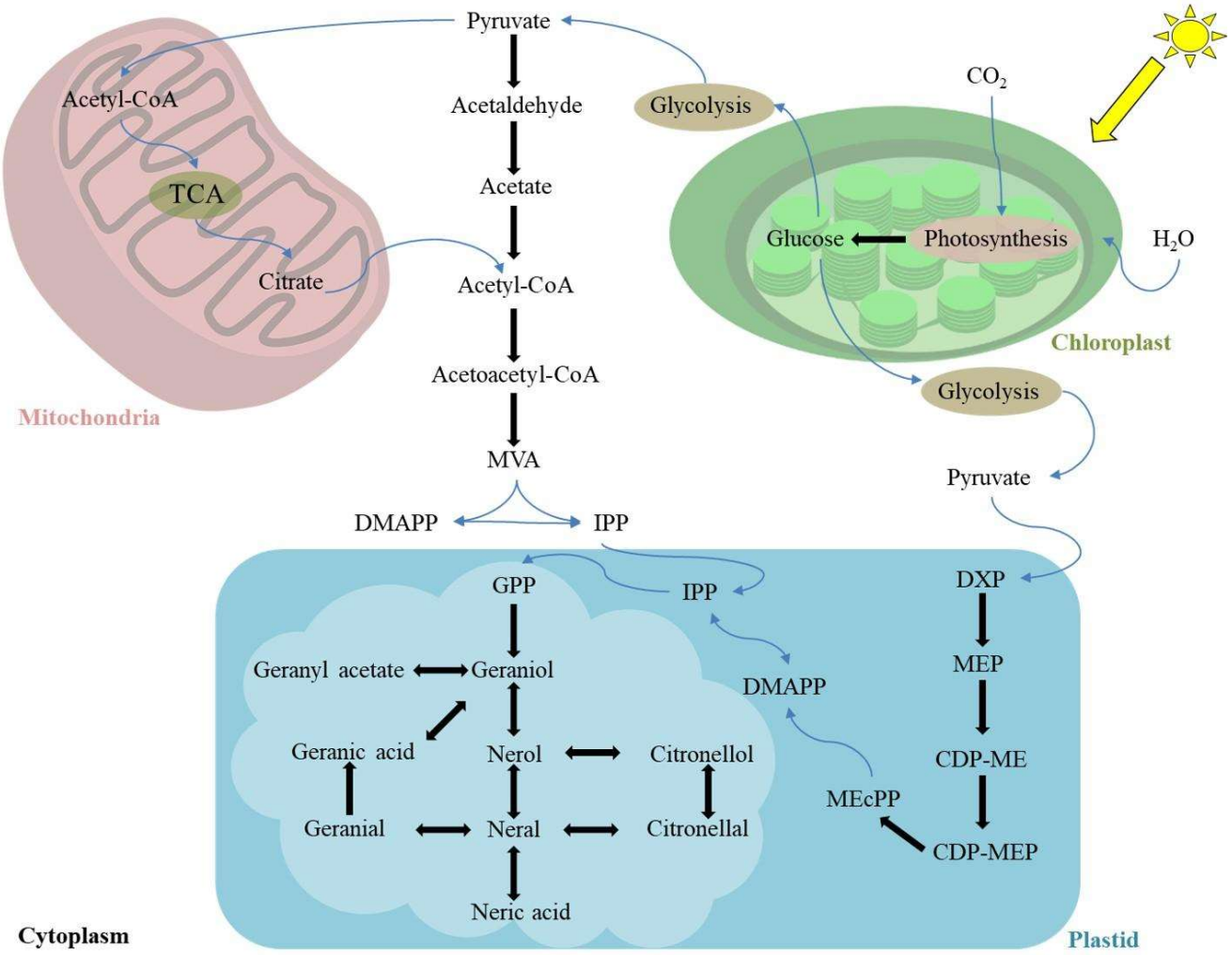

Figure 2. A mechanistic model for the biosynthesis of lemongrass essential oil and its crosstalk with other metabolic processes. *Different cellular organelles work in tandem for oil production in lemongrass leaves. The lemongrass chloroplast like most of the other plants produces glucose through photosynthesis. The glucose undergoes glycolysis in the cytoplasm and yields pyruvate, a 2-carbon compound. The lemongrass uses the pyruvate as a substrate for the biosynthesis of isopentenyl diphosphate (IPP) units either through the cytoplasmic mevalonate (MVA) pathway or plastidic methylerythritol phosphate (MEP) pathway in their young and rapidly growing leaves. Alternatively, mitochondria can import pyruvate and yield citrate through the tricarboxylic acid (TCA) cycle. The citrate can transform into Acetyl-CoA and join the MVA pathway to yield IPP units. The IPP produced through both pathways is converted into geraniol mediated by geranyl diphosphate (GPP) in lemongrass plastids. The geraniol is considered as a precursor for essential oil biosynthesis in lemongrass and yields all the major components through multiple reversible and irreversible reactions. The plastidic bubble highlights these reactions along with their substrates. DMAPP, dimethylallyl diphosphate; DXP, 1-deoxy-D-xylulose-5-phosphate; MEP, 2-C methylerythritol 4-phosphate; CDP-ME, 4-diphosphocytidyl-2-C-methyl-D-erythritol; CDP-MEP, 4-diphosphocytidyl-2-C-methyl-D-erythritol-2-phosphate; MEcPP, 2-C-methyl-D-erythritol 2,4-cyclodiphosphate.*

3. LEO therapeutics

Recent decades mark an exponential upsurge in establishing the bioactivities of lemongrass extract and essential oil. Feeding studies establish that LEO has antimicrobial, anticancer, anti-amoebic, anti-diarrhoeal, anti-filarial, antitussive, antiseptic, larvicidal, insecticidal, miticidal, ovicidal, acaricidal, analgesic, anesthetic, anti-inflammatory, antioxidant, antinociceptive, antihypertensive, anti-obesity, anxiolytic, and antimutagenicity potential, cardio-protective, anti-rheumatic, and hematological properties [7,17–29]. These bioactivities are the direct product of the individual and

synergistic effect of different major and minor LEO components [11]. The LEO therapeutics is an emerging alternative for synthetic pharmaceuticals due to its naturality, biocompatibility, and inexpensiveness.

3.1. Antimicrobial potential

The lemongrass oil and extract are effective against a wide variety of disease-causing microbes [31]. Several studies have used LEO as an antibacterial [21,32,33], antifungal [30,34], and antiviral [21,35,36] agent. Similarly, lemongrass extract inhibited the growth of *Bacillus cereus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Candida albicans*, and *Staphylococcus aureus* with different levels of susceptibility [37]. The EO components with different functional groups exhibit different levels of antimicrobial potential where phenols and aldehydes have the highest activities while esters and hydrocarbons have the least [38]. However, the antimicrobial activity of lemongrass is extensively attributed to the citral (aldehyde) present in its oil [26,39,40]. It is suggested low concentration of LEO inhibits microbial growth and development (bacteriostatic, fungistatic, and virustatic) while higher concentration renders irreversible destruction leading to microbial death (bactericidal, fungicidal, and virucidal) [41,42]. On a similar note, one study addressed LEO antimicrobial potential against 42 microorganisms, including 20 bacteria, 15 fungi, and 7 yeasts [43]. Furthermore, Singh et al. [41] studied 1114 strains of different microbes including molds, yeasts, and bacteria from 29 genera and 105 species, and circled out about 425 LEO sensitive microbial isolates.

3.1.1. Antibacterial activity

The antibacterial characteristic of LEO is well established [16,38,44–48]. It is suggested that LEO induces the destruction of bacterial biofilms and hinders further bacterial growth and development [49]. Furthermore, LEO components can destabilise the bonds between the lipid bilayer and neutralise the bacteria through membrane disintegration [50]. The LEO can confer structural changes as well in different bacteria. It was reported to cause complete disfiguration and distortion in the *Pseudomonas* spp. [51]. Furthermore, LEO blocks biofilm formation in bacterial colonies [52]. It can disrupt the cell membrane and inhibit cytoplasmic metabolism, making LEO effective against both gram-negative and gram-positive bacteria [32,47,53]. Multiple recent studies against MDR (multidrug-resistant) bacteria [54,55] showed that a low concentration of LEO retarded growth and biofilm formation while a higher concentration of LEO conferred complete elimination of *Salmonella* Heidelberg.

It is believed that the geranial and neral are responsible for the antibacterial activity of lemongrass oil. However, when a mixture of principal oil components and the whole EO were tested, the whole EO exhibited enhanced efficacy against bacteria [43]. This implies that minor components including limonene, linalool, and myrcene have specific as well as a synergistic mechanism with major components and can play a decisive role in augmenting oil effectivity [51,56].

The bacteriostatic and bactericidal characteristics of LEO primarily depend on the bacteria and oil concentration [57,58]. However, several other factors such as oil composition, extraction method, plant developmental stage, and environmental variables including temperature can influence the oil's effectiveness. Therefore, lemongrass oils from different species might exhibit effects of different nature and intensity. Nevertheless, the host organism can also decide oil effectiveness to a certain extent depending on its morpho-physiological attributes [59]. Therefore, EOs react differently with gram-positive and gram-negative bacteria differently owing to their dissimilar cell wall structure [57,60].

3.1.2. Antifungal activity

Antifungal activity of LEO has been reported against multiple fungi [38,61–63]. Volatiles from lemongrass oil such as phenols, flavonoids, and flavones are effective against numerous fungal strains [64,65]. Helal et al. [66] reported that LEO caused plasma membrane disruption and disorganisation of mitochondria and resulted in Ca^{2+}, K^{+}, and Mg^{2+} leakage. The loss of ions can further affect signal transduction and fungal germination. Moreover, Alviano et al. [67] observed that LEO components induce cell size reduction and inhibit the spore germination in *Candida albicans.* LEO can directly act upon the fungal lipid bilayer owing to its readily volatile and lipophilic nature. It can form a charge-transfer complex with the lipid bilayer, destabilising membrane and inhibiting further membrane synthesis, and retards fungal spore formation and cellular respiration [68]. Boukhatem et al. [51] found that the vapour form of LEO inhibits mycotic growth and development more effectively than the liquid phase, probably because of the direct accumulation of the LEO vapours on fungal mycelium. It was also suggested that lemongrass oil induces ROS production in fungi and afflicts severe oxidative damage that leads to subsequent cellular death [30].

The LEO components including citral, geraniol, myrcene, limonene, and linalool have significant antifungal activity [40,44,69]. Geraniol increases the outward leakage rate of potassium ions, while citral damages the microtubules and exhibits cytotoxicity in fungi [25]. Linalool, a monoterpene alcohol, comprises numerous fungicidal properties [67]. It retards the overall development and propagation of different fungi through the respiratory restriction of their aerial mycelia [51]. Additionally, other aldehydes of LEO can confer antimycotic activity through cross-linkage reaction within the fungal membrane [51].

It was suggested that EOs can be used in the food preservation and packaging industry [70]. EOs can remain effective for a longer duration against fungal spore production, ensuring improved shelf life for food products [62,71]. Edible coating of EOs including LEO on stored fruits, meat, and dairy products discourages the fungal attack and food spoilage through restricting fungal growth and reproduction [72–76]. Moreover, different EOs have different antimicrobial mechanisms, and thus acquisition of resistance by microbes against the wide array of compounds in EOs is rare [77]. The edible coatings of EOs have increased antimicrobial potential over the free EOs due to their altered surface charge and amplified action on multiple target sites in the mycotic membrane [60]. This elongates edibility and maintains physicochemical qualities including taste and odour of such products [64,78].

3.1.3. Antiviral activity

In addition to fungi and bacteria, the LEO is equally effective against numerous viruses. The antiviral activity of lemongrass oil was tested against herpes simplex virus-I (HSV-I) [35] and murine norovirus (MNV) [79]. The studies demonstrated that 0.1% and 2% of LEO concentrations were potent enough to inhibit the replication of HSV-I and MNV, respectively. Furthermore, LEO can weaken the HIV transcription and virus reactivation by interfering with the Tat/TAR-RNA complex. As the Tat protein enhances the efficiency of viral transcription, LEO's interference with the Tat/TAR-RNA complex results in the downregulation of HIV activity [80]. The lemongrass volatiles were also able to cause more than 50% inhibition of the tobacco mosaic virus at 100 μg/ml concentration [42]. Human mastadenovirus (HAdV) causes numerous ailments such as respiratory infection, gastroenteritis, hepatitis, meningoencephalitis, pneumonia, and multiple others. Lemongrass extracts also induced cytotoxicity in the human lung adenocarcinoma cell line and kidney cell lines of the monkey and rendered antiviral activity against HAdV

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[81]. In the recent pandemic upsurge, the efficacy of LEO was suggested against influenza and coronaviruses SARS-CoV-2 as well, enhancing the relevance and importance of lemongrass oil even more [36,82].

3.2. Antioxidant related effects

Plant and animal cells produce various oxidative compounds such as H_2O_2, O_2^-, and OH^-, which can damage lipids, proteins, and DNA and can induce several health complications including cancer, aging, and neurological disorders in humans [24]. However, another group of compounds known as antioxidants has the potential to counter these effects [83]. Lemongrass possesses antioxidants that render protective measures against reactive species [84,85]. Lemongrass extracts have been reported to reduce reactive species concentration, lipid peroxidation, and decolourisation of 2,2-diphenyl-1-picrylhydrazyl [86,87]. Lemongrass extract can also buttress the endogenous antioxidant defence system in alveolar macrophages cells through augmenting the superoxide dismutase activity and glutathione formation [88]. Several plant extracts have been studied for their antioxidant beneficial properties. In particular, regulation of redox status in cells may affect the levels of methyl group donor S-adenosylmethionine (SAM). SAM is a cofactor for histone methyltransferases and DNA methyltransferases. A consumption of glutathione, as occurs during oxidative stress, with increase of its oxidised form, GSSG, may inhibit S-adenosylmethionine (SAM) synthetase, with a reduction of SAM synthesis [89] influencing the epigenetic modifications of proteins and DNA. Citral was shown to increase intracellular oxygen radicals while inhibition of glutathione synthesis increased citral anticancer effect [90]. Citral was shown to modulate oxidative stress preferentially in cancer cells and to induce the endoplasmic reticulum stress exerting thus an antiproliferative action [90]. Lemongrass has a competitive advantage over other synthetic antioxidants such as butylated hydroxytoluene since they can induce haemorrhages: in this optic, lemongrass oil is regarded 'safe' for human consumption [91]. This opens a new vista for lemongrass oil in food preservation and safety industries including meat, and dairy industries [51]. In the food industry, the oxidation of lipids is an important determinant of meat and dairy products. However, their highly rich nutritional profiles are prone to lipid peroxidation and quality deterioration. In this regard, coating such products with LEO minimises lipid peroxidation and increases their shelf life and quality [92]. Furthermore, the antioxidative nature of citral is exploited in animal skin cancer models [93]. Soares et al. [94] reported that LEO has high antioxidant activity compared to the methanolic crude extract of lemongrass. The antioxidant activity of LEO can further be enhanced through mixing it with other potent antioxidative agents. On this note, a mixture of LEO with *Ocimum gratissimum*, and *Thymus vulgaris* oil had enhanced effectiveness against *Bipolaris oryzae* and *Alternaria alternata* [95].

3.3. Anticancer activity

According to the World Health Organization (WHO), cancer caused an approximated 10 million deaths, or one in six deaths, in 2020. This situation is not going to be relieved, as there is an estimated increase of 45% in cancer mortality rate between 2008-2030. Among these, the most common types are breast cancer, lung cancer, colorectal cancer, prostate cancer, skin, and stomach cancer. The ongoing conventional chemotherapies, radiotherapy treatment, and surgeries have shown a large number of involuntary side effects due to insufficient knowledge of treatment specificity, and are not recommended for long-term usage [96].

Medicinal plants emerge as potential candidates in the cancer world and raise hopes for the scientific community. Scientists are constantly looking for natural sources to uncover

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the potential plant-based therapeutic agents having immense anticancer properties [97]. In this sense, the essential oil of lemongrass counts for its cytotoxicity on human cancer cells. Its active ingredients including geraniol, geranyl acetate, α-bisabolol, and iso-intermedeol have individually been found to impart cytotoxic effects on cancer cells [98]. Lemongrass EO has been exhibited inhibition of human mouth epidermal carcinoma (KB) and murine leukemia cell lines (P388) [99]. Besides, citral, the major component of the EO of lemongrass, plays potential role as anti-proliferative against several types of cancer cells such as the two human prostate cancer cell line LNCaP and PC-3 [100], HL60, and ovarian cancer cells, U937 [101,102], cervical cancer cell lines [103], and breast cancer cell line, MCF-7 [104]. Interestingly, citral does not exert cytotoxicity to normal epithelial cells but exhibited toxic effects against human breast cancer cell lines, and confirmed its cancer-specific efficacy [105].

Although a large number of studies evinced the anticancer activity of lemongrass, scarce data are available on its mode of action. Studies based on different cancer cell types substantiated citral efficacy via activated procaspase-3, induction of apoptosis, and cell cycle arrest in the G2/M phase [106,107].

Table 1. Effects of different components of lemongrass on several distinct cancer cell lines

Components	Experimental model	Mechanism of action	References
Citral	A549 (human lung carcinoma) NCI-H1975 (human lung adenocarcinoma) NCI-H1650 (human lung adenocarcinoma) NCI-H1299 (human lung large cell carcinoma)	Growth arrest of cell cycle at sub G1 phase Up-regulation of procaspase-3 Decrease of Bcl-2 and increase of expression of Bax	[107]
Citral	Prostate cancer cells PC3 and PC3M (metastatic) Colony forming assay 10, 15, 25, 50, 100 μg/ml	Inhibition of colony formation, suppression of expression of AMPK pathway genes *SREBP1, ACC, HMGR*	[108]
	ATCC-CRL-1739 / AGS stomach cancer cells 5, 10 and 20 µg/mL	216 up-regulated genes 396 downregulated genes Apoptosis, block of colony formation and migration	[109]
Citral	Human colorectal cancer HCT116 and HT29 cells	Induction of phosphorylation of p53, triggering ROS mediated mitochondrial intrinsic apoptosis cytotoxicity	[110]
	HT29, SW620 lines		[111]

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Geraniol	A549 human lung adenocarcinoma cells in culture and in vivo in nude mice	Decrease of level of membrane-bound Ras protein, decreased the level of cholesterol and HMGCR protein	[112]
Geraniol	*In vitro* murine endothelial-like eEND2 cells and HDMEC (dermal microvascular endothelial cells), *In vivo*, CT26 cell lines from undifferentiated colon carcinoma of the BALB/ c mouse	block of VEGF/ VEGFR signal transduction and suppression of cAKT and ERK signalling pathways	[113]
Geraniol	Human hepatoma (HepG2) and human lung adenocarcinoma (A549) cell lines	growth arrest in G0/G1 interphase of the cell cycle, increased the production of ROS	[114]
Citronellol	In vitro, non-small lung cancer cell (NCI-H1299) In vivo, injected NCI-H1299 into BALB/c nude mice	Arrest of cell cycle at G1 phase, down-regulation of expression of cyclin E, and cyclin D, increase in expression of TNF-α, and activation of RIP1/RIP	[115]
Citronellol	Triple negative breast cancer MDA-MB-231 cell line	Decrease in expression of Bcl-2 gene and protein and increase in Bax expression.	[116]
Citronellol	DMBA(7,12-dimethylbenz(*a*) anthracene) induced mammary cancer in rats	Down-regulation of expression of NF-kB, IL-6, and TNF-α. Suppression of activity of COX-2.	[117]
α-bisabolol	CML-T1, Jurkat, and HeLa cell lines	cytotoxicity via mitochondria and lysosome-initiated caspase cascade and induction of autophagy and apoptosis	[118]
α-bisabolol	KLM1, KP4, and Panc 1 human pancreatic cancer cell lines	Up-regulation of *KISS1R*	[119]
α-bisabolol	Endometrial cancer cell lines RL95-2, ECC001, ECC003 Ishikawa cell line	Decrease of activity of COX-2, induction in PARP cleavage, increase of apoptosis	[120]

	ECC E6/E7 cell line	via XIAP/ caspase 3 pathway	
Limonene	Bladder cancer line T24; colon cancer LS174T line Bladder cancer cells;	Arrest of cell cycle in the G2/M phase; block of cancer cell migration; apoptosis; inhibition of PI3K/AKT pathway induces cell cycle G2/M, suppresses migration. Induces chromatin concentration, nuclear fragmentation, increases Bax, caspase 3, decreases Bcl-2	[121,122, 141]
Linalool	HeLa, H520 lung cancer line, BCC-1/KMC skin cancer	Anti-proliferative	[170]

Citral consists of a double bond in conjugation with an aldehyde (α,β-unsaturated) group in its core structure, that serves as a potent caspase 3 activator, responsible for pro-apoptotic activity [106]. Moreover, citral-induced apoptotic activity was associated with DNA fragmentation and induced caspase 3 activity against hematopoietic cancer cell lines and ovarian cancer cell lines. The Src-tyrosine kinase is expressed in small cell lung cancer and can phosphorylate transcription factor Stat3(Y705) [123], which sequentially enhances the expression of downstream genes engaged in anti-apoptotic activity i.e Bcl-xL and Mcl-1 [124]. An experimental study showed the inhibitory effects of lemongrass EO and citral on phosphorylation of Src(Y416) blocking its activation, resulting in reduced phosphorylation of Stat3 (Y705). Non-phosphorylated Stat3 disrupts cell growth and signal pathways that upregulate the expression of Bcl-xL and Mcl-1 [125]. Citral dependent apoptosis induction has also been observed against prostate cancer cell lines. Citral induced gene activation initiates AMPK (an enzyme necessary in the fatty acid metabolism) phosphorylation resulting in the activation of BAX and downregulation of Bcl-2, which initiates an apoptosis cascade in prostate cancer cell lines [108]. Citral-mediated breast tumor growth inhibition via inhibition of ALDH1A3 was reported [126]. Up-regulation of retinoic acid (RA) signalling by ALDH1A3 can cause breast cancer growth, and citral inhibited the expression of RA inducible genes mediated by ALDH1A3 [126]. Microtubule affinity regulating kinase 4 (MARK4), an AMP-activated protein kinase [127], is reported to mediate apoptosis, inflammation, and distinct regulatory pathways [128]. Alterations in MARK4 expression hamper the cell cycle and eventually cause cancer. Citral potentially binds to MARK4 and inhibits its kinase activity, and is being considered an effective strategy to prevent the growth of cancer cells and other MARK4 associated diseases [129]. Citral has been reported inducing the phosphorylation of p53 protein and the expression of Bax while reducing the expression of anti-apoptotic factor Bc-2 and Bcl-xL in human colorectal cancer lines i.e HT116 and HT29 [110]. Citral interferes with the ERK1/2 pathway and reduces the translocation of ERK1/2 protein to the nucleus. There is a certain possibility of the involvement of ERK1/2 in melanoma carcinogenesis and progression in presence of mutated *N-Ras* and *B-Raf*. Therefore, citral could negatively affect cancer growth by inhibiting the final step of the MAPK cascade [130].

Geraniol, the second major constituent of lemongrass EO, has garnered heed for its potentiality in cancer treatment. It has been reported that geraniol induces the production of reactive oxygen species (ROS) and inhibits the phosphorylation of tyrosine kinases, which, in turn, induce apoptosis of cancer cells [131]. Several studies have been conducted to gain insights into its anti-cancer activity [112–114]. Ornithine decarboxylase (ODC) plays a prime role in the synthesis of polyamines, providing stabilization to DNA structure [132]. A decrease in ODC activity after geraniol treatment has been observed in the intestinal adenocarcinoma Caco-2 cell line, which, in turn, caused DNA synthesis inhibition and cell cycle arrest in the S phase [132]. Polyamine metabolism is a potential target in the development of cancer-preventive drugs, therefore, geraniol mediated decline in ODC activity might have a useful clinical role [133]. Geraniol-induced inhibition of the proliferation of A453 and A549 human lung cancer cell lines has been reported. Geraniol alters the tubulin polymerization and disrupts the active property of both the studied cell lines, resulting in cell apoptosis. Geraniol arrested the G0/G1 phase in A431 cells, with no effects on sub-diploid cells, and the G2/M phase of A549 with increased population of sub-diploid cells, in a dose-dependent manner. Inhibitory effects of geraniol might be interrelated with the observed alteration in the ODC activity [134]. Geraniol caused inhibition of cell cycle progression, exerting altered expression of cyclins D1, A, B1, CDK2, and cyclin kinase inhibitor proteins p21 and p27 [135]. Geraniol has been reported to induce the expression of pro-apoptotic proteins Bcl-2, Bax, Bak, and caspase3/8/9 in several human cancer cell lines [114,136]. Moreover, the considerable increase in these proteins indicates that geraniol induces apoptosis through the mitochondrial intrinsic pathway [137]. The antiangiogenic activity of geraniol has been confirmed by both *in vivo* and *in vitro* studies. Geraniol suppresses the endothelioma cell line and reduces the Ki67-positive cells and CD3-microvessel, by suppressing the expression of VEGFR-2 in Balb/c mice [138]. This activity might play a role in reducing tumor growth, as the tumor needs a new blood vessel to grow. Geraniol arrested the proliferation of two pancreatic cancer cell lines i.e MIA PaCa-2 and BxPC in hamsters when injected with PC-1 pancreatic ductal adenocarcinoma cells. In both the cell lines, it arrested the G1 phase of the cell cycle along with increased expression of cyclin kinase inhibitor proteins i.e $p21^{cip1}$ and $p27^{kip1}$ while suppressed those of cyclin A, B1, and CDK 2 [139].

D-limonene, another constituent of lemongrass EO, was also reported to possess antineoplastic activity. D-limonene enhances the activity of carcinogen metabolizing enzymes such as cytochrome P450, responsible for the conversion of carcinogens into less harmful forms and blocks their interaction with DNA [140]. Treatment of D-limonene on LS174T human colon cancer cells inhibited the P13K/Akt pathway, and induced cell apoptosis. An increase in PARP cleavage and activation of caspase-3 indicates the involvement of mitochondrial apoptotic pathway [121]. Limonene-mediated induction of apoptosis via increased expression of Bax and caspase-3 and decreased Bcl-2 expression has been reported in T24 bladder cancer cells. Moreover, Limonene arrested the cell cycle in the G2/M phase and wound healing and transwell assay using Matrigel has confirmed the limonene mediated suppression of cancer cell migration and invasion [141]. Another component of the EO of lemongrass, citronellol, is also found to exert cytotoxic effects on several cancer cell lines [115,116,142]. Citronellol showed its anti-cancer activity via increased reactive oxygen species production, alterations in mitochondrial permeability, DNA fragmentation, changes in cytochrome c activities, and activation of caspase, against the MCF-7 human mammary tumor cell line [142]. The cytotoxicity of α-bisabolol has been reported against human and rat malignant glioma cancer cell lines. In α-bisabolol treated cell line, rapid loss of inner transmembrane potential and an increase in cytochrome-c translocation indicate that α-bisabolol can trigger apoptosis through mitochondrial

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intrinsic pathway [143]. Another experimental study has confirmed the cytotoxic effect of α-bisabolol against several cancer cell lines. α-bisabolol arrested cell cycle and initiated cancer cell death via BID (BH3-only activator protein)- dependent mechanism [144]. It induces the permeability of the outer mitochondrial membrane and plays crucial role during apoptosis [145]. α-bisabolol induced damage to lysosomal and mitochondrial membranes via BID resulted in autophagy, and regulated cell death, enlightens its mode of action [144].

All of the mentioned components of lemongrass EO have presented their chemo-preventative effects via arrest of different phases of the cell cycle, suppression of cyclins and cyclin-dependent kinases, DNA fragmentation, and anti-angiogenic activity, against different cancer cell lines. Several distinct signalling pathways have been reported in different experimental studies exhibiting anti-cancer activities of these mentioned components (Table 1).

It should be taken into consideration that often individual components were shown not effective as the essential oil, possibly because association of multiple components potentiates the activity of each molecule. LEO effects on doxorubicin-resistant ovarian carcinoma cells were shown not dependent on citral [146]. The natural mixture of bioactives present in LEO is responsible for the beneficial effects, such as regulation of multidrug resistance and P-glycoprotein efflux pump inhibition in human ovarian carcinoma cells [146] and colon cancer cells [147].

Furthermore, other studies showed anticancer effect of LEO, while anticancer activity could not be attributed to its single constituents [148]. Anticancer activity of essential plant oils has been usually used as a paragon to compare essential oils from different sources. For instance, zingiber essential oil (ZEO) components nerol, citral, limonene, pinene, and camphene sum up to 55-60% of ZEO bioactives. ZEO was shown to be active against colorectal cancer in rats [149]. On the other side, when specific bioactives have been studied as anti-cancer agents, pleiotropic effects have been observed, without precise indication of the main target or signalling pathway. For instance, resveratrol and stilbenes are known to regulate different signalling pathways [150]. Biochemical interaction with enzymes, regulation of non-coding RNAs, and activation of signalling pathways and transcription factors are among the main effects observed.

Epigenetic modifications play a key role in cancer proliferation. Many chromatin remodeling complex components are found mutated, silenced, or overexpressed in cancers. Epigenetic mechanisms may be taken into account to explain the regulation of various protein-coding and protein non-coding genes. One of the causes of gene transcription is the level of DNA methylation on promoters, controlled by DNA methyltransferases. A second mechanism is dependent on chromatin remodelling complexes and the recruitment of Polycomb repressing complexes and histone modifying enzymes [151]. A great involvement of non-coding RNAs is at the basis of these mechanisms: therefore, expression of long and small non-coding RNAs determines whether an antioncogenic pathway is repressed or downregulated, or oncogenes are set free to induce cell transformation. The most well-known group of RNAs are microRNAs [152,153]. When they are abundant, they silence mRNA transcription by sequestering them and destining them to degradation. Long non-coding RNAs such as competing endogenous RNAs (ceRNAs) may sponge a group of miRNAs and the relative abundance determines if the miRNA can exert its effects or is bound to the sponge [154]. Therefore chromatin accessibility (opening or compaction), access to transcription machinery, and promoter methylation are the principal mechanisms that are targeted by plant extracts, essential oils, and individual bioactives. This has been clearly reviewed for stilbenes [150] and other plant bioactives [154].

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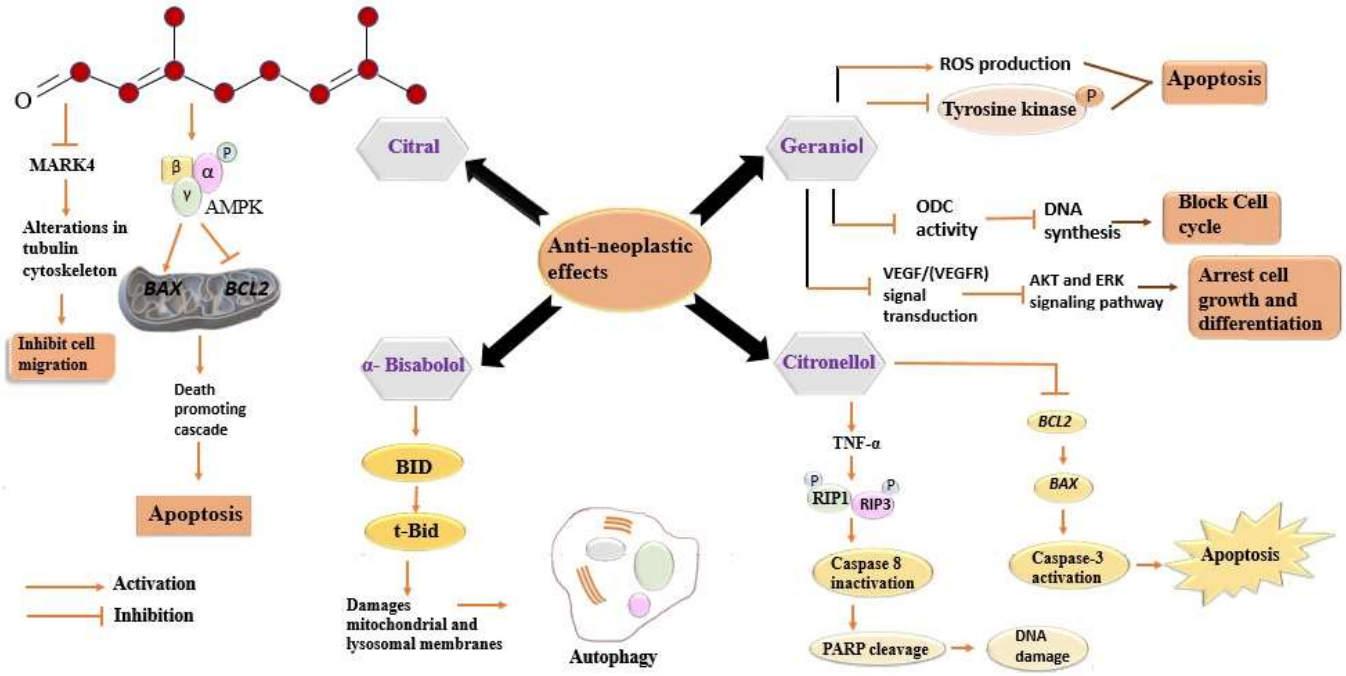

Figure 3. Distinctive signalling pathways activated in cancer cells via different components of LEO. *Every component acts differently against cancer cells and involves diverse signalling pathways. All of the involved pathways lead to inhibition of cell migration, cell cycle, and DNA synthesis. All of these events eventually cause cell death (apoptosis). MARK4, Microtubule affinity-regulating kinase 4; AMPK, 5' adenosine monophosphate-activated protein kinase; BAX, BCl2- associated X protein; BCL2, B-cell lymphoma 2; BID, BH3-only activator protein; tBid, truncated Bid, ROS, reactive oxygen species; ODC, ornithine decarboxylase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; AKT, Ak strain transforming; ERK, extracellular regulated kinase; TNF-α, tumor necrosis factor; RIP1, receptor-interacting serine-threonine protein kinase 1; RIP3, receptor-interacting serine-threonine protein kinase 3; PARP, poly ADP ribose polymerase, DNA, deoxyribonucleic acid.*

3.4. Miscellaneous

The lemongrass tea relieves stress, removes cough and nasal congestion. The LEO is exploited in the production of various mouthwashes [155]. The distinct fragrance of lemongrass is exploited in the flavour and perfume industries. Asian cuisine has long used lemongrass in numerous traditional dishes preparation. LEO coating on berries slows down the increase in total anthocyanin concentration, a known marker for the ripening of berry fruits, thus delaying berry ripening and spoilage [156]. The lemongrass oil and its components such as citral, myrcene, and citronellol show anti-malarial potential against *Plasmodium* spp. as well as confer total mortality of stage III and stage IV larvae in *Anopheles funestus* s.s [157–159]. Furthermore, multiple reports suggest LEO can suppress larval growth and production in various insects [160–164]. Lemongrass active constituent citral in combination with other components can regulate neuroreceptor activities, signal transduction, hormonal balance, membrane integrity, and cytotoxicity in insects [165,166]. Other minor components including caryophyllene, caryophyllene oxide, and germacrene-D discourage insect invasion and are effective against common houseflies and mosquitoes as well [167]. LEO can retard the activities of different neurotransmitters such as acetylcholine esterase and octopamine, activate olfactory receptor neurons, and induce related neurotoxic responses in insects [11,168,169]. Concerning this, a recent review [11] can be referred to for further reading on the insecticidal property of LEO and its underlying mechanism. (Figure 4)

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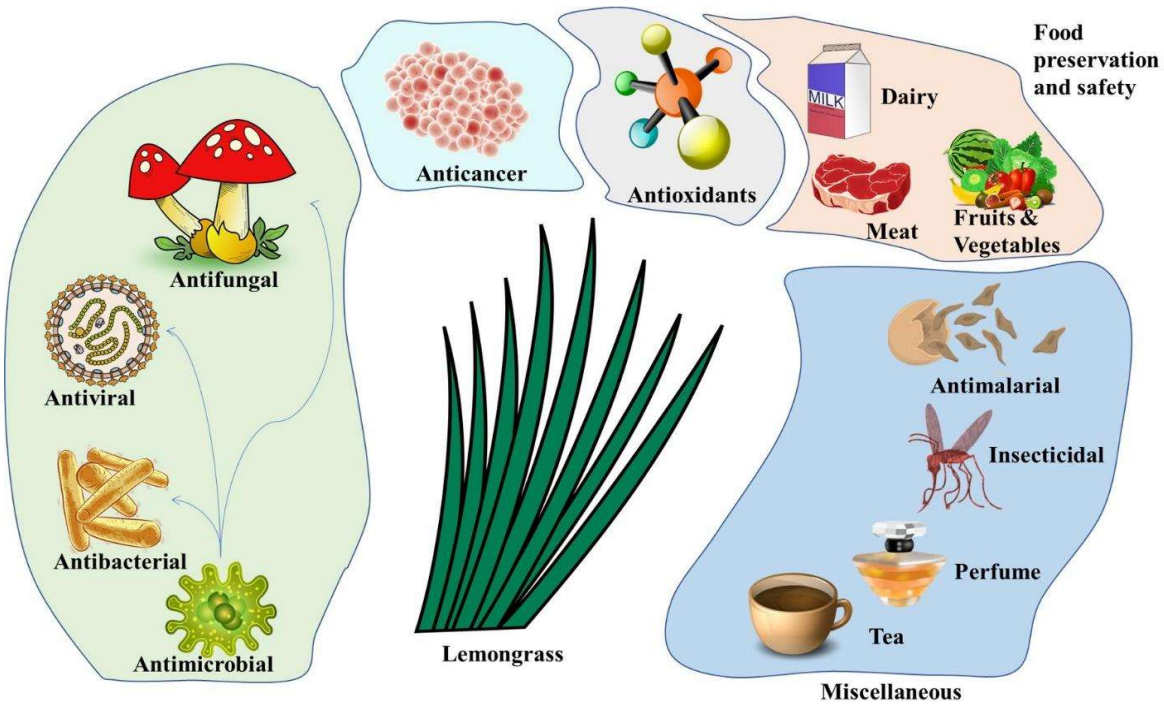

Figure 4. The relevance of lemongrass in the contemporary world. *The past decades observed a sudden rise in the lemongrass economy given its unique properties and sustainable nature. The lemongrass and its essential oil consist of multiple bioactive components which enrich lemongrass with antibacterial, antifungal, and antiviral activities. This bioactivity is exploited in preserving meat, fruits, vegetables, and dairy products. The antioxidant and cytotoxic potential of lemongrass has rendered promising results in recent cancer studies putting lemongrass again in the spotlight. Additionally, the figure traces the contours of multiple other lemongrass-driven benefits such as tea and perfumes and combating malaria and insects.*

4. Conclusions and future trends

The bioactive phytoconstituents present in lemongrass essential oils exhibit a myriad of medicinal properties including antimicrobial, anticancer, antioxidant, insecticidal, and antimalarial activities. Although recent years have seen an upsurge in lemongrass production, it is still far behind the global demand. Given its potential applicability in diverse sectors, lemongrass farming requires a revolutionised future. Harvesting of plant metabolites from controlled growth conditions (hairy root cultures, greenhouse) may establish a standard production of individual LEO bioactive components. Moreover, since citral is considered as the key marker for lemongrass quality and medicinal potential, improved lemongrass varieties with higher citral content are the need of the hour. Although LEO and its constituents have shown anticancer activity *in vitro*, and in some case in animal studies, only few researchers up to now tested the delivery of its bioactive components combined with nanoparticles or delivery systems [111,126,171]. This is required in order to bypass the metabolism of bioactives by microbiota and by cellular enzymes, to provide stability and bioavailability at the active concentrations tested in the studies. The anticancer effect of lemongrass ethanolic extracts on cancer cells having an increased level of ROS was shown to affect the increase in apoptosis levels [172]. Thus, it is possible that different bioactive contents may be put in relationship with different aactivity against cancer cells. Additionally, further studies on the antioxidant and anticancer mechanisms exerted by lemongrass components are required either *in vitro* as well as *in vivo*, to validate these preliminar data.

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