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Recent updates on bioactive properties of linalool

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Natural products, including essential oils and their components, have been used for their bioactivities. Linalool (2,6-dimethyl-2,7-octadien-6-ol) is an aromatic monoterpene alcohol that is widely found in essential oils and is broadly used in perfumes, cosmetics, household cleaners and food additives. This review covers the sources, physicochemical properties, application, synthesis and bioactivities of linalool. The present study focuses on the bioactive properties of linalool, including anticancer, antimicrobial, neuroprotective, anxiolytic, antidepressant, anti-stress, hepatoprotective, renal protective, and lung protective activity and the underlying mechanisms. Besides this, the therapeutic potential of linalool and the prospect of encapsulating linalool are also discussed. Linalool can induce apoptosis of cancer cells *via* oxidative stress, and at the same time protects normal cells. Linalool exerts antimicrobial effects through disruption of cell membranes. The protective effects of linalool to the liver, kidney and lung are owing to its anti-inflammatory activity. On account of its protective effects and low toxicity, linalool can be used as an adjuvant of anticancer drugs or antibiotics. Therefore, linalool has a great potential to be applied as a natural and safe alternative therapeutic.

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Introduction

Linalool (2,6-dimethyl-2,7-octadien-6-ol) is an acyclic monoterpene alcohol which naturally occurs in a variety of aromatic plants.[1,2] Linalool is widely distributed in essential oils of over 200 monocotyledonous and dicotyledonous plant species around the globe.[3,4] It is often found in plants of genus *Cinnamomum* (family *Lauraceae*), *Coriandrum* (family *Apiaceae*), *Lavandula* (family *Lamiaceae*) and *Citrus* (family *Rutaceae*) (Table 1).[4,6] Factors affecting the linalool content in essential oils include plant tissues used, geographical environment, harvest time, extraction techniques and drying time and temperature.[7,8] Besides essential oils, linalool also exists in floral volatiles, herbal extracts, and tea.[9–13]

Linalool is a colourless or faint yellow liquid at room temperature.[14] It is highly volatile with a refreshing, floral and woody scent, which is similar to the odour of bergamot essential oils and French lavender. Linalool is poorly soluble in water but easily dissolved in organic solvents, such as alcohol, chloroform, and ester.[14–16] Linalool is chemically reactive

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because of its carbon double bonds and hydroxyl group. Linalool can be oxidized into furanoid and pyranoid.[4] Moreover, linalool can form hydroperoxides after prolonged exposure to air, which is a potent sensitizer.[17,18] The physical and chemical properties of linalool are displayed in Table 2.

Owing to the hydroxy group on the third carbon, linalool exhibits chiral properties. The two enantiomers of linalool are 3*R*-(−)-linalool (licareol) and 3*S*-(+)-linalool (coriandrol) (Fig. 1). The enantiomers present different scents. 3*R*-(−)-Linalool has a woody, floral and lavender-like aroma, while 3*S*-(+)-linalool is sweet, floral, herbaceous with a citrus and fruity hint.[4] In natural plants, linalool is a racemate of both enantiomers, among which 3*R*-(−)-linalool is more common. 3*R*-(−)-Linalool mainly exists in rosewood oil and ho oil, while 3*S*-(+)-linalool mainly comes from coriander oil and orthodon oil. It is reported that plant organs and growth stages influence the enantiomeric ratio of linalool in a natural and spontaneous way.[19,20]

Because of its unique aroma, linalool is widely used in perfume, household cleaners and cosmetic products (shampoo, bath products, shower gel, soap, lotion, face cream, antiperspirant, and hair spray).[2,3,15,16] Linalool is also widely used in processed food and beverages as a fragrance and flavour agent.[4] It is approved and generally recognized as safe (GRAS) by the Food and Drug Administration (FDA).[16] The International Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an acceptable daily intake (ADI) for linalool of 0–0.5 mg per kg body weight per day.[4] In addition, linalool is also used in furniture care products, waxes, insect repellents and vitamin E synthesis.[4,21] Therefore, the annual consumption of linalool is greater than 1000 tons around the world.[1,15,16]

Linalool is biosynthesized in plants in three phases (Fig. 2). The first phase is the formation of C_5 units, isopentenyl pyrophosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP). The C_5 units are generated in two alternative pathways, mevalonate (MVA) pathway in the cytoplasm or 2-methyl-erythritol 4-phosphate (MEP) pathway in the chloroplasts.[22] In the second phase, IPP and DMAPP are then condensed into geranyl diphosphate (GPP), the precursor of monoterpenes. The reaction is catalysed by geranyl diphosphate synthase. In the third phase, GPP is converted into linalool under the catalytic action of linalool synthase.[23] In addition, linalool can be produced as a by-product in the biosynthesis of geraniol and nerol.[4]

Besides extraction from natural sources, linalool can be produced by chemical synthesis or biotransformation. The chemical synthesized linalool contains traces of dihydrolinalool, dehydrolinalool and chlorinated impurities which provide a metallic odour to linalool.[4] Ferraz *et al.* engineered *Escherichia coli* to produce linalool *via* expression of linalool/nerolidol synthase gene from *Streptomyces clavuligerus*.[44] The metabolic engineering produced commercially attractive linalool of high purity.

The present review will talk about the sources, physical and chemical properties, application, and synthesis of linalool. Moreover, we will concentrate on the biological properties of linalool and the underlying mechanisms, including anticancer, antimicrobial, neuroprotective, anxiolytic, antidepressant, anti-stress, hepatoprotective, renal protective, and lung protective activity. The potential of linalool to be used as an adjuvant of anticancer drugs or antibiotics and the prospect of encapsulated linalool are also discussed.

Bioactive properties of linalool

Antiproliferative and anticancer activity

Cancer is an important cause of morbidity and mortality in every region of the world. It is estimated that there were 19.3 million new cases of cancer and almost 10 million cancer deaths in 2020.[45] Current treatment options for cancer include surgery, radiation therapy and chemotherapy, among others.[46] There is an urgent need for more effective cancer therapies with low side effects. Linalool has been reported to have antiproliferative activity on a variety of cancer cell lines such as hepatocarcinoma cells,[26,47,48] leukaemia cells,[49] breast cancer cells,[50] lung adenocarcinoma,[51] epidermoid carcinoma cells and prostate cancer cells (Table 3).[52]

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In the Mediterranean region, coriander is often used as seasoning and in folk medicine. Usta *et al.* discovered that among all the components of coriander seed essential oils, the effect of linalool on different cell lines was the most potent.[26] The viability of HepG2 was reduced by 50% and 100% by 0.4 μM and 2 μM linalool, respectively. Similarly, linalool isolated from essential oil of ginger rhizome has been used as herbal medicine since ancient times. The *in vitro* cytotoxicity IC50 values of the isolated linalool were 25.23 and 46.01, exerting medium and weak anticarcinogenic effects against epidermoid carcinoma (HEP2) and human prostate cancer (PC-3) cell lines, respectively.[52] Jabir *et al.* found that the numbers of breast cancer (MCF-7) cells were reduced by linalool.[50] In addition, the clonogenicity, the ability of a single cell to grow into a colony, is inhibited slightly by linalool at the concentration of 10 μg mL^{-1}.

Linalool inhibits proliferation of a wide range of cell lines *via* cell cycle arrest. In leukaemia cells, the G_0/G_1 phase cells were reduced significantly after treatment of linalool. Moreover, the sub-G_1 phase cells were increased at the same time.[49] Similarly, the treatment of linalool in breast cancer cells significantly increased the sub-G_1 phase cells.[53] A significant G_0/G_1 phase arrest was observed in human hepatocarcinoma cell line HepG2 after exposure to linalool. The S phase cells were decreased concomitantly, whereas no differences in the G_2/M population were found.[48] Similar results were obtained in human lung adenocarcinoma A549 cells in a more recent research.[51] The possible molecular mechanism of linalool-mediated G_0/G_1 cell cycle arrest is the down-regulation of the expression of cyclin A, cyclin E, CDK4 and p53, and up-regulation of the expression of negative regulators of G_1 progression, p21 and p27.[48]

Linalool exerts anticancer activity by inducing apoptosis. Apoptosis is a controlled mechanism which inhibits the survival of cells with irreparable damage and prevents malignant transformation.[60] In leukaemia cells, treatment with linalool increased early apoptotic cells and late apoptotic cells, decreasing viable cells, while no obvious change was found in necrosis cells, which demonstrated that linalool reduced non-proliferation leukaemia cells at least partially by causing apoptosis.[49] Jabir *et al.* found that in breast cancer (MCF-7) cells, linalool caused membrane bleeding and disruption, loss of contact with adjacent cells and formation of lysosome vacuoles.[50] Furthermore, a cellular apoptotic DNA ladder and smear of MCF-7 cells was observed, which suggested that linalool induced cellular component damage and altered cellular metabolic function. Rodenak-Kladniew *et al.* assayed caspase-3 activity, PARP level and DNA fragmentation to examine the ability of linalool to induce apoptosis. Caspase-3 triggers intrinsic and extrinsic apoptosis *via* specific protein cleavage.[48] In human hepatocarcinoma HepG2 cells, the activity of caspase-3 was improved after exposure to linalool for 48 h. PARP is a substrate of caspase-3 and is a marker of apoptosis. Treatment with linalool for 48 h decreased the level of PARP and increased its cleavage products, which confirmed that the caspase in HepG2 was activated. DNA fragmentation, which is produced by caspase-activited endonucleases, is another hallmarker for late apoptosis. DNA broken in HepG2 cells was increased after the treatment with linalool for 48 h. These results showed that linalool led to apoptosis in HepG2 cells after exposure for 48 h. Interestingly, contradicting results were obtained in a more recent study, which showed that, although the cell viability of human lung adenocarcinoma A549 cells was inhibited up to 80–85%, apoptosis was not induced by linalool.[51] Activiated caspase-3, changes of procaspase-9 and PARP levels were not observed. These results demonstrated that linalool led to cell death in A549 cells *via* a pathway that was different to apoptosis. The mitogen-activated protein kinase (MAPK) signaling pathway is involved in linalool-induced apoptosis. MAPKs in mammals include JNK, p38 MAPK, and ERK. Gong *et al.* revealed that linalool inhibited p-ERK1/2 protein expression and improved p-JNK protein expression in T cell acute lymphoblastic leukemia cells.[58] Furthermore, ERK1/2-selective inhibitor PD98059 enhanced cancer cell apoptosis. In another study, specific ERK inhibitors also potientiated anticancer activity of linalool, indicating the MAPK signaling pathway was involved in linalool-induced apoptosis.[48] Gunaseelan *et al.* evaluated the effects of linalool on chronic ultraviolet-B (UVB) radiation-mediated photocarcinogenesis in mouse skin. The results showed that linalool administration inhibited the expression of anti-apoptotic B-cell lymphoma-2 (Bcl-2) and improved the expression of proapoptotic BCL2-associated X (Bax). This implied that linalool suppressed the photocarcinogenesis progress by inducing apoptosis in chronic UVB-irradiated mouse skin cells.[61,62]

Linalool induces reactive oxygen species (ROS) production, which leads to apoptosis of cancer cells. ROS generation was observed in linalool-treated hepatocellular carcinoma (HCC) HepG2 cells.[48] Moreover, apocynin (a specific NADPH oxidase inhibitor) neither inhibited ROS generation, nor prevented loss of cell viability induced by linalool. *N*-Acetyl-L-cysteine, a ROS scavenger, only partially rescued cell growth. These results suggest that ROS generation contributes at least in part to the anticancer effects of linalool. Likewise, linalool

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Table 1 The plant essential oil sources of linalool

Plant family	Latin name	English name	Tissue used	Growing location	Extraction methods	Analysis methods	Main components	Ref.
Annonaceae	*Cananga odorata* Hook. F. & Thomson	Ylang-ylang	Flowers	Varanasi, India	Hydro-distillation	GC, GC-MS	Linalool (24.6%), benzyl acetate (22.4%), *p*-methyl anisole (11.0%)	24
Apiaceae	*Coriandrum sativum*	Coriander	Fruits	Korba, Tunisia	Hydro-distillation	GC-MS, GC-FID	Linalool (79.2%), γ-terpinene (6.3%), camphor (2.6%), α-pinene (2.3%), geranyl acetate (1.8%), *p*-cymene (1.7%)	25
Apiaceae	*Coriandrum sativum*	Coriander	Seeds	Beirut, Lebanon	Hydro-distillation	GC-MS	Linalool (56.5%), *trans*-anethole (22.4%)	26
Apiaceae	*Coriandrum sativum* L.	Coriander	Fruits	Belgorod, Russia	Hydro-distillation	GC-MS, GC-FID	Linalool (70.1%), α-pinene (5.5%), camphor (5.0%), γ-terpinene (4.4%)	27
Apocyanaceae	*Carissa macrocarpa* (E_{CKL}.) A.DC.	Natal plum	Stems	Monastir, Tunisia	Hydro-distillation	GC-FID, GC-MS	Linalool (30.9%), hexahydrofarnesyl acetone (24.9%), heptadec-1-ene (11.8%), (*E*)-nerolidol (9.9%), intermedeol (8.6%), pentadecanal (7.2%)	28
Lamiaceae	*Aeollanthus suaveolens* Mart. ex Spreng	—	Leaves	Amapá, Brazil	Hydro-distillation	GC-MS	Massoialactone (64.8%), linalool (7.9%), (*E*)-β-farnesene (6.2%)	29
Lamiaceae	*Lavandula angustifolia*	Lavender	Flowers	Not mentioned	Hydro-distillation	GC-MS	Linalool (30.6%), linalyl acetate (20.4%)	30
Lamiaceae	*Ocimum basilicum* L.	Basil	Leafy stems	Al Butana, north Sudan	Hydro-distillation	GC-MS	Methyl chavicol (51.9%), linalool (20.0%)	31
Lamiaceae	*Ocimum basilicum* L.	Basil	Fresh whole plants	Dakar, Senegal	Hydro-distillation	GC, GC-MS	Estragole (73.3%), linalool (12.8%)	32
Lamiaceae	*Ocimum basilicum* L.	Basil	Fresh whole plants	Kaolack, Senegal	Hydro-distillation	GC, GC-MS	Estragole (79.0%), linalool (11.5%)	
Lamiaceae	*Origanum majorana* L.	Oregano	Aerial part	Errachidia, Morocco	Hydro-distillation	GC-MS	(−)-Alpha terpineol (29.3%), L-terpinen-4-ol (25.6%), beta-linalool (6.3%), 5-isopropyl-2-methylbicyclo [3.1.0] hexan-2-ol (4.9%), beta-phellandrene (4.0%)	33
Lamiaceae	*Thymus vulgaris* L.	Thyme	Whole plant	Lublin, Poland	Hydro-distillation	GC-MS	Thymol (34.8%), *p*-cymene (14.2%), carvacrol (6.2%), β-caryophyllene (5.5%), linalool (3.8%), terpinen-4-ol (2.6%), caryophyllene oxide (2.3%), borneol (2.2%)	34
Lauraceae	*Cinnamomum camphora* (L.) Presl.	Camphor tree	Leaves	Jiangxi, China	Hydro-distillation	GC-FID, GC-MS	Linalool (91.2%), camphor (0.1%)	35
Lauraceae	*Cinnamomum camphora* var. *linaloofera Fujita*	Camphor tree	Branches and leaves	Not mentioned	Hydro-distillation	GC-MS	Linalool (69.9%), camphor (10.9%), nerolidol (10.9%), safrole (8.2%)	36
Magnoliaceae	*Magnolia sirindhorniae*	Magnolia	Fresh buds	Lucknow, India	Hydro-distillation	GC-MS	Linalool (58.9%), β-elemene (4.4%), β-caryophyllene (3.5%)	37
Magnoliaceae	*Magnolia sirindhorniae*	Magnolia	Fresh flowers	Lucknow, India	Hydro-distillation	GC-MS	Linalool (51.0%), β-elemene (7.5%), β-caryophyllene (6.4%)	
Moringaceae	*Moringa peregrina*	Moringa	Seeds	Al Ain, United Arab Emirates	Hydro-distillation	GC, GC-MS	Geijerene (33.4%), linalool (23.4%), caryophyllene oxide (19.3%), *n*-hexadecane (12.6%), carvacrol (1.9%)	38
Nyctinaginacea	*Bougainvillea glabra*	—	Leaves	Lagos, Nigeria	Hydro-distillation	GC-MS	(*E*)-Nerolidol (31.4%), (*E*)-β-ionone (10.3%), linalool (10.1%)	39
Piperaceae	*Piper pseudofuligineum*	Pepper	Leaves	Hainan Island, south China	HS-SPME	GC-MS	β-Pinene (12.0%), α-pinene (6.7%), cinene (4.6%), myrcene (2.8%), linalool (1.6%)	40
Piperaceae	*Piper retrofractum*	Pepper	Leaves	Hainan Island, south China	HS-SPME	GC-MS	Ocimene (15.6%), linalool (12.9%), α-caryophyllene (9.6%), germacrene D (7.2%)	
Poaceae	*Cymbopogon citratus*	Citronella	Leaves and stalks	Amhara, Ethiopia	Hydro-distillation	GC-MS	Citral (71.3%), myrcene (19.0%), 4,5-epoxycarene (2.8%), linalool (1.7%), (*S*)-cisverbenol (1.1%), undecan-2-one (1.0%)	41
Rutaceae	*Zanthoxylum armatum*	Sichuan pepper	Leaves	Nepal	Hydro-distillation	GC-MS	Linalool (38.7%), undecan-2-one (22.8%), limonene (19.8%)	42
Rutaceae	*Citrus aurantium* L.	Bitter orange	Petals	Rasht, northern Iran	Maceration method	GC-MS	D-Glucuronic acid (9.5%), D-limonene (5.5%), octadecenoic acid (4.0%), daphnetin (3.7%), hexadecanoic acid (2.1%), linalool (2.1%), pyrrolidinone (1.2%), phthalic acid (0.7%)	43

GC, gas chromatography. GC-MS, gas chromatography-mass spectrometry. GC-FID, gas chromatography-flame ionization detector.

Table 2 Physical and chemical properties of L-linalool and D-linalool

Properties	L-Linalool	D-Linalool	Ref.
Synonyms	(*R*)-3,7-Dimethyl-1,6-octadien-3-ol; 1,6-octadien-3-ol,3,7-dimethyl-, (*R*)-2,6-Dimethyl-2,7-octadien-6-ol	(*S*)-3,7-Dimethyl-1,6-octadien-3-ol; 1,6-octadien-3-ol,3,7-dimethyl-, (*S*)-; (*S*)-linalool; (*S*)-(+)-linalool	15 and 16
CAS registry number	126-91-0	126-90-9	15 and 16
EINECS number	204-811-2	204-810-7	15 and 16
RIFM number	128		14
Formula	$C_{10}H_{18}O$		14–16
Molecular weight	154.53		15 and 16
Boiling point	198 °C		14
Melting point	Less than 20 °C		14
log K_{ow} (calculated)	3.38		15 and 16
Vapor pressure (calculated)	~0.00826 mmHg (at 25 °C)	~0.00498 mmHg (at 25 °C)	15 and 16
Water solubility (calculated)	683.7 mg L^{-1} (at 25 °C)		14–16
Henry's law	0.0000423 atm m^3 mol^{-1} (at 25 °C)		15 and 16
Specific gravity	0.861 g mL^{-1} (at 20 °C)		14
UV spectra	Does not significantly absorb in the region of 290–700 nm		14
Appearance	Colourless to very faint yellow liquid		14
Odour	Woody, floral and lavender-like aroma	Sweet, floral, herbaceous with a citrus and fruity hint	14
	Refreshing, floral, woody odour similar to that of bergamot oil and French lavender		

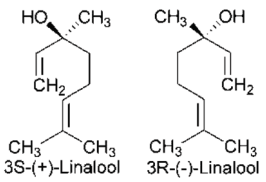

Fig. 1 Linalool enantiomers.

decreased adenosine triphosphate (ATP) levels and glutathione (GSH) levels and increased ROS levels in HepG2 cells.[26] Nevertheless, the results implied that the decrease of ATP levels and GSH levels, as well as the increase of ROS levels, precede cell death and are not consequences of cell death.

Mitochondria are one of the intracellular targets of linalool. The ROS production induced by linalool led to mitochondrial damage. The collapse of mitochondria membrane potential was observed, which was a major stimulus for apoptosis, indicating that linalool triggered apoptosis by altering mitochondrial integrity.[48] Usta *et al.* isolated mitochondria of HepG2 cells and examined the activity of complex I (NADH oxidase and NADH-UQ reductase) and complex II (succinate dehydrogenase). The results showed that complex I and complex II were both inhibited by linalool, which decreased the flow of electrons in the respiratory chain, leading to the drop in intracellular ATP levels.[26] The derangements of mitochondrial functions were the reason for the death of the HepG2 cells. A down-regulation of intracellular ATP levels was also observed in the study of Becker *et al.*[63]

Inhibition of angiogenesis is another approach through which linalool exerts anticancer effects. Angiogenesis contributes to a series of diseases including cancer. Accordingly, inhibition of angiogenesis is a promising therapy against cancer. Linalool inhibited proliferation, migration, tube formation and spheroid sprouting of human dermal microvascular endothelial cells (HDMECs) without cytotoxicity.[63] The underlying mechanisms of the inhibition were the induction of extracellular signal-regulated kinase phosphorylation, the down-regulation of intracellular ATP levels and the activation of the transient receptor potential cation channel subfamily M (melastatin) member 8. Vascular sprouting of rat aortic rings was suppressed by linalool. Moreover, the implementation of matrigel plugs containing linalool significantly reduced the microvessel density in BALB/c mice.

Linalool has a protective effect on normal cells. Gu *et al.* found that linalool suppressed the growth of leukaemia cells, while the proliferation of normal hematopoietic cells was almost not affected by linalool.[49] Similarly, linalool was found to suppress the growth of A549 tumour cells, while it had no cytotoxicity to normal WI-38 cells.[51] However, linalool was reported to cause high haemolysis and rupturing of human red blood cells, which was due to its ability to penetrate the cell membrane. The *in vivo* toxicity of linalool was investigated in the research of Jabir *et al.*[50] After intraperitoneal injection of linalool, the body weight and total blood cell count of the experimented BALB/c mice were not affected. In liver tissues, there were no significant changes in the hepatic cords, mild vacuolar and hepatic lobules. In kidney tissues, no atrophy of the glomerular and renal tubular epithelial cells was observed in the study. Similarly, in the spleen, the results showed no significant reduction in the number of lymphocytes in the lymphoid nodules of the spleen. Consequently, the exposure to linalool induced no histopathological changes in the liver, kidney, and spleen of the experimented animals.

Due to the susceptibility to heat, light and oxygen of linalool, encapsulation is used to improve its stability and bioavailability.[64] Encapsulation is a method of building a functional barrier between the core and wall material and is widely applied to enhance the bioactive and physicochemical pro-

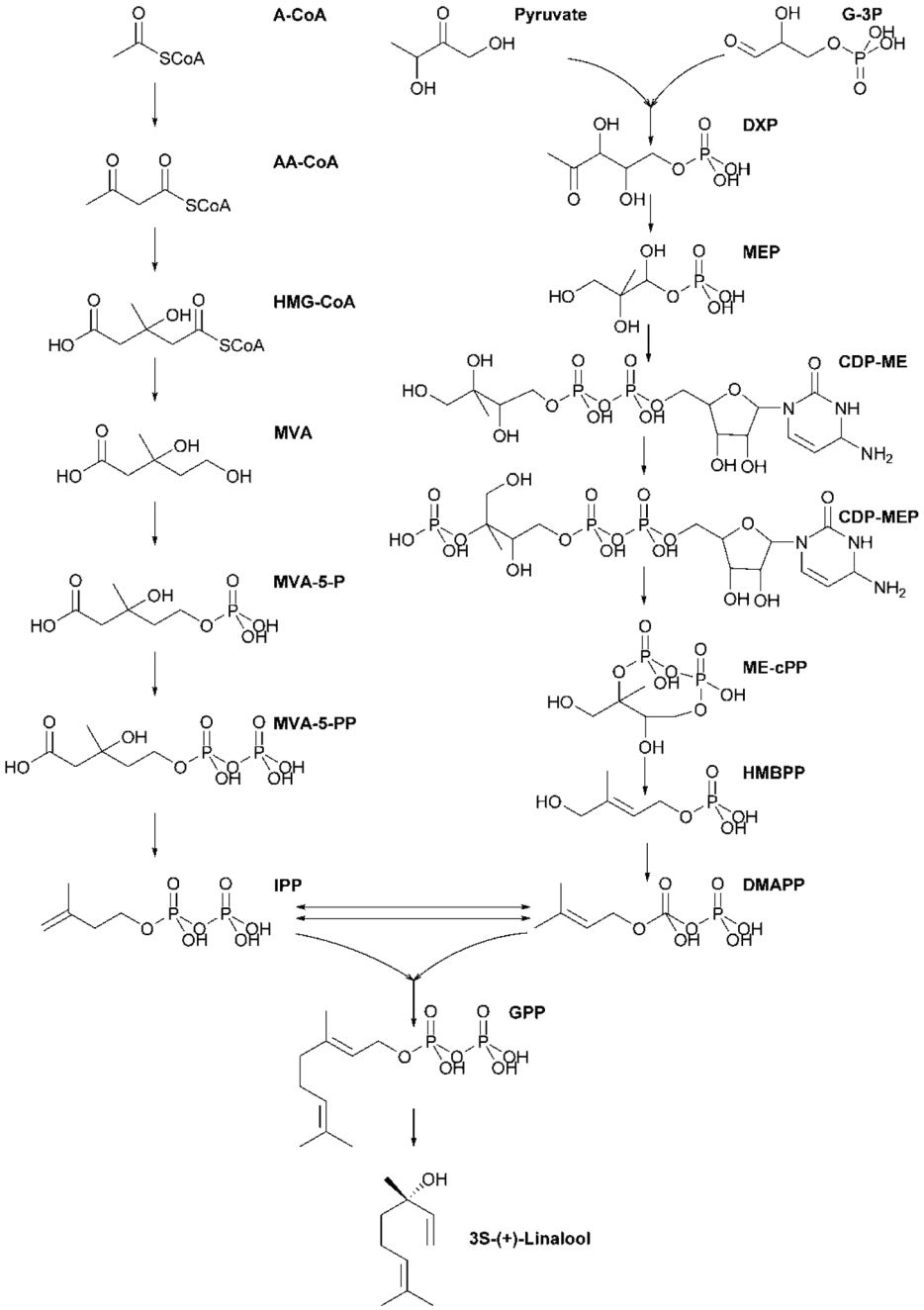

Fig. 2 Biosynthesis of *S*-(+)-linalool[5] A-CoA, acetyl-CoA; AA-CoA, acetoacetyl-CoA; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; MVA, mevalonate; MVA-5-P, mevalonate 5-phosphate; MVA-5-PP, mevalonate pyrophosphate; IPP, isopentenyl pyrophosphate; DMAPP, dimethylallyl pyrophosphate; GPP, geranyl diphosphate; G-3P, glyceraldehyde 3-phosphate; DXP, 1-deoxy-D-xylulose 5-phosphate; MEP, 2-*C*-methyl-D-erythritol 4-phosphate; CDP-ME, 4-diphosphocytidyl-2-*C*-methyl-D-erythritol; CDP-MEP, 4-diphosphocytidyl-2-*C*-methyl-D-erythritol 2-phosphate; ME-cPP, 2-*C*-methyl-D-erythritol 2,4-cyclopyrophosphate; HMBPP, 1-hydroxy-2-methyl-2-(*E*)-butenyl 4-pyrophosphate.

perties of essential oils.[65] Solid lipid nanoparticles were used to encapsulate linalool in the research of Rodenak-Kladniew *et al.*[66] The encapsulated linalool displayed a spherical shape and the mean diameters were around 100 nm with a narrow size distribution. The capsulation percentages of linalool in solid lipid nanoparticles were higher than 80%. The encapsulated linalool showed excellent *in vitro* controlled release properties for at least 72 h. The results showed a good incorporation of linalool in lipid carriers which was higher than 80%. Furthermore, the anticancer effects of encapsulated linalool were higher than that of free linalool. In the study of Jabir *et al.*, linalool was loaded on gold nanoparticles and then the complex was conjugated with CALNN peptide.[50] The average size of linalool-gold nanoparticles-CALNN was 18–25 nm. The

Table 3 Anticancer mechanism of linalool in different cell lines

Cell lines	Inhibitory concentrations	Mechanisms	Ref.
Human hepatocarcinoma cells (HepG2)	Linalool treatment of 0.4 μM and 2 μM for 24 h decreased cell viability of 50% and 100%, respectively	Inhibits mitochondrial complexes I and II, increases ROS and decreases ATP and GSH levels	26
Acute myeloid leukaemia (Kasumi-1, HL-60), human Burkitt's lymphoma (Raji) and human acute T-lymphoblastic leukaemia cells (Molt-4)	IC50 values at 48 h ranging from 49.53 to 127.14 μM	Induces robust apoptosis *via* up-regulating p53 and cyclin-dependent kinase inhibitors	49
Colorectal (SW 620), breast (T-47D), liver (HepG2) and lung (A549) cancer cells	IC50 values at 24 h were 222, 224, 290 and 438 μM, respectively	Leads to apoptosis, induces Th1 cellular immune response	54
Human lung adenocarcinoma cells (A549) and human hepatocarcinoma cells (HepG2)	IC50 values at 24 h were 1160 and 1191 μM, respectively	Inhibits the mevalonate pathway (MP), probably at different points	47
Human colon cancer cells (HCT 116)	Linalool treatment of 250 μM L^{-1} for 24 h stopped cell proliferating	Induces apoptosis by inducing cancer-specific oxidative stress	55
Human glioblastoma cells (U87-MG)	Linalool treatment of 25–100 μM for 24–72 h significantly reduced cell viability in a dose- and time-dependent manner	Increases the expression of acetylated SOD2, decreases the interaction between SOD2 and SIRT3, improves mitochondrial ROS production and apoptosis	56
Human hepatocarcinoma cells (HepG2)	Linalool treatment of 1.0–2.5 mM after 24–48 h and 0.5–2.5 mM after 72 h significantly decreased cell viability in a dose- and time-dependent manner	Oxidative stress generation and modulation of Ras/MAPK and Akt/mTOR pathways	48
Breast cancer cells (MCF-7)	Linalool treatment of 10 μg mL^{-1} after 48 h exerted low cytotoxicity	Exerts cell growth arrest and induces apoptosis	50
Human ovarian cancer cells (SKOV-3)	Linalool treatment of 10 μg mL^{-1} after 48 h slightly inhibited cell proliferation	Induces apoptosis, inhibits NF-κB translocation	57
Human acute T-lymphoblastic leukaemia cells (Jurkat, H9, Molt-4 and Raji)	IC50 values at 48 h were 31.35, 22.16, 25.80 and 25.19 μM, respectively	Induces apoptosis *via* MAPK signaling pathways, JNK activation and ERK inhibition	58
Human lung adenocarcinoma cells (A549)	IC50 values at 24 h and 48 h were 1.79 and 1.13 mM, respectively	Induces cell cycle arrest, increases ROS production and mitochondrial membrane potential depolarization, inhibits cell migration	51
Human prostate cancer cells (22Rv1)	IC50 values at 48 h were 3.384 mM	Induces apoptosis, reduces the expression of Ki-67 and PCNA	59

IC50, half maximal inhibitory concentration.

CALNN peptide, which could be specifically trapped by the endoplasmic reticulum, improved the cellular uptake of linalool-gold nanoparticles in living cells. Therefore, the linalool-gold nanoparticles-CALNN could be transported to the nucleus of breast cancer MCF-7 cells. Linalool exhibited low cytotoxicity and low morphology variation of the MCF-7 cells, while linalool-gold nanoparticles-CALNN showed high anticancer activity and morphology variation in the cells. In addition, the complex displayed higher inhibition of colony formation compared with free linalool.

Linalool is found to have synergistic effects with other anticancer drugs. Miyashita & Sadzuka combined linalool with doxorubicin (DOX), an anthracycline antitumor agent.[67] The results showed that linalool improved the DOX influx system and increased the concentration of DOX in P388 leukaemia cells. The mechanism is that linalool could affect DOX transport through concentrative Na^+-dependent nucleoside transporter 3. Moreover, the combination of linalool with DOX decreased more tumour weight than DOX alone in BDF1 mice. Consequently, linalool is an effective DOX modulator which can increase DOX concentration in tumour cells and improve the antitumor activity of DOX. Wi *et al.* encapsulated linalool nanoemulsions and DOX with liposomes as a two-in-one hybrid system.[68] The combination therapy suppressed HeyA8 epithelial ovarian tumour growth in mice compared with DOX encapsulated liposomes. Rodenak-Kladniew *et al.* combined linalool and statins, both of which had anticancer and anticholesterogenic activity.[47] The results proved that linalool exerted multiple effects on lipid metabolism and cell viability *via* inhibiting the mevalonate pathway (MP). Furthermore, the combination of linalool and simvastatin had synergistic antiproliferation and anticholesterogenesis effects on HepG2 human-hepatoma cells. In a more rencent study, the synergistic effects between linalool and simvastatin were also oberved in human lung adenocarcinoma A549 cells.[51] The combination increased G_0/G_1 cell cycle arrest and sensitized the A549 cells to apoptosis. Therefore, linalool is a promising sensitizer which is capable of enhancing the anticancer activity of DOX or simvastatin.

Linalool has antiproliferative activity on a variety of cell lines with low cytotoxicity to normal cells. The anticancer effects of linalool are exerted *via* different approaches, and the underlying mechanism still needs to be revealed. More *in vivo* studies are in need too. Encapsulation is a potential approach to enhance the stability and antiproliferative effects of linalool. Linalool is also an effective modulator to other anticancer drugs which can enhance the antiproliferative effects of them.

Antibacterial and antifungal activity

In recent decades, reduced antimicrobial effectiveness, increased infection, and growing antibiotic resistance have become a public health problem globally.[69] Thus, there is an urgent need for effective strategies to solve these problems. Linalool is reported to exhibit the function that it can inhibit a wide spectrum of bacteria and fungi, such as *Escherichia coli*, *Salmonella enterica*, *Staphylococcus aureus*, *Listeria monocytogenes*,[70] *Acinetobacter baumannii*,[71] *Pseudomonas aeruginosa*,[27] *Proteus mirabilis*,[72] *Candida albicans*,[73] *Microsporum canis* and *Microsporum gypseum* (Table 4).[74]

Linalool inhibits bacterial growth *via* disruption of the cell membrane. Liu *et al.* investigated the antibacterial mechanism of linalool on *Pseudomonas aeruginosa*.[75] The results revealed that the cell membrane integrity was destroyed, and the normal morphology of the cell was disrupted, which was proved by the release of nucleic acids and the decrease of membrane potential. In addition, the respiratory chain of the cell was interrupted by respiratory chain dehydrogenase. In another study, the disruption of cell membrane integrity was also observed.[76] Moreover, linalool can reduce the virulence of bacteria. Skalicka-Woźniak *et al.* illustrated that in *Escherichia coli*, linalool bound to the major and minor grooves of plasmid DNA and changed its structure.[34] Therefore, the pKM101 plasmid transfer between *Escherichia coli* was inhibited, and the virulence and resistance spread were reduced.

Linalool is able to inhibit the biofilm formation of bacteria and fungi, including *Acinetobacter baumannii*,[71] *Candida albicans*,[73] *Proteus mirabilis*[72] and *Salmonella typhimurium*.[76] Biofilm is a group of surface-attached bacteria that aggregates in a hydrated polymeric matrix synthesized by themselves.[77] The formation of biofilm is one of the important causes of antibiotic resistance and persistent infection, making the cure for infection difficult.[78] In the study of Durgadevi *et al.*, linalool exerted antibiofilm effects against the crystalline biofilm of *Proteus mirabilis*, which was a leading cause of catheter-associated urinary tract infections.[72] Untreated samples showed a highly structured and dense layer of biofilm, while in linalool-treated samples, there were fewer loads of interlinked cells adhering to the slide. The linalool-induced inhibition of biofilm formation was through reducing production of the virulence enzyme urease and driving crystal formation in the biofilm. Similarly, linalool inhibited biofilm formation and dispersed the formed biofilm of *Acinetobacter baumannii*, changed the bacterial adhesion process to surfaces, and interfered with the quorum sensing system.[71] In addition, linalool has antibiofilm effects on fungi as well. Manoharan *et al.* investigated the antibiofilm activity of linalool against *Candida albicans*, which was one of the most common fungal pathogens that caused infections in humans.[73] In the study, linalool inhibited hyphal formation, which was the main cause of its antibiofilm activity.

Encapsulation is often used to improve the antimicrobial activity of linalool.[79] Zhou *et al.* encapsulated linalool with amylose and oxidized amylose.[80] The results indicated that the encapsulated linalool showed excellent antimicrobial effects against *Escherichia coli* and *Staphylococcus aureus.* In addition, oxidized amylose-linalool inclusion complex displayed better antimicrobial activity than amylose-linalool inclusion complex. The reason was that amylose-linalool inclusion complex would aggregate and retrograde fast in the aqueous system, which was disadvantageous for the release of linalool. Lyu *et al.* also demonstrated the high antimicrobial activity of oxidized amylose encapsulated linalool and its effects on wound healing.[81] In the study of Aytac *et al.*, cyclodextrin/linalool-inclusion complex nanofibers were fabricated with a maximum loading of 12% (w/w).[82] The nanofibers exhibited high thermal stability and fast-dissolving characteristics. Furthermore, linalool released from the nanofibers suppressed the growth of *Escherichia coli* and *Staphylococcus aureus* to a great extent. Similar results were also obtained in more recent research.[83] Jabir *et al.* loaded linalool on glutathione-modified gold nanoparticles and investigated its antimicrobial activity.[84] The results revealed that the linalool loaded glutathione-modified gold nanoparticles (LIN-GNPs) improved the permeability of linalool to the cell wall, induced ROS production, and led to nuclear acid damage of bacteria. Therefore, the antimicrobial effects of LIN-GNPs were higher than that of pure linalool. In addition, the anti-parasitic effects of LIN-GNPs against *Leishmania tropica* were also observed. In the study of Hu *et al.*, emulsified linalool droplets were modified with carbon–carbon double bonds, followed by the precipitation polymerization with *N*-vinyl caprolactam, a thermal sensitive monomer.[85] The prepared linalool capsules displayed thermal-redox dual responsive properties, high antioxidant activity and high antimicrobial activity. Hollow mesoporous silica spheres were applied to encapsulate linalool in another research study.[70] The linalool-loaded hollow mesoporous silica spheres presented a high loading capacity of 1500 mg g^{-1}, and efficiently improved the antimicrobial activity of linalool. In another study, linalool was loaded with poly (butylene adipate-*co*-terephthalate) (PBAT) nanocapsules.[86] The results implied that the encapsulation efficiency was better with higher PBAT contents, because the wall thickness of the nanocapsules was improved. Moreover, the nanocapsules showed high antimicrobial activity against *Escherichia coli*. Linalool nanoemulsions also possess great antimicrobial properties. Prakash *et al.* prepared linalool nanoemulsions with Tween 80 and water using ultrasonic assisted emulsification.[76] The nanoemulsions showed improved antimicrobial effects against *Salmonella typhimurium* because of the enhanced ability to destroy cell membrane integrity.

In addition, the nanoemulsions displayed higher antibiofilm activity and effectively decreased *Salmonella typhimurium* biofilm on the surface of fresh cut pineapple.

Linalool has synergistic antibacterial effects with essential oils and antibiotics. Herman *et al.* added linalool into essential oils and studied its antimicrobial effects.[89] The results proved that linalool-enriched essential oils displayed stronger inhibition effects to a wide spectrum of microorganisms than essential oils alone. Consequently, the synergistic effects

between linalool and essential oils could improve its antimicrobial activity and decrease its concentration in products, which was beneficial to the sensory qualities of the products. In another study, the synergistic interaction between linalool and antibiotics against bacteria was investigated.[27] The synergy against Gram-positive bacteria (methicillin-resistant *Staphylococcus aureus*, *Staphylococcus epidermidis*) and Gram-negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*) was observed. The susceptibility of bacteria to antibiotics was improved. Furthermore, the antibiotic resistance was reversed by the synergistic effects.

Neuroprotective effects

Linalool has been reported to exert protective effects on the central nervous system, including alleviating the damage induced by neurotoxic chemicals,[90–92] Alzheimer's disease[91,93–95] and ischemic stroke,[96–98] improving memory,[99,100] exerting anxiolytic effects,[101–103] antidepressant effects[104] and anti-stress activity.[100,105]

Linalool can offer protection for the central nervous system against neurotoxic chemicals, such as acrylamide, glutamate, hydrogen peroxide (H_2O_2), D-galactose and aluminium trichloride. Acrylamide is neurotoxic to the central and peripheral nervous system and can be formed during the process of food heating. The protective effects of linalool against acrylamide in Wistar rats were examined in the study of Mehri *et al.*[90] The results showed that the acrylamide-induced gait abnormalities of rats were significantly reduced by linalool. The increased glutathione levels were also reduced by the injection of linalool. Malondialdehyde (MDA) is one of the products of lipid peroxidation induced by oxidative stress. The reduction of MDA showed that linalool decreased the lipid peroxidation in

Table 4 Antibacterial effects of linalool

Bacteria	MIC	MBC	Inhibitory effects	Ref.
Acinetobacter baumannii	2–8 μL mL^{-1}	2–8 μL mL^{-1}	Linalool showed good antimicrobial properties and fast bactericidal action, inhibited biofilm formation, dispersed established biofilms, changed bacterial adhesion to surfaces and interfered with the quorum-sensing system.	71
Escherichia coli	1.6 mg mL^{-1}	—	Saturated amylose-linalool inclusion complex solutions showed excellent antimicrobial activity. Oxidized amylose-linalool inclusion complex had higher antimicrobial activity than amylose-linalool inclusion complex, which aggregates and retrogrades fast and hence releases linalool slowly.	80
Staphylococcus aureus	0.8 mg mL^{-1}	—		
Escherichia coli	0.77 mg mL^{-1}	0.77 mg mL^{-1}	Linalool alone had low activity against Gram-positive and Gram-negative bacteria, while linalool-gold nanoparticles presented considerable antibacterial effects against Gram-positive bacteria by acting on cell membranes, stimulating ROS production, and damaging nucleic acids.	84
Staphylococcus aureus	1.54 mg mL^{-1}	3.08 mg mL^{-1}		
Staphylococcus aureus	5.36 μg mL^{-1}	—	Linalool was the main antibacterial component of coriander essential oil, which increased antibiotic susceptibility and reversed antibiotic resistance.	27
Staphylococcus epidermidis	5.36 μg mL^{-1}	—		
Pseudomonas aeruginosa	5.36 μg mL^{-1}	—		
Escherichia coli	5.36 μg mL^{-1}	—		
Proteus mirabilis	0.8 mg ml^{-1}	—	Linalool showed strong antimicrobial effects against *P. mirabilis* by reducing production of urease that raises urinary pH, driving formation of crystals in the biofilm and inhibiting formation of crystalline biofilm.	72
Salmonella typhimurium	1.25%	1.25%	Linalool alone had weak antibacterial activity, while linalool nanoemulsions showed high antibacterial and antibiofilm activity through increased ability to disrupt cell membrane integrity.	76
Escherichia coli	0.686 mg mL^{-1}	1.716 mg mL^{-1}	Linalool showed moderate antimicrobial effects. Gram-positive bacteria are slightly more sensitive than Gram-negative bacteria.	87
Salmonella enterica	0.420 mg mL^{-1}	0.686 mg mL^{-1}		
Staphylococcus aureus	0.420 mg mL^{-1}	1.716 mg mL^{-1}		
Escherichia coli	200 μg L^{-1}	250 μg L^{-1}	Linalool had significant antibacterial activity, which is the main antibacterial component of the vapor-phase *Cinnamomum camphora* essential oil.	36
Escherichia coli	2 mg mL^{-1}	5 mg mL^{-1}	Linalool showed strong antimicrobial effects to *E. coli* and *S. enterica*, while showing moderate effects to *S. aureus* and *L. monocytogenes.* Linalool-functionalized hollow mesoporous spheres could efficiently break the structure of microbial cell membranes and improve the bactericidal activities of linalool	70
Salmonella enterica	2 mg mL^{-1}	5 mg mL^{-1}		
Staphylococcus aureus	4 mg mL^{-1}	10 mg mL^{-1}		
Listeria monocytogenes	4 mg mL^{-1}	10 mg mL^{-1}		
Pseudomonas aeruginosa	431 μg mL^{-1}	862 μg mL^{-1}	Linalool had strong antibacterial activity against *P. aeruginosa via* destroying respiratory chain and membrane integrity by releasing nucleic acids and decreasing membrane potential.	75
Escherichia coli	1600 mg L^{-1}	—	Linalool showed weak antimicrobial effects. *E. coli* was more susceptible than *S. typhimurium*. Chitosan nanoparticles loaded with monoterpenes showed more antibacterial activity than pure monoterpenes.	88
Staphylococcus typhimurium	1800 mg L^{-1}	—		

MIC, minimum inhibitory concentration. MBC, minimal bactericidal concentration.

the brain tissue of rats. This indicated that linalool exerted protective effects on the nervous system *via* inhibition of oxidative stress, which was an important pathway of acrylamide neurotoxicity. In addition, the effects of linalool injection before or simultaneously with acrylamide administration were better than that after acrylamide administration. Glutamate could evoke oxidative stress and mitochondrial dysfunction in neuronal cells. An *in vitro* model of immortalized neuronal HT-22 cells indicated that linalool reduced glutamate-induced cell death by inhibiting ROS, reducing calcium levels, and restoring the membrane potential of mitochondria.[92] Furthermore, linalool enhanced uncoupled respiration, which contributed to its neuroprotective activity. Similarly, linalool was found to counteract H_2O_2-induced oxidative stress in PC12 cells.[106] Linalool protected PC12 cells through inhibiting lactate dehydrogenase release, counteracting ROS overproduction and decreasing cell apoptosis induced by H_2O_2. It is reported that combined injection of D-galactose and aluminium trichloride leads to cognitive deficits and pathological changes, such as abnormal cholinergic system, mitochondrial dysfunction, amyloid-β peptide deposition, and oxidative stress. Xu *et al.* found that linalool treatment alleviated cognitive impairments induced by D-galactose and aluminium trichloride in mice.[107] Besides this, linalool improved the suppressed superoxide dismutase (SOD) activity and glutathione peroxidase (GPx) activity, whereas it attenuated the increased acetylcholinesterase (AChE) activity and MDA content. Nuclear factor-erythroid 2 related factor 2 (Nrf2) is a critical regulator for various inflammatory and immune responses *via* regulating oxidative stress. In this study, linalool enhanced the expression of Nrf2 and heme oxygenase-1 (HO-1), which was reduced by D-galactose and aluminium trichloride. The increase of synapse plasticity-related proteins was also observed. Accordingly, linalool protected the nervous system from D-galactose and aluminium trichloride through inhibiting oxidative stress, reversing cholinergic system dysfunction, enhancing protein expression of Nrf2/HO-1 pathway, and increasing synaptic plasticity.

Linalool exerts protective effects against neuropathological impairments induced by Alzheimer's disease (AD). AD is a progressive neurodegenerative disease which is characterized by the destruction of nerve cells in the brain. AD leads to memory loss and language problems, damages basic bodily functions, and is ultimately fatal. According to a recent report, an estimated 6.2 million Americans of 65 and older are living with AD.[108] In 2019, over 121 thousand deaths from AD were recorded, making AD the sixth-leading cause of death in America. The costs of health care for patients with AD or other dementia are substantial, and dementia is one of the costliest conditions to society. Therefore, discovering a therapy for AD is in urgent need. Guáqueta *et al.* studied the effects of oral administration of linalool on triple transgenic models of AD mice.[93] The experimented mice showed enhanced learning and spatial memory and better risk assessment behaviour. Extracellular β-amyloidosis, tauopathy, astrogliosis, microgliosis, and levels of pro-inflammatory markers in the hippocampi and amygdalae of linalool-treated mice were reduced significantly. These results implied that linalool restored cognitive and emotional functions and reversed histopathological hallmarks of AD. Amyloid β (Aβ)-mediated oxidative stress and apoptosis are the main pathogenesis of AD. The effects of linalool against $A\beta_{1\text{-}40}$-induced cognitive deficits in mice were investigated in the study of Xu *et al.*[91] The cognitive performance of the experimental mice was improved by linalool administration. Furthermore, linalool alleviated hippocampal cell injury, apoptosis and oxidative stress induced by $A\beta_{1\text{-}40}$ *via* the activation of Nrf/HO-1 signalling. A study of $A\beta_{42}$-induced neurodegeneration in flies showed that the survival rate of AD model flies was improved by linalool, while the survival of wild-type flies was not affected even at high linalool concentrations.[95] Instead of reducing the amount or aggregation of $A\beta_{42}$, linalool elicited protective effects by inhibiting ROS production, oxidative stress, and inflammatory response in the brains of flies. The protective effects of linalool against Aβ were also investigated *in vitro*.[94] The results of neuronally differentiated PC12 cells exposed to $A\beta_{1\text{-}42}$ oligomers were in accordance with previous *in vivo* studies. Linalool enhanced the cell viability and attenuated the nuclear morphology abnormalities. Moreover, ROS production and the activity of caspase-3 were inhibited by linalool.

Linalool can also provide protection for the central nervous system against the injury of ischemic stroke. Stroke is one of the leading causes of mortality and disability globally.[109] Ischemic stroke accounts for approximately 80–85% of all cases of stroke and leads to disruption of cerebral blood flow and oxygen deprivation.[110] An *in vitro* model of ischemic stroke was established to investigate the effects of linalool on oxygen-glucose deprivation/reoxygenation-induced cortical neuronal injury.[98] The results showed that linalool significantly alleviated the cortical neuronal injury and inhibited microglial migration *via* its antioxidant and anti-inflammatory effects. Besides inhibiting the progression of ischemic stroke injury, linalool can also attenuate the impairment caused by long-term ischemia. Guáqueta *et al.* found that oral administration of linalool protected neurons and astrocytes from one-month global cerebral ischemia in Wistar rats.[96] The linalool-treated rats displayed faster neurological recovery and better motor and cognitive performances. Additionally, the altered phospholipid profiles in the hippocampus and periphery of the injured rat brains were attenuated by linalool. Further study discovered that intranasal administration of linalool allowed faster delivery to the central nervous system than oral administration.[97] Daily intranasal administration of linalool led to acute and chronic recovery from ischemia, which mainly attributed to the reduction of microgliosis and its anti-inflammatory effects.

Linalool exhibits effects on the improvement of memory, too. Lee *et al.* found that linalool ameliorated the memory loss behavioural impairment induced by deprivation of rapid eye movement (REM) sleep.[100] The REM-sleep deprived mice showed better memory and behavioural performances after linalool treatment, which worked through the release of seroto-

nin and the reduction of cortisol. A study of 69 young healthy adults showed that dermal application of linalool exerted a relaxing effect and improved cerebral blood flow in basal ganglia.[99] Furthermore, dermal application of linalool decreased the error rate in a working memory task. However, no changes were observed after inhalation of linalool.

Several studies have confirmed the anxiolytic, antidepressant, and sedative effects of linalool. Cheng *et al.* discovered that linalool displayed excellent anxiolytic activity in mice without any side effects on motor activity.[103] Moreover, linalool decreased serotonin, dopamine, and norepinephrine in the frontal cortex and hippocampus of mouse brains, which contributed to anxiolytic effects on the animal models. Santos *et al.* investigated the antidepressant effects of three essential oils on Wistar rats.[104] The results illustrated that the antidepressant effects of the essential oils were attributed to their high proportion of linalool. Furthermore, the antidepressant activities of essential oils were better than that of pure linalool, which suggested synergistic effects between linalool and other compositions of essential oils. In addition, no impairments of spontaneous locomotion and memory retention were observed in the experimented rats. Yoshida *et al.* revealed the anti-stress effects of linalool inhalation on restraint stressed rats and the underlying molecular mechanism.[105] The results showed that linalool influenced the overall gene expression in the hypothalamus, including genes associated with synaptic transmission. Furthermore, the expression of major histocompatibility complex class I and anxiolytic neuropeptides such as oxytocin and neuropeptide Y were upregulated by linalool inhalation. Anti-stress activity of linalool was observed in REM-sleep deprived mice too.[100] Ota *et al.* detected the cerebral blood flow changes of healthy male volunteers before and after linalool inhalation.[111] The results found significant cerebral blood flow reductions in the right superior temporal gyrus to insula and the anterior cingulate cortex after inhalation, which contributed to the anxiolytic effects of linalool. It is reported that linalool exerts sedative effects through modulation of a glutamate neurotransmitter by binding to glutamatergic *N*-methyl-D-aspartate (NMDA) receptors.[112] Xu *et al.* discovered that the combined therapy of linalool and Shenque acupoint enhanced sleep quality *via* improved sleep rate shortened sleep latency and prolonged sleep duration in mice and rats.[113]

Hepatic and renal protective activity

Linalool is reported to attenuate hepatic damage induced by a variety of toxic chemicals, such as carbon tetrachloride (CCl_4), benzene, lipopolysaccharide (LPS) and D-galactosamine (GalN). LPS induces the production of inflammatory cytokines, which results in liver tissue injury. GalN is a specific hepatotoxic chemical agent which inhibits macromolecule synthesis. An acute liver injury model of mice was established by LPS/GalN to evaluate the protective effects of linalool and to investigate the underlying mechanism.[114] The serum ALT and AST levels of linalool-treated mice were significantly reduced, which showed the condition of liver injury was attenuated by linalool. The increase of *Bcl-2* expression and the decrease of caspase-3 and caspase-8 expression indicated that linalool improved survival and inhibited the apoptosis of liver cells. Tumour necrosis factor-α (TNF-α), IL-6, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) are important inflammatory mediators and play a critical role in the development of LPS/GalN-induced liver injury. Linalool decreased the levels of TNF-α, IL-6, iNOS and COX-2 through the inhibition of the nuclear factor-κB (NF-κB). Linalool administration reduced hepatic MDA levels and activated Nrf2, which suggested linalool decreased oxidative stress and induced antioxidant defence. In conclusion, linalool alleviated LPS/GalN-induced liver injury in mice by reducing the inflammatory response *via* NF-κB inhibition and by inducing antioxidant defence *via* Nrf2 activation. CCl_4-induced oxidative stress is responsible for liver injury and mostly leads to the progression of fatty liver, necrosis, fibrosis, cirrhosis, and hepatocellular carcinoma. In a CCl_4-induced liver injury model of rats, the linalool-mediated decrease of MDA, AST and ALT levels was also observed.[115] In addition, the activity of GSH and catalase (CAT) was improved by linalool administration. In another study, besides inhibiting TNF-α, IL-6 and NF-κB expression, the levels of serum total protein, serum albumin and antioxidants were also decreased by linalool in CCl_4-induced liver injured rats.[116] Ben Hsouna *et al.* discovered the hepatoprotective effects of *Lobularia maritima* essential oil, which contained a high content of linalool.[117] The increase of CCl_4-induced hepatic TBARS contents were significantly attenuated by pre-treatment of *Lobularia maritima* essential oil, which implicated that the lipid peroxidation in the liver of CCl_4-treated rats was inhibited. Furthermore, CCl_4 resulted in excessive necrosis and neutrophilic infiltration. However, the severe hepatic damage was markedly alleviated by injection of *Lobularia maritima* essential oil. In addition, *Lobularia maritima* essential oil exerted anti-inflammatory effects against LPS through the down-regulation of the expression of inflammatory cytokines and mediators, such as IL-1, IL-6, TNF-α, NO, iNOS, COX-2. Benzene is a volatile hydrocarbon that leads to the injury of a variety of organs, including the liver, through oxidative stress. In benzene-induced liver injured rats, post-treatment of linalool counteracted the elevation of hepatic MDA levels. The levels of non-enzyme antioxidant (GSH) and antioxidant enzymes (SOD and CAT) were improved by linalool treatment. Moreover, benzene led to DNA damage in the liver of rats through generating free radicals and increasing DNA fragmentation, which was significantly attenuated by linalool administration. Accordingly, linalool alleviated the benzene-induced oxidative toxicity in the liver of rats *via* its antioxidant activity.[118]

Linalool can also protect the kidneys from injury induced by CCl_4, 7,12-dimethylbenz-[*a*]anthracene (DMBA), streptozotocin, DOX and cisplatin. In the study of Mazani *et al.*, CCl_4-induced nephric damages were attenuated by linalool *via* down-regulation of NF-κB expression.[116] Ciftci *et al.* examined the macro and trace elements in the kidneys of guinea pigs to evaluate the protective effects of linalool against DMBA.[119] The increased calcium and cadmium levels were reduced, while

the inhibited magnesium, zinc and iron levels were improved by linalool in DMBA-treated guinea pigs. The results indicated that linalool protects the kidneys from oxidative stress by mediating the levels of macro and trace elements.

Diabetes is the leading cause of impaired kidney function and nephropathic changes, such as oxidative stress, renal injury, matrix accumulation and podocyte abnormalities.[120] In the study of Deepa & Anuradha, linalool inhibited inflammatory response by reducing the expression of TGF-β1, TNF-α and NF-κB in diabetic rats.[121] Besides this, structural integrity of the rat kidneys was improved by linalool. Similar results were also observed in another study.[122] In addition, linalool attenuated the ultrastructural changes in the kidneys of streptozotocin-induced diabetic rats, including basement membrane thickening, podocyte number reduction and filtration barrier integrity loss. Therefore, linalool can alleviate the renal damages caused by diabetes *via* the inhibition of an inflammatory response.

Linalool is reported to alleviate nephrotoxicity caused by anticancer drugs, such as cisplatin and DOX. DOX is a widely used anticancer drug and has many side effects, including renal damage. In the study of Altinoz *et al.*, DOX caused an escalation of MDA levels and a decline of SOD, CAT and GSH levels, while the changes in oxidation system parameters were significantly attenuated by linalool.[123] Similarly, the DOX-induced increase of the renal function markers (blood urea nitrogen and creatinine) was inhibited by linalool treatment. Cisplatin is another broadly used anticancer drug with severe side effects on the kidneys. In cisplatin-treated rats, the linalool-induced increase of SOD, CAT and GSH levels and decrease of MDA, blood urea nitrogen and creatinine levels were also observed. According to Mohamed *et al.*, cisplatin decreased the mortality rate, reduced body weight, and increased the kidney index in rats.[124] Pre-treatment of linalool exerted protective effects on rat kidneys through inhibiting blood urea nitrogen and creatinine. Nrf2 and HO-1 levels were increased by cisplatin, while the pre-treatment of linalool led to a further augmentation in Nrf2 and HO-1 levels. The down-regulation of TLR protein expression (TLR4, MYD88 and TRIF) and the decrease of inflammatory mediators (TNF-α, IL-1β, IL-6 and NF-κB) were observed in rats pre-treated with linalool. Oral administration of linalool inhibited the increased expression of cisplatin-induced apoptotic markers such as caspase-3 protein, caspase-9 protein, and *Bax* gene and amplified the suppressed expression of anti-apoptotic gene *Bcl-2*. Cisplatin resulted in a severe dilated tubular lumen, cell loss, brush border impairment, swelled renal tubular epithelial cell, degenerated necrotic proximal tubules and tubular casts, while the severe renal lesions were attenuated by linalool administration. Therefore, linalool protected kidneys from cisplatin-induced impairments by declining oxidative stress, inflammatory response, and cell apoptosis *via* HMGB1/TLR4/NF-κB and Nrf2/HO-1 pathways.

Lung protective activity

Linalool is reported to protect lungs from metal pollution, inflammation, and nicotine. In the study of Shabir *et al.*, non-acute hypercontraction was caused by low concentrations of lead and cadmium, which was ameliorated by linalool in the rat tracheal system.[125] It was revealed that linalool attenuated the pollutant-induced hypercontraction of rat trachea *via* the inhibition of signalling cascades.

Linalool can protect lungs from the infection of *Pasteurella multocida* and *Klebsiella pneumoniae*. *Pasteurella multocida* is a highly versatile pathogen and causes infections of upper and lower respiratory tracts in a wide range of animals as well as in humans.[126] According to Wu *et al.*, linalool diminished lung neutrophil accumulation and improved the clearance of *P. multocida*.[127] Moreover, linalool inhibited the inflammatory response induced by *P. multocida* through elevating nuclear Nrf2 protein translocation and decreasing TNF-α and IL-6 levels in lung tissue. *Klebsiella pneumoniae* is an opportunistic bacterium and causes nosocomial infections including respiratory infections. Yang *et al.* discovered the bactericidal effects of linalool against carbapenemase-producing *K. pneumoniae* alone and combined with meropenem.[128] On the one hand, linalool improved the surface charge and membrane permeability of *K. pneumoniae*. On the other hand, linalool caused oxidative stress by generating ROS, which led to the disruption of bacterial membranes and intracellular leakage of nuclear acids and proteins. Therefore, linalool can be used as an adjuvant along with antibiotics to reduce antibiotic resistance.

Linalool exhibits the effects on pulmonary inflammation induced by lipopolysaccharide (LPS) and ovalbumin. Inflammation is part of the body's self-defence system, but it also leads to acute and chronic inflammatory diseases. Inflammation can result in edema and neutrophil sequestration, and ultimately leads to severe pulmonary injury and acute respiratory distress syndrome.[129] In the research of Huo *et al.*, the effects of linalool on LPS-induced lung injured mice were revealed. Pre-treatment of linalool suppressed the elevated production of cytokines (TNF-α and IL-6) and the inflammatory cells in mice with LPS-induced acute lung injury.[130] Furthermore, LPS led to pathological changes such as areas of inflammatory infiltration, thickening of the alveolar wall, and pulmonary congestion, which were ameliorated by linalool. In an *in vitro* study of LPS-treated H292 airway epithelial cells, linalool reduced the secretion of chemoattractant protein-1, which contributed to the recruitment of the inflammatory cells.[131] They also investigated the anti-inflammatory activity of linalool on ovalbumin-induced allergic asthma in mice. The results showed that linalool alleviated asthma by inhibiting airway inflammation and mucus hypersecretion. In addition, oral administration of linalool reduced the levels of iNOS expression, down-regulated MAPKs and NF-κB, and inhibited the airway hyperresponsiveness in ovalbumin-treated mice.

Interestingly, linalool exerts protective effects on lungs *via* attenuating the impact of cigarette smoking. There were an estimated 1.14 billion people who were smokers globally in 2019.[132,133] Smoking leads to a series of diseases, including chronic obstructive pulmonary disease and tracheal, bronchus and lung cancer.[133] Ma *et al.* investigated the effects of linalool on cigarette smoke-induced acute lung inflammation in

mice.[134] Cigarette smoke is a toxic mixture of 4000 chemicals and causes lung inflammation through increasing inflammatory cell infiltration and escalating inflammatory cytokines and chemokines. Linalool alleviated cigarette smoke-induced histopathological changes, including thickening of the alveolar wall and the increased infiltration of inflammatory cells. The production of inflammatory cytokines (TNF-α, IL-6 and IL-1β) and chemokines (IL-8 and MCP-1) were inhibited by linalool. Linalool-mediated inhibition of MPO activity indicated that the neutrophil accumulation in lung tissue was suppressed by linalool. The results implied that linalool ameliorated cigarette smoke-induced lung inflammation by inhibiting NF-κB activation. Yunusoğlu *et al.* reported that linalool attenuated nicotine acquisition and reinstatement, and accelerated the extinction of nicotine-induced conditioned place preference in mice.[135] In the conditioned place preference phases, linalool exhibited similar effects with varenicline, which was a smoking deterrent. Accordingly, linalool can protect lungs from the impact of nicotine use disorder.

Conclusions

Linalool is an aromatic monoterpene alcohol which is widely found in EOs. In the present article, we reviewed the recent advances in the bioactivities of linalool, including anticancer, antimicrobial, neuroprotective, hepatoprotective, renal protective and lung protective activity. Linalool kills cancer cells mainly by generation of ROS and oxidative stress, while at the same time protects normal cells by anti-inflammation. The toxicity to cancer cells, protective effects on normal cells, and the synergistic effects, provide linalool with great potential to be used as an adjuvant of anticancer drugs. Moreover, the protective effects also make linalool promising to be used as ingredients of functional foods. Similarly, the antimicrobial effects against a wide range of pathogens and the synergistic effects make linalool prospective to be used as an adjuvant of antibiotics, which is helpful in overcoming the growing problem of microbial resistance. In addition, linalool can be used as a natural plant-based food preservative to avoid microbial contamination, ensure food safety, improve food flavour, and prolong shelf life.

In spite of the interesting findings on bioactivities of linalool, the application of linalool is limited by its poor water solubility, low stability, and high volatility. Encapsulation is a practical solution to overcome the physical and chemical limitations of linalool which improves the solubility of linalool, protects linalool from oxygen and ultraviolet rays and enables linalool to achieve sustained release. Moreover, the structure of capsules can be functionalized to target certain cells to improve its bioactivity further.

However, there are still problems to be solved. Although linalool *per se* is not toxic to the human body, the hydroperoxides of linalool are a potent skin sensitizer. Future studies are warranted to overcome the challenges of contact allergies and evaluate safe dosage limits. In addition, most of the studies investigate the racemate of linalool. Therefore, the differences in bioactivity between 3*R*-(−)-linalool and 3*S*-(+)-linalool need to be explored in future research.

Author contributions

Q. A., J. N. R., X. L., and G. F. wrote and revised the manuscript. S. S. Q., Y. S., and Y. L. revised the manuscript. Q. A., G. F., and S. Y. P. conceived the idea for the project and obtained the funding.

Conflicts of interest

There are no conflicts to declare.

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