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Review Paper

Beyond Linalool and Linalyl Acetate Emerging Bioactive Constituents, Molecular Target and Therapeutic Potential of Lavandula Species

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ABSTRACT

Lavandula species are known for their aromatic, medicinal and therapeutic properties and the majority of the pharmacological studies have been directed towards the linalool and linalyl acetate. Recent phytochemical studies, however, have found that lavender has a wider variety of bioactive compounds with monoterpenes, sesquiterpenes, phenolic acids, flavonoids, coumarins, triterpenoids, sterols and other metabolites that are not volatile. These compounds are involved in various biological processes by multi-target molecular mechanisms. New evidence indicates modulation of Gabaergic, glutamatergic, cholinergic, serotonergic and dopaminergic neurotransmission and a regulation of Nrf2/HO-1, NF- κ B, MAPK, NLRP3 inflammasome, PI3K/Akt/mTOR and AMPK signaling pathways. These interactions could be responsible for the reported antioxidant, anti-inflammatory, neuroprotective, anxiolytic, antimicrobial, analgesic, metabolic, cardiovascular, dermatological and anticancer properties of Lavandula. The review points out the phytochemical diversity of Lavandula other than the key volatile constituents, summarizes new molecular targets, and assesses the therapeutic potential of minor constituents and unexplored phytochemicals. It also addresses analytical improvements, pharmacokinetic considerations, formulation strategies, safety issues, and the current limitations in translation. A more comprehensive mechanistic and phytochemical approach can help facilitate the development of standardised Lavandula-based interventions and facilitate the discovery of multi-target phytotherapeutic agents in the future.

INTRODUCTION

Medicinal and aromatic plants are significant natural sources of therapeutically active

compounds, and their importance has increased significantly in light of the increasing interest in natural products, multi-target pharmacology and

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plant-derived drug discovery. The genus *Lavandula* from the family Lamiaceae is one of the most prominent among these plants, due to its wide traditional uses, commercial importance and the broad spectrum of biological activities reported. The genus *Lavandula* is found primarily throughout the Mediterranean region, in North Africa, in parts of Asia and Europe, and a few of the species are used for their essential oils, fragrances, cosmetics, food, and medicine throughout the world. These are the species that have been more studied, such as *Lavandula angustifolia*, *L. latifolia*, *L. stoechas*, *L. dentata*. Traditionally the preparations from these plants were used for the management of anxiety, insomnia, headache, pain, digestive disturbances, skin disorders, microbial infections and inflammatory conditions [1].

The essential oil of *Lavandula* is the most known and renowned part of *Lavandula* for its pharmacological properties, in particular the monoterpenes linalool and linalyl acetate. They frequently occur in lavender essential oils in high concentrations and have been associated with anxiolytic, sedative, analgesic, anti-inflammatory, antimicrobial, and neuroprotective effects. Accordingly, many experimental and clinical studies have focused on these two compounds as the key agents in the pharmacology of lavender. While useful for mechanistic and therapeutic information, this has led to a relatively limited view of the chemical and pharmacological diversity of the genus [2].

Recent phytochemical studies have shown that *Lavandula* spp. possess a far wider variety of volatile and non-volatile compounds which can be independently or synergically active. These include monoterpenes including 1,8-cineole, camphor, borneol, terpinen-4-ol, lavandulol, α -terpineol and β -caryophyllene; and several phenolic compounds such as rosmarinic acid, caffeic acid, chlorogenic acid, apigenin, luteolin,

quercetin derivatives and other flavonoids and phenolic acids [3]. Other phytochemicals found in various species of *Lavandula* include: terpenoids, coumarins, sterols and glycosides. Although there are indications of antioxidant, neuroprotective, anti-inflammatory, antimicrobial, anticancer, cardiometabolic and cytoprotective activity, the pharmacological significance of many of these components is not fully understood [4].

A key new idea is that the therapeutic effects of *Lavandula* are not likely to be due to a single compound targeting a single molecular target. In contrast, its bioactivity seems to be a result of a complex network of phytochemicals that can modulate several receptors, enzymes, transcription factors, ion channels, inflammatory mediators, and intracellular pathways. Mechanisms reported involve modulation of GABAergic, serotonergic, cholinergic, and glutamatergic neurotransmission, regulation of Nrf2/HO-1 pathway, NF- κ B pathway, MAPK pathway, PI3K/Akt pathway, the NLRP3 inflammasome, apoptotic signaling, and oxidative stress-related pathways. This multi-target activity is especially significant in the case of complex diseases, like neurodegenerative disorders, metabolic dysfunction, chronic inflammation, cancer, and cardiovascular diseases, which involve several disease processes' activity at the same time [5,6].

The use of new analytical technologies has also led to the discovery of new constituents in *Lavandula*, which have also been found to be present in the plant. Today, high-resolution GC-MS, LC-MS/MS, UHPLC, NMR spectroscopy, metabolomics, molecular networking, and chemometric analyses enable comprehensive characterization of the species-specific chemical fingerprints. Simultaneously, molecular docking, network pharmacology, transcriptomics, proteomics and other systems biology techniques are also gaining ground to predict and validate compound-target interactions. These advances



offer a chance to transcend the traditional essential-oil profiling approach in Favor of a more holistic view of *Lavandula* pharmacology. Hence, this article reviews the bioactive components of *Lavandula* species other than linalool and linalyl acetate in a critical way focusing on new phytochemicals, molecular targets, signalling pathways and therapeutic uses. It also assesses the latest developments in analytical technology, preclinical and clinical data, pharmacokinetic issues, safety considerations, formulation options and important translation issues. This review will discuss how phytochemical diversity of *Lavandula* could be supported by its mechanism of action and therapeutic potential and how it can be used to identify potential directions for future pharmacological and drug development research [7].

2. Botanical Diversity and Chemotaxonomy of *Lavandula* Species

Lavandula is a genus of aromatic shrubs and perennial herbs in the family Lamiaceae, widely distributed throughout the Mediterranean basin, North Africa, the Middle East and parts of Asia. A few species are also introduced and commercially grown in temperate regions of Europe, North America, Australia and other parts of the world for their use in perfumery, cosmetics, aromatic products, food and herbal medicine. All members of the genus have opposite leaves, spike-like terminal or interrupted inflorescences, bilabiate flowers and glands that produce and store essential oils. Though these similarities in botanical makeup, significant morphological and phytochemical variation is observed within species and subspecies [8].

Lavandula angustifolia Mill., *L. latifolia* Medik., *L. stoechas* L., *L. dentata* L. and the hybrid *L. × intermedia* Emeric ex Loisel. are among the most famous species that have medicinal or commercial value. *L. angustifolia* is especially well-known for

its essential oils, which contain high concentrations of linalool and linalyl acetate. *L. latifolia* or spike lavender, on the other hand, generally has higher amounts of 1,8-cineole and camphor. *L. stoechas* is botanically and chemically distinguishable and often contains high levels of camphor, fenchone and related monoterpenes. Lavandin, *L. × intermedia*, is a cross between *L. angustifolia* and *L. latifolia* and, due to its high essential-oil content, is a popular variety for cultivation [9].

Chemotaxonomy, which is based on the characteristic secondary metabolite profile, is a useful complementary method to the traditional botanical classification, which can be used to identify species, subspecies, populations and chemotypes. For chemotaxonomic purposes, the composition of essential oils has proved to be useful in particular, within *Lavandula*. The relative abundance of linalool, linalyl acetate, camphor, 1,8-cineole, borneol, terpinen-4-ol, lavandulol, fenchone and β -caryophyllene may aid in the discrimination of closely related taxa and identification of chemically distinct populations. Importantly, these differences are not only taxonomic indicators, but can make a significant difference in biological activity, safety, fragrance quality and therapeutic activity [10].

The genus is also characterised by its chemotaxonomic complexity, as evidenced by non-volatile metabolites. Many species of *Lavandula* grow these phenolic acids, including Rosmarinus, caffeic and chlorogenic acids, and flavonoids, such as luteolin, apigenin, quercetin derivatives, and glycosides, which are very different among the various species. These compounds can be used to support species authentication and can account for pharmacological effects not explained by the volatile compounds. The new metabolomics approach to LC–MS-based analysis and multivariate chemometrics has thus broadened the



scope of chemotaxonomic analysis from the traditional essential-oil profiling [11].

The genotypic variation and geographical origin of *Lavandula* appears to have a strong influence on the phytochemical variability of the plant. The geographic origin and the influence of the genotypic factor are strong factors affecting the phytochemical variability of *Lavandula*. Therefore, the chemical fingerprint and biological activity of plants in the same species can vary considerably. The variability indicates the need for authenticated botanical materials, standard cultivation techniques, and thorough chemical characterization for use in pharmacological research. The combination of classical taxonomy and GC–MS, LC–MS/MS, metabolomics and chemometric analysis can offer a more reliable approach to the identification of lavender chemotypes with therapeutic interest as well as to the development of reproducible quality control for future medicinal and pharmaceutical uses [12].

3. Phytochemical Landscape Beyond Linalool and Linalyl Acetate

The Chemistry and Biology of Phytochemicals other than Linalool and Linalyl Acetate The phytochemical profile of a species of *Lavandula* is far richer than people think from the presence of linalool and linalyl acetate. These two constituents are key factors in the flavor and a few of the medicinal effects of lavender essential oils, but the overall biological complexity of the genus stems from the presence of a broad range of volatile and non-volatile metabolites. The qualitative and quantitative content of these metabolites may vary significantly depending on the species, the chemotype, geographical origin, phenological stage, isolation method and environmental conditions. Pharmacological research is, therefore, becoming more focused on minor terpenoids, phenolic acids, flavonoids, coumarins, triterpenoids, sterols and other special metabolites

that can have complementary or synergistic biological effects [13].

3.1. Emerging Monoterpenes

Monoterpenes are a significant component of *Lavandula* essential oil and some of them have biological activity other than linalool. The typical constituents found include 1,8-cineole, camphor, borneol, terpinen-4-ol, α -terpineol, lavandulol, fenchone, limonene, α -pinene, β -pinene and myrcene. The metabolites are abundant in different species. For instance, *L. latifolia* and *L. stoechas* tend to have relatively high levels of 1,8-cineole and camphor, while *L. angustifolia* typically has a lower content of camphor and a better terpenoid profile of oxygenated monoterpenes. Some of these compounds have shown antimicrobial, anti-inflammatory, antioxidant, bronchodilatory, analgesic and neuroactive effects. In whole essential oils, they may play a special role in affecting potency, selectivity, and bioavailability due to additive or synergistic interactions [14].

3.2. Sesquiterpenes and Oxygenated Terpenoids

The sesquiterpenes tend to be found in smaller amounts than the monoterpenes but can be important pharmacologically, such as β -caryophyllene which has been found to interact with cannabinoid CB2 receptors and has shown anti-inflammatory and immunomodulatory properties. Other sesquiterpenes reported are germacrene D, caryophyllene oxide, β -farnesene, and several bisabolene derivatives. Also, oxygenated terpenoids like borneol, camphor, terpinen-4-ol, and lavandulol can affect the permeability of membranes, susceptibility of microorganisms, neuronal excitability and inflammatory responses. The quantitative dominance of the constituents has limited value to



determine the activity of essential oils, as these components can contribute much more to the pharmacological activity than the ones in larger amounts [15-17].

3.3. Phenolic Acids

In the non-volatile fraction of *Lavandula* the presence of several phenolic acids is reported as having great antioxidant and cytoprotective potential. Among the phenolics most often reported is rosmarinic acid, which has a wide range of properties, including as free radical scavenger, anti-inflammatory, neuroprotective, and antimicrobial. Other hydroxycinnamic acid derivatives such as caffeic acid, chlorogenic acid, ferulic acid, p-coumaric acid and their related derivatives have also been found in various *Lavandula* species. These molecules have the ability to regulate oxidative stress directly by neutralizing the radicals but also by regulating endogenous antioxidant pathways. They are particularly important if aqueous, hydroalcoholic or methanolic extracts are investigated as these can have a significantly different pharmacological profile to that of volatile oils [18].

3.4. Flavonoids and Flavonoid Glycosides

Flavonoids represent another major group of non-volatile constituents in the genus. Luteolin, apigenin, quercetin, kaempferol and related aglycones have been detected in a variety of species, frequently glycosides. These metabolites have antioxidant, anti-inflammatory, neuroprotective, cardioprotective and enzyme-modulating effects. Luteolin and apigenin derivatives are of particular pharmacological importance, as these have the potential to affect inflammatory signaling, oxidative stress, neuronal viability and vascular function. The solubility, stability, absorption and metabolism of a flavonoid glycoside may be different from that of its

aglycone, and the aglycones should not be viewed as pharmacologically equivalent to the glycosides. Their occurrence could also prove to be a helpful chemotaxonomic marker for the separation of species and populations [19].

3.5. Coumarins and related Phenolics

Lavandula is further chemically diversified by coumarins and related phenolic compounds. These metabolites have been less studied than the terpenes and flavonoids, but can be involved in antioxidant, antimicrobial, vascular, and enzyme-modulatory effects. This concentration may differ among species, tissue and extraction conditions. Further research on the pharmacological relevance of this group is underexplored, and detailed compound isolation and target-based research should clarify if any couplet of the studied compounds make a significant contribution to the *Lavandula* therapeutic profile [20].

3.6. Triterpenoids and Sterols

Triterpenoids and phytosterols form another less emphasized but potentially important fraction. In general, the members of the genus are reported to contain ursolic acid, oleanolic acid, and other related pentacyclic triterpenoids which exhibit anti-inflammatory, antioxidant, hepatoprotective, metabolic, and anticancer properties. Other non-volatile extracts include plant sterols including β -sitosterol and stigmasterol, which could also be responsible for anti-inflammatory, lipid-modulating and membrane-related effects. They are not as volatile as others and their importance in essential-oil studies has not been realized, but they could be of major concern in whole plant preparations and traditional extracts [21].

3.7. Other non-volatile secondary metabolites

Other secondary metabolites reported in *Lavandula* are tannins, glycosides, lignan-like



compounds, organic acids and other polyphenol compounds. The ability to affect astringencies, antimicrobial effects, redox balance, enzyme inhibition and interactions with proteins and cell membranes. This is particularly important in the case of decoctions, tinctures and hydroalcoholic extracts, in which the volatile fraction is only part of the phytochemical profile. The phytochemistry of *Lavandula* is best understood as a complex and dynamic chemical network, not just two marker

compounds. Comprehensive metabolite profiling coupled with bioactivity-guided fractionation, pharmacokinetic studies and target validation should be performed in future studies. This could reveal hitherto overlooked constituents of the plants having therapeutic value themselves and reveal the inter-relationship of the minor volatile and non-volatile metabolites in determining the overall pharmacological activity of the *Lavandula* spp [22-25].

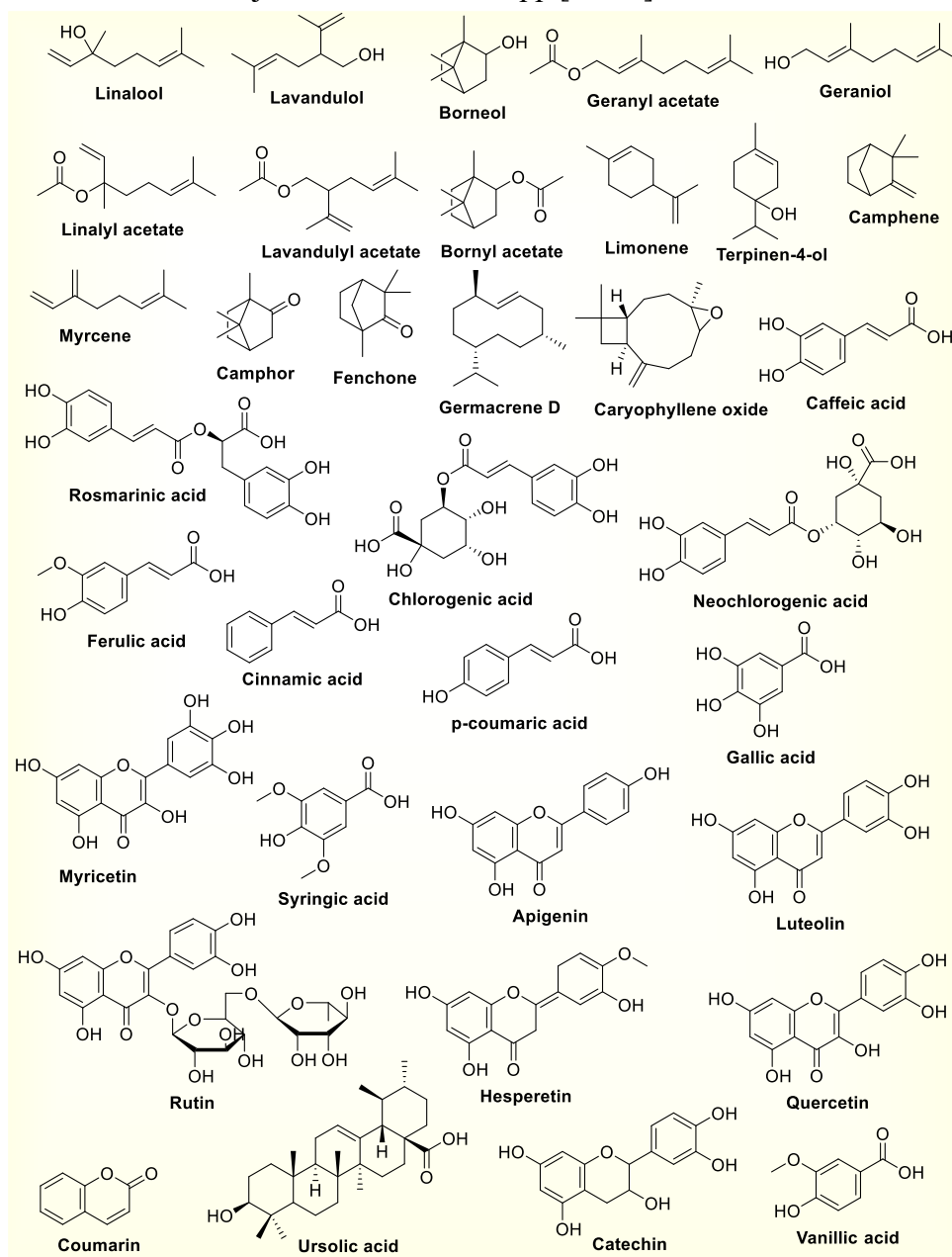


Fig.1: Structures of phytoconstituents present in *Lavandula* spp.

4. Emerging molecular targets and mechanistic basis of *Lavandula* bioactivity

The pharmacological activity of *Lavandula* species is increasingly understood as the result of multi-component and multi-target interactions rather than the action of a single dominant phytoconstituent. While linalool and linalyl acetate remain the most extensively characterized components, emerging evidence indicates that other monoterpenes, sesquiterpenes, phenolic acids, flavonoids, and triterpenoids may modulate neurotransmitter systems, ion channels, oxidative-stress pathways, inflammatory signaling, cell-survival cascades, and metabolic regulators. This multi-target pharmacology is particularly relevant to neurological, inflammatory, metabolic, and degenerative disorders, where disease progression involves interconnected molecular pathways. However, the strength of evidence differs substantially among targets, and many mechanisms remain based primarily on in vitro or animal studies rather than direct clinical validation [26].

4.1. GABAergic neurotransmission

One of the most frequently suggested mechanisms of action of *Lavandula* for its anxiolytic, sedative, anticonvulsant and sleep-promoting activity is modulation of γ -aminobutyric acid (GABA) signaling. GABA is the primary inhibitory neurotransmitter in the C.N.S., and increasing GABAergic tone decreases the excitability of the neurons. A number of lavender constituents seem to have a direct effect on GABAergic neurotransmission by modulating the receptors or a more indirect effect by regulating the release of neurotransmitters. While linalool has been extensively investigated in this area, other terpenoids such as borneol, terpinen-4-ol and α -terpineol could also play inhibitory roles on neurons. Some monoterpenes have been shown to

engage GABA_A receptor mediated signaling and can enhance inhibitory postsynaptic currents. These can decrease hyperexcitability in the limbic and cortical circuits involved in anxiety, sleep and susceptibility to seizures. Importantly, the effects of whole essential oils cannot be completely mimicked by isolated linalool, indicating that minor components may produce effects at receptor or membrane levels, which are synergistic to linalool. Alterations in the chloride conductance, sensitivity of the receptors or interactions with benzodiazepine associated receptors may also be involved in GABAergic modulation. However, there is no direct evidence of receptor binding for some of the constituents of *Lavandula*. Further electrophysiological and receptor-subtype specific studies will be needed to determine if various compounds are orthosteric, allosteric modulators or indirect regulators of GABAergic transmission [27-29].

4.2. Glutamatergic and NMDA receptor modulation

Glutamate is the primary excitatory transmitter in the mammalian brain and excessive glutamatergic signaling, via N-methyl-D-aspartate (NMDA) receptors, is linked to excitotoxicity, oxidative stress, neuronal calcium overload, and neurodegeneration. The *lavandula*-derived compounds have been suggested to reduce the over-activity of the glutamatergic neurotransmission, which explains their potential in neuroprotection, anticonvulsant and anxiolytic properties. Linalool has been found to have inhibitory effects on glutamate release in an experimental model, while other terpenoids can modulate presynaptic calcium influx and vesicular neurotransmitter release. Lavender constituents may help to decrease the availability of glutamate or suppress overactivation of the NMDA receptor to prevent downstream calcium-dependent injury and mitochondrial dysfunction. This mechanism is



especially important in ischemic injury, epilepsy and neurodegenerative diseases. Other phenolics like rosmarinic acid and flavonoids can have additional antioxidant and anti-inflammatory effects to further safeguard against glutamate-induced toxicity. These compounds may not only act on NMDA receptors but also reduce the production of reactive oxygen species, and maintain mitochondrial function after excitotoxic signaling. Therefore, *Lavandula* bioactivity can be directly achieved by modulation of neurotransmitter activity and/or indirectly by protection of neuronal cell damage caused by over-activation of glutamate [30].

4.3. Cholinergic signaling and acetylcholinesterase inhibition

The cholinergic system plays a key role in learning, memory, attention, and autonomic regulation. Cholinergic neurotransmission is decreased in various cognitive diseases, especially Alzheimer's disease. Experimental studies have shown that extracts and constituents of *Lavandula* have acetylcholinesterase (AChE)-inhibitory activity, which could be a mechanism for cognitive and neuroprotective effects. Inhibition of AChE would inhibit the breakdown of acetylcholine and possibly increase the concentration of acetylcholine in the synaptic clefts. The monoterpenes 1,8-cineole, α -pinene, and others have been studied for their cholinesterase inhibitory activity, but with varying potencies. Other constituents such as phenolics and flavonoids can also act in a complementary way at the catalytic or peripheral sites of AChE. In addition to direct enzyme inhibition, antioxidant and anti-inflammatory properties can prevent cholinergic neuronal loss and minimize secondary loss of cholinergic functions resulting from oxidative or inflammatory damage. Thus, the cholinergic effects of *Lavandula* might be the result of a combination of enzyme inhibition and

protection of nerve cells, not just one of these mechanisms [31].

4.4. Serotonergic and dopaminergic pathways

The serotonin and dopamine are the two important monoamines associated with mood, motivation, reward, cognition, and stress adaptation. Experimental results indicate possible anxiolytic and antidepressant activity of lavender preparations due to anxiolytic/antidepressant activity in serotonergic neurotransmission. Mechanisms suggested involve modulation of serotonin receptor function, alterations in serotonin turnover, and indirect regulation of monoamine release. Some papers have proposed interaction with 5-HT receptor subtypes, with the participation of the distinct compounds of *Lavandula* still not fully clarified. Volatile constituents of the oil, such as linalool, borneol, and others, may have indirect effects on monoaminergic neurotransmission via ion-channel modulation or via effects on neuronal excitability. A dopaminergic effect is less well described but it may play a role in motor function, motivation and neuroprotection. The flavonoids and phenolic acids could be beneficial in the protection of the dopaminergic neurons from oxidative stress and inflammatory injury, potentially relevant to the neurodegeneration seen in Parkinson's disease. The above actions are currently considered as mechanistic possibilities, based primarily on preclinical evidence [32].

4.5. Voltage-gated calcium and ion-channel modulation

Many volatile phytochemicals are important and key ion channels. Lavandin is able to interact with several constituents that affect voltage gated calcium channels, potassium channels and other membrane ion conductances. Blocking the overactive calcium influx can decrease



neurotransmitter release, smooth-muscle contraction, excitotoxicity and hyperexcitability. Linalool has been shown to exhibit calcium channel-modulating properties and structurally similar monoterpenes may also exhibit similar membrane effects. These compounds inhibit the influx of calcium into the presynaptic terminal and therefore could help to decrease the release of glutamate and other excitatory neurotransmitters. Ion-channel modulation can thus have an anticonvulsant, an analgesic, an anxiolytic, a vasorelaxant and a spasmolytic effect at the same time. Another possibility is the effect on membrane fluidity. Lipophilic terpenes can partition into phospholipid bilayers, thereby affecting the conformation of the channels indirectly. Sometimes, when mixtures of essential oils are used, the effects are found to be stronger than those of isolated constituents, which may be due to these physicochemical interactions [33].

4.6. Nrf2/HO-1 antioxidant signaling

Oxidative stress is a universal pathogenic mechanism in neurodegeneration, inflammation, metabolic disorders and cardiovascular damage. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key transcription factor for endogenous antioxidant defenses. In response to oxidant stress, Nrf2 enters the nucleus and stimulates the expression of genes that code for heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase-1, glutathione-related enzymes, and others that protect cells. The polyphenolic compounds found in *Lavandula*, such as rosmarinic acid, caffeic acid derivatives, luteolin, apigenin and other flavonoids, can either stimulate or maintain the Nrf2 signaling pathway. Inducing Nrf2/HO-1 activity can boost intracellular antioxidant capacity, glutathione homeostasis, and decrease lipid peroxidation and oxidative DNA damage. This route is an important mechanistic link between the reported neuroprotective,

hepatoprotective, cardioprotective, and anti-inflammatory properties of non-volatile lavender extracts and their phytochemical richness. However, the evidence of direct causality is still limited for many preparations of *Lavandula* using the inhibition of Nrf2 and knockout models [34].

4.7. NF- κ B and MAPK inflammatory pathways

Nuclear factor-kappa B (NF- κ B) is one of the main pathways that govern inflammatory gene expression. NF- κ B activation leads to the upregulation of cytokines, chemokines, inducible nitric oxide synthase, and cyclooxygenase-2. The MAPK pathways (p38, JNK, and ERK) also play a role in the regulation of inflammatory responses and signaling of cellular stress. Several *Lavandula* constituents have been shown to have the ability to inhibit the expression of inflammatory mediators possibly by inhibiting NF- κ B activation and by modulating MAPK phosphorylation. In particular, compounds such as rosmarinic acid, luteolin, apigenin, β -caryophyllene, and related compounds are of particular interest because each of them has been linked to anti-inflammatory signaling in various experimental systems. Inhibition of these pathways can lead to diminished production of tumor necrosis factor- α , interleukin-1 β , interleukin-6, nitric oxide and prostaglandins. These effects offer a plausible mechanistic foundation for anti-inflammatory effects reported in models of neuroinflammation, skin inflammation, metabolic disease, and tissue injury [35].

4.8. NLRP3 inflammasome regulation

The NLRP3 inflammasome has become a significant molecular target for chronic inflammatory and degenerative diseases. By activating the NLRP3 complex, caspase-1 is activated and starts to mature interleukin-1 β and interleukin-18. The excessive activation of the



inflammasome is involved in neurodegeneration, metabolic syndrome, cardiovascular diseases, and chronic inflammatory diseases. Certain *lavandula*-related phytochemicals, such as the phenolic compounds and anti-inflammatory terpenoids, may indirectly inhibit the activation of the NLRP3, through their anti-oxidant, anti-mitochondrial and anti-NF- κ B effects, respectively, in more general pharmacological studies, so that the β -caryophyllene and rosmarinic acid are likely candidates for this effect. However, direct evidence of chemically characterized *Lavandula* extracts to inhibit the NLRP3 is relatively scarce. This pathway, therefore, is an opportunity for research rather than a proven clinical pathway [36].

4.9. PI3K/Akt/mTOR signaling

Phosphoinositide 3-kinase (PI3K) /Akt/mTOR pathway is involved in cell survival, metabolism, protein synthesis, apoptosis and autophagy. Inflammatory disorders, insulin resistance, neurodegeneration and cancer are associated with this pathway dysregulation. Polyphenols such as flavonoids and phenolic acids, found in *Lavandula*, can exert modulatory effects on the PI3K/Akt signaling pathway and so boost cell survival when it is exposed to oxidative or inflammatory stress. Modulation of Akt activation could be anti-apoptotic and promote mitochondrial integrity, while modulation of mTOR activity could influence autophagic clearance and metabolic adaptation. Pathway regulation can be both pathway-dependent and disease-dependent. Controlled activation of Akt can promote the survival of neurons, while inhibition of the PI3K/Akt/mTOR pathway can inhibit the proliferation of cancer cells and induce apoptosis. The context-dependent pharmacology underscores the importance of studying individual compounds in predetermined experimental models [37].

4.10. AMPK and metabolic signaling

The role of AMPK and metabolic signaling. AMP-activated protein kinase (AMPK) is a crucial sensor of cellular energy status that is involved in glucose metabolism, lipid oxidation, mitochondrial function and autophagy. AMPK is an important target in natural-product research due to their close relationship with metabolic dysfunction and oxidative stress. Some of the phenolic and flavonoids found in *Lavandula* could be able to activate AMPK or affect downstream metabolic pathways, which could help to increase insulin sensitivity, mitochondrial function, and lipid management. AMPK activation may also dampen inappropriate mTOR signaling and encourage autophagy, which connects metabolic regulation and cellular quality control. There is less evidence of *Lavandula* and AMPK signaling than for antioxidant or inflammatory pathways. However, this mechanism can account for some of the newly observed antidiabetic, cardiometabolic and mitochondrial actions and should be explored in more detail with pharmacological pathway inhibitors and molecular validation. In summary, there is convergence in the molecular pharmacology of *Lavandula* among the various neurotransmitter systems, ion channels, antioxidant defense mechanisms, inflammatory cascades and metabolic signaling networks. The genus shows a very wide spectrum of activity, which is explained by the various mechanisms involved in the genus: GABAergic, glutamatergic, cholinergic, monoaminergic, Nrf2/HO-1, NF- κ B/MAPK, NLRP3, PI3K/Akt/mTOR, and AMPK pathways. However, further research is needed to shift from association with biomarkers towards direct target validation, concentration–response relationships, correlation with PK parameters and isolation of compounds versus chemically standardized whole extracts [38].



5. Biological activities of the *Lavender* Plant

Lavender is one of the most extensively researched medicinal and aromatic plants (MAPs) due to its several pharmacological activities. Their pharmacological effects are due to the presence of monoterpenes, sesquiterpenes, phenolic acids, flavonoids, coumarins, triterpenoids and other secondary metabolites. However, in recent years, a number of other compounds have been found which also play a very important role in the biological properties of lavender including 1,8-cineole, camphor, borneol, terpinen-4-ol, β -caryophyllene, rosmarinic acid, caffeic acid, luteolin, apigenin and related constituents. The pharmacological profile of *Lavandula*, therefore, is to be understood as being multi-component, multi-target rather than as the action of a single predominant compound [39].

5.1. Antioxidant activity

Oxidative stress plays a role in the pathogenesis of neurodegenerative diseases, cardiac disorders, diabetes, inflammatory diseases, cancer and premature ageing. Lavender extracts and essential oils have been shown to have antioxidant activity via both direct and indirect mechanisms. Phenolic acids like rosmarinic acid, caffeic acid, and chlorogenic acid, can scavenge ROS and suppress the lipid peroxidation. Other flavonoids like the luteolin, apigenin and quercetin derivatives also help by donating hydrogen atoms/electrons to the reactive radicals. Lavender phytochemicals can also enhance the activity of endogenous antioxidant enzymes like superoxide dismutase, catalase and glutathione-associated enzymes, as well as direct radical scavenging. The Nrf2/HO-1 pathway has also been suggested as a key cytoprotective pathway. By these activities, lavender compounds can help decrease oxidative damage to lipids, proteins, mitochondria and DNA [40].

5.2. Anti-inflammatory activity

One of the most constant biological activities reported for *Lavandula* species is anti-inflammatory. Essential oils and non-volatile extracts could inhibit the synthesis of inflammatory mediators such as tumor necrosis factor- α , interleukin-1 β , interleukin-6, nitric oxide and prostaglandins. These effects are linked to regulation of key inflammatory pathways like NF- κ B and mitogen-activated protein kinase pathways. Of relevance to this activity are the following: β -Caryophyllene may also exhibit immunomodulatory effects via cannabinoid CB2 receptor signaling, luteolin, apigenin, and rosmarinic acid. Lavender phytochemicals also can affect cyclooxygenase, lipoxygenase, inducible nitric oxide synthase and inflammasome-related pathways. These effects have given a mechanistic rationale for the traditional applications of lavender for inflammatory skin diseases, pain, wounds, and musculoskeletal pain [41].

5.3. Anxiolytic and Sedative activity

Lavender is famous for its relaxing and anxiolytic effects. Under experimental and clinical conditions it has been studied for its effects on anxiety, psychological stress, insomnia and nervousness. These effects may be due to a number of mechanisms. Enhancement of inhibitory GABA signaling has been shown to decrease the excitability and anxiety of neurons, and is thought to be especially relevant, as modulation of this system is being studied. Lavender compounds might also act on the serotonergic pathways and voltage-dependent calcium channels. Overall, the regulation of GABA, serotonin and neuronal ion conductance could account for the sedative and anxiolytic properties seen after inhalation or oral administration of standardized lavender



preparations. These activities also encourage the use of lavender in aromatherapy and for mild anxiety and sleeping disorders in complementary medicine. Pharmacological effects, however, are highly dependent on the formulation, composition, route of administration and doses of the drug [42].

5.4. Antidepressant activity

Lavender extracts and essential oils also have been found to exhibit antidepressant-like activity in experimental models. These actions can include modulation of serotonergic and dopaminergic neurotransmission, reduction of oxidative stress and attenuation of neuroinflammation. The phenolic constituents can have protective effects on neuronal cells from inflammatory and oxidative damage, and the volatile constituents can modulate monoamine turnover and neuronal signaling. It is well-documented that there is a relationship between mood regulation and neuroinflammation, and lavender may be of particular interest to investigate this since it has both neurotransmitter modulating and anti-inflammatory properties. However, better clinical research is needed to establish the mechanisms as clinically reproducible antidepressant efficacy in humans [43].

5.5. Neuroprotective activity

Lavender's neuroprotective activity is an area of interest. Experimental evidence indicates that *lavandula* phytochemicals could be protective against oxidative stress, excitotoxicity, inflammatory and mitochondrial damage to neurons. These effects may be mediated by the regulation of Nrf2/HO-1, NF- κ B, PI3K/Akt and apoptotic pathways. Several constituents of lavender may help to decrease the level of glutamate-induced excitotoxicity and too much calcium. Phenolic acids and flavonoids also can play other roles, such as inhibiting activation of

pro-apoptotic proteins and maintaining mitochondrial function. All these activities have led to the interest of lavender compounds for the following diseases: Alzheimer's disease, Parkinson's disease, ischemic brain injury, and age-related cognitive impairment [44].

5.6. Antimicrobial activity

Lavender essential oil is active against many gram-positive and gram-negative bacteria. The antimicrobial properties are mainly related to the lipophilic nature of terpenoid constituents that can disrupt microbial cell membranes, increase microbial cell membrane permeability, disturb ion gradients and induce leakage of intracellular components. Antibacterial activity is probably provided by compounds like linalool, terpinen-4-ol, 1,8-cineole, camphor, borneol and α -terpineol. Lavender preparations have been demonstrated to be antifungal against a number of filamentous fungi and yeasts as well. Some suggested mechanisms include disruption of fungal membranes, disruption of membrane function by altering ergosterol, and oxidative imbalance. One of the most interesting properties of the constituents of essential oils is the effect they have on microbial biofilms and quorum sensing. Antibiofilm activity could expand the range of therapeutic applications of lavender, as formation of biofilm is associated with persistent and drug-resistant infections [45].

5.7. Analgesic and antinociceptive activity

Lavender is generally used to alleviate headache and muscle pain, as well as other types of pain. Experimental studies indicate that lavender essential oils and extracts have analgesic and antinociceptive effects. The proposed mechanisms are: inflammatory mediator inhibition, calcium channel modulation, GABAergic modulation and peripheral nociceptive pathways interference.



Lavender's anti-inflammatory effect could also help to alleviate the pain that comes with inflammation of the tissue. Other results indicate that terpenoids may interact with transient receptor potential channels and neuronal membrane excitability, which need further confirmation [46].

5.8. Anticonvulsant activity

Several volatile constituents of lavender have been shown to have anticonvulsant or seizure-modulating effects in experimental models. These effects may be due to reduced glutamatergic neurotransmission, increased GABAergic inhibition, and decreased calcium dependent neuronal excitability. Lavender phytochemicals have the potential to decrease the susceptibility to seizures by decreasing the release of too much excitatory neurotransmitter and by stabilizing the function of the neuronal membrane. There is, however, still a lack of clinical evidence to support lavender as a stand-alone anti-epileptic agent [47].

5.9. Cardiovascular activity

Lavender can have a number of positive actions on the cardiovascular system. Some of the volatiles may alter calcium influx into the vascular smooth muscle cell and thus help to relax it, possibly decreasing vascular resistance. Endothelial cells might be protected and vascular oxidative stress might be lowered via antioxidant and anti-inflammatory actions. There may also be changes in the nitric oxide availability and endothelial function due to the effect of phenolic compounds. Additionally, the non-volatile extract contains phytosterols and triterpenoids that can affect lipid metabolism and vascular inflammation. These effects need to be confirmed clinically, but they offer a potential rationale for future cardiovascular study [48].

5.10. Antidiabetic and metabolic activity

Experimental research has indicated that *lavandula* extracts have potent metabolic effects. It has been suggested to have anti-diabetic activity through its ability to inhibit α -amylase and α -glucosidase, enhance glucose utilization, reduce oxidative stress, and improve insulin sensitivity. AMPK, PI3K/Akt and other metabolic pathways may also be affected by phenolic acids and flavonoids. AMPK activation may promote glucose uptake, enhance fatty-acid oxidation, and promote mitochondrial function. Lavender may also lower the metabolic inflammation and dyslipidemia caused by its antioxidant and anti-inflammatory properties. However, the evidence is mostly preclinical, and there need to be standardized human trials to draw therapeutic conclusions [49].

5.11. Anticancer activity

The experimental evidence is accumulating that constituents from lavender may have anticancer activity. The effects reported include growth inhibition, induction of apoptosis, modulation of oxidative stress, suppression of inflammatory signaling, and interference with cell-cycle progression. Phenolic compounds, flavonoids, and terpenoids could affect proteins involved in apoptosis (bax, bcl-2, and caspases). Modulation of PI3K/Akt/mTOR pathways, MAPK pathways and NF- κ B pathways have also been suggested. They may be capable of inhibiting migration, invasion and angiogenic signaling, and may therefore have antimetastatic activity. The evidence is mostly from cell culture and animal studies however and the concentrations used in vitro may not be clinically achievable. So, for the time being, lavender's use in anticancer therapy is considered to be an investigative one [50].



5.12. Wound-healing and dermatological activity

Lavender is popular for topical use, thanks to its antimicrobial, anti-inflammatory, antioxidant, and tissue-repair properties. Experimental research indicates that preparations of lavender can stimulate wound contraction, re-epithelialization, collagen synthesis, and tissue remodeling. The antimicrobial effects can help to decrease microbial contamination and the anti-inflammatory effects can help to prevent extended inflammation. Antioxidant effects can also prevent newly formed tissue from being damaged by oxidative stress. All of these combined actions can be used in minor wounds, inflammatory skin diseases and cosmetic formulations. Lavender has also been investigated for its anti-acne, anti-dermatitis and anti-psoriasis inflammatory activity as well as its photoaging activity, but clinical evidence is not of a high quality [51].

5.13. Gastroprotective and antispasmodic activity

Recent studies suggest that lavender has an antispasmodic and gastroprotective action, which support the traditional use in digestive complaints. Constituents of essential oils may be able to relax gastrointestinal smooth muscle through modulation of calcium channels or other ion conductances. Additional, antioxidant and anti-inflammatory activity may help to further protect gastric mucosa by phenolic compounds. Gastrointestinal benefits might therefore be due to a reduction of oxidative injury, modulation of gastric motility and attenuation of smooth-muscle spasm [52].

5.14. Immunomodulatory and cytoprotective activity

Compounds found in lavender may affect immune-cell signaling, the production of

cytokines, oxidative response, and inflammatory transcription factors. Macrophage activation and NF- κ B signaling pathways and inflammasome-associated pathways are other mechanisms of immunomodulation. Reduction of oxidative stress and inflammatory signaling is cytoprotective across various tissues, such as the brain, liver, kidney, heart and skin. This multi-system protection is especially important for chronic conditions that involve a vicious cycle of oxidative and inflammatory processes. Lavender's biological activity is equally and much more than just its essential oil. Modulation of neurotransmission, oxidative stress, inflammation, microbial viability, ion channels, mitochondrial function, metabolic signaling, apoptosis and immune responses can be achieved simultaneously due to its phytochemical complexity. This profile of multiple targets offers a mechanistic explanation of its reported anxiolytic, neuroprotective, antimicrobial, anti-inflammatory, antioxidant, analgesic, metabolic, cardiovascular, dermatological and potentially anticancer properties. Concurrently, the level of evidence varies greatly from one biological activity to another. There are still numerous mechanistic assertions which are made about isolated compounds, in vitro experiments or animal models. Chemically standardized preparations, identification of the active minor constituents, dose-response studies, pharmacokinetic studies, direct validation of molecular targets and appropriately designed clinical trials, however, should be emphasized for further research. Such research will be fundamental in identifying the biological activities of *Lavandula* that are ideal for a potential transition from conventional or experimental use to clinical use [53-55].

FUTURE PERSPECTIVES

Future studies on *Lavandula* species should go beyond the traditional interest of linalool and



linalyl acetate and consider the chemical diversity of the genus as a whole. The minor volatiles, phenolic acids, flavonoids, coumarins, triterpenoids and other non-volatiles may play a significant role in the pharmacological effects of lavender, either alone or as a synergy. Comprehensive metabolomic profiling, using high-resolution analytical platforms, NMR and GC–MS/MS and LC–MS/MS, will thus be necessary for identifying underexplored compounds and species- and chemotype-specific chemical fingerprints. Direct validation of molecular targets and pathways should be a high priority. Several mechanisms were proposed, including those related to GABAergic, glutamatergic, cholinergic, Nrf2/HO-1, NF-κB, MAPK, NLRP3, PI3K/Akt/mTOR, and AMPK signalling; however, many of these mechanisms have only been supported by preclinical evidence. Further research is needed to use receptor binding assays, pathway specific inhibitors, gene silencing and advanced cellular and animal models to determine causal relationships between individual components and biological effects. To further investigate the multi-target effects of *Lavandula* phytochemicals, integration of network pharmacology, molecular docking, molecular dynamics, transcriptomics, proteomics and metabolomics data are recommended. AI and ML methods could help speed up compound prioritization, target prediction, chemotype classification and identification of promising therapeutic combinations. In addition to the above, the following should be investigated for translational research: Pharmacokinetics and bioavailability, Penetration of the blood–brain barrier, Active metabolites and metabolites, Dose standardization, Toxicity and herb–drug interactions. Poorly bioavailable constituents could be more stable and tissue targeted via advanced delivery systems such as nanoemulsions, liposomes, polymeric nanoparticles, and intranasal

formulations. Most importantly, there is a need to fill this gap between the experimental results and clinical use through well-designed randomized clinical trials, involving chemically standardized preparations. The synergy of such multidisciplinary approaches may be able to change the perception of *Lavandula* as a conventional aromatic plant to a scientifically proven multi-target therapeutic agent.

CONCLUSION

Lavandula spp. is a very diversified and pharmacologically versatile group of medicinal plants, and the therapeutic potential of these species is not limited to the traditionally emphasised constituents, linalool and linalyl acetate. Many studies have revealed the biological activity of lavender with increasing phytochemical evidence showing that the monoterpenes, sesquiterpenes, phenolic acids, flavonoids, coumarins, triterpenoids, sterols and other non-volatile metabolites are important contributors to the biological activity of lavender. These constituents exert several molecular mechanisms and signal pathways that include antioxidant, anti-inflammatory, neuroprotective, anxiolytic, antimicrobial, analgesic, metabolic, cardiovascular, dermatological, and possibly anticancer activities.

Mechanism of action for *Lavandula* is especially interesting due to the simultaneous modulation of GABAergic, glutamatergic, cholinergic, serotonergic, dopaminergic systems and regulation of Nrf2/HO-1, NF-κB, MAPK, NLRP3, PI3K/Akt/mTOR, AMPK pathways. The combination of multiple targets pharmacology could be beneficial in complex disorders in which oxidative stress, inflammation, mitochondrial dysfunction, altered neurotransmission, and metabolic imbalance occur simultaneously. The biological significance of each minor component



and their inter-dependencies from complex extracts are not fully understood, however.

One of the drawbacks of existing studies is the dominance of in vitro and animal studies, as well as the use of different species, chemotype, extraction, dosage and phytochemical standardization within the studies. Chemically characterized preparations, direct molecular target validation, pharmacokinetic studies, toxicity studies, and well-designed clinical trials should therefore be the focus of future investigations. Use of advanced analytical platforms, multi-omics technologies, network pharmacology and novel drug delivery systems could further expedite the identification of clinically relevant constituents. In general, *Lavandula* must be regarded not only as a plant for the production of aromatic essential oil, but as a source of a wide spectrum of bioactive molecules, with significant therapeutic and drug-discovery potential. To realize the therapeutic potential of this phytochemical and mechanistic diversity, a broader perspective will be needed if the diversity of these plants is to be turned into standardized and evidence-based therapies.

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