



Phytochemical insights and therapeutic benefits of *Aloysia citrodora* (lemon verbena): implications for chronic disease prevention and functional food development

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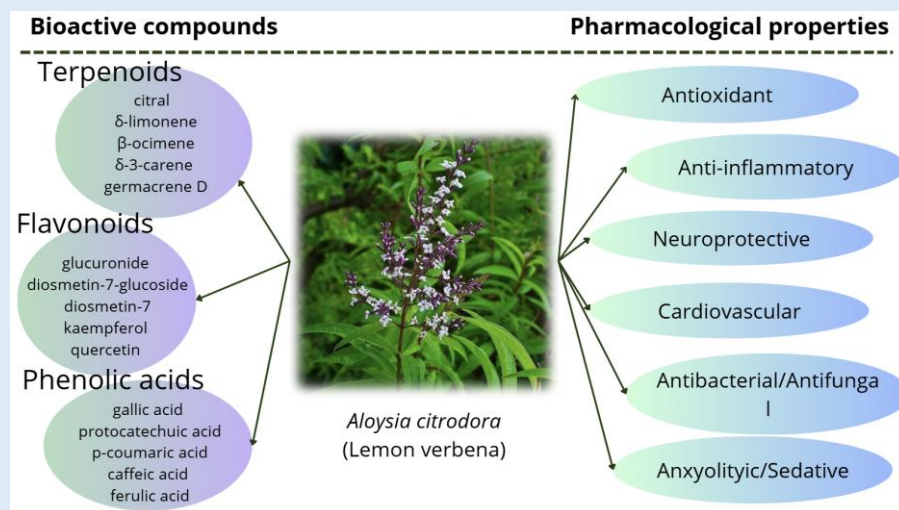
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ABSTRACT

Aloysia citrodora Paláxu (Lemon Verbena) is a South American aromatic plant traditionally used for its calming and digestive effects. In recent years, it has attracted scientific attention due to its wide range of pharmacological properties. This review summarizes the biological activities of its key phytochemicals—verbascoside, citral, limonene, linalool, geraniol, and other phenolic glycosides—based on a systematic search of PubMed, ScienceDirect, and Web of Science. Preclinical studies have demonstrated significant antioxidant, anti-inflammatory, antimicrobial, anxiolytic, and potential anticancer effects. These activities are mainly linked to secondary metabolites such as verbascoside and citral, which influence oxidative stress, inflammation, and apoptosis-related pathways. In vivo data also indicate that lemon verbena polyphenols may improve insulin sensitivity, regulate lipid metabolism, and reduce adiposity—suggesting benefits for managing obesity and type 2 diabetes. Its mild sedative action supports its traditional use for stress relief and insomnia.

Despite these promising results, clinical evidence remains limited. *A. citrodora* holds potential as a functional food ingredient and phytotherapeutic agent for chronic disease prevention. However, well-designed human studies are needed to confirm its efficacy, clarify its mechanisms, and ensure its safe use in health promotion.



Graphical abstract: Bioactive Constituents and Therapeutic Potentials of *Aloysia citrodora*

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INTRODUCTION

Aloysia citrodora Paláu is an evergreen shrub from the Verbenaceae family, belonging to the angiosperm group of plants. Also known as lemon verbena or lemon beebrush, it is native to the tropical regions of South America and was brought to the Old World by Europeans in the 17th century. The plant grows to a height of 3 m and blooms in late spring to early summer, but outside the tropics, flowering is either delayed until late summer or is absent entirely. When grown outside the tropics, it can become a deciduous plant [1].

The leaves are long, up to 8 cm, lanceolate, and glossy. When bruised, they emit a strong lemon smell due to the presence of specialized cells with essential oils (EO).

Aloysia citrodora (or *A. triphylla*) has a rich ethnobotanical history rooted in South American traditional medicine. Indigenous cultures, particularly the Inca civilization, utilized the plant under names such as "wari pankara" for the management of digestive

disorders, bronchial ailments, cardiac complaints, and nervous system disturbances. Traditional healers known as "kallawayas" administered it as a sedative and antispasmodic agent [2].

In modern ethnomedicinal contexts, such as those documented in Jordan, *A. citrodora* continues to be widely recognized for its therapeutic use in managing insomnia, anxiety, digestive issues, bronchitis, and heart-related symptoms, demonstrating the continuity of its traditional applications into modern herbal practices [3].

Experimental studies demonstrate that *A. citrodora* displays notable antioxidant, anti-inflammatory, antimicrobial, anxiolytic, and potential anticancer effects [4]. These effects are primarily attributed to its secondary metabolites, particularly verbascoside and citral, which modulate oxidative stress, inflammation, and apoptotic pathways. Additionally, in vivo studies suggest that lemon verbena's polyphenolic compounds can enhance insulin sensitivity, regulate lipid metabolism, and reduce adiposity, indicating potential benefits in managing

obesity and type 2 diabetes. The plant's mild sedative effects also support its use in stress relief and insomnia. Furthermore, recent findings suggest it may promote gut health through microbiota modulation and protection against gastrointestinal pathogens. Despite these promising effects, most current data are derived from in vitro and animal studies. Human clinical trials remain limited, and inconsistencies in extraction methods, compound concentrations, and dosing strategies hinder the development of standardized therapeutic recommendations.

The diverse array of phytochemicals identified in *A. citrodora* underscores the plant's potential as a functional food, aligning with the foundational principles of functional food science and emphasizing the role of bioactive compounds in managing chronic conditions such as hypercholesterolemia [5, 6]. Emerging conceptual frameworks in this field—such as the Quantum theory, which highlights molecular-level interactions, and the Tempus theory, which emphasizes the role of timing in bioactive efficacy, suggest that optimizing both dosage and circadian alignment may enhance the therapeutic potential of *A. citrodora* phytochemicals [7].

METHODS

A comprehensive literature search was conducted using the databases PubMed, ScienceDirect, and Web of Science to identify relevant studies on the phytochemistry and pharmacological activities of *Aloysia citrodora*. The search included publications from 2012 to 2025, using keywords such as "*Aloysia citrodora*", "*lemon verbena*", "*verbascoside*", "*citral*", "*essential oil*", and "*phytochemical composition*". Only peer-reviewed, English-language articles reporting original data or reviews on the plant's bioactive compounds and therapeutic effects were included.

Chemical Composition of *Aloysia citrodora*

Aloysia citrodora is characterized by a rich and diverse phytochemical profile, with its essential oil (EO) and

various extracts containing significant amounts of terpenoids, phenolic acids, and flavonoids [8, 9]. These compounds collectively contribute to the plant's distinctive aroma and its wide range of pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, and neuroprotective activities [10].

Terpenoids: The EO of *A. citrodora* is predominantly composed of mono- and sesquiterpenoids, which account for its aromatic and many of its bioactive properties. Dominant monoterpenes identified include citral (a mixture of geranial and neral), δ -limonene, β -ocimene, and δ -3-carene. Key sesquiterpenes found are germacrene D, trans-caryophyllene, bicyclogermacrene, and α -curcumene [11]. These terpenoids exhibit various functional roles. For instance, citral (geranial + neral) is recognized for its antimicrobial, antioxidant, anti-inflammatory, and apoptosis-inducing activities, particularly in cancer cells and inflammatory models [12]. Limonene and caryophyllene possess analgesic, anti-inflammatory, and anticancer properties, and are also used in insect-repellent formulations [13]. Sesquiterpenes such as germacrene D and bicyclogermacrene demonstrate antioxidant, cytotoxic, and plant defense properties. Terpenoid concentrations can vary seasonally and are influenced by environmental factors such as drought stress and UVB radiation, which can notably increase compounds like caryophyllene, α -pinene, and geranial [11]. Chemotypic differences among geographically distinct *A. citrodora* populations have also been observed, which are important for standardization in herbal product development [11].

Phenolic Acids: *A. citrodora* is particularly abundant in phenolic acids, which contribute to its antioxidant, anti-inflammatory, neuroprotective, and food-preserving properties. Seven phenolic acids have been specifically identified in Lemon Verbena leaves: gallic acid, protocatechuic acid, p-coumaric acid, caffeic acid, ferulic acid, sinapic acid, and syringic acid [12]. Aqueous extracts (infusions and decoctions) generally show higher

concentrations of these compounds and stronger antioxidant capacities compared to hydroalcoholic ones [13]. Studies have also confirmed the presence of trans-ferulic acid, hesperidin, and p-coumaric acid [14]. Phenolic acids exhibit high bioavailability and potent antioxidant and anti-inflammatory effects *in vivo*, supporting the plant's role in gut health and protection against lipid oxidation [15-18].

Flavonoids: Lemon verbena is a significant natural source of flavonoids, a subclass of polyphenolic compounds recognized for their strong antioxidant, anti-inflammatory, neuroprotective, and chemopreventive properties. Key flavonoids identified in *A. citrodora* include: luteolin, luteolin-7-glucoside, luteolin-7-diglucuronide, apigenin, apigenin-7-glucuronide,

diosmetin-7-glucoside, diosmetin-7-neohesperidoside, kaempferol, quercetin, isorhamnetin, and chrysoeriol-7-glucoside. These compounds are present in both aqueous and hydroalcoholic extracts and significantly contribute to the plant's medicinal efficacy [11, 19, 20].

The therapeutic potential of *Aloysia citrodora* is illustrated in Table 1, which summarizes its major pharmacological activities, associated phytochemicals, biological targets, and experimental models [Table 1]. The therapeutic potential of *Aloysia citrodora* is illustrated in Table 1 and in graphical abstract 1, which summarizes its major pharmacological activities, associated phytochemicals, biological targets, and experimental models [Table 1; graphical abstract 1].

Table 1. Therapeutic Activities and Supporting Evidence for *Aloysia citrodora*

Pharmacological Activity	Supporting Compounds	Biological Targets / Applications / Models Effects	Studied
Antioxidant	Verbascoside, Luteolin-7-diglicuronide, Ferulic acid	ROS scavenging, non-chelation, homeostasis, phase II metabolism	Adipocytes Under redox glucotoxic stress, antioxidant assays <i>in vitro</i> and <i>in vivo</i>
Anti-inflammatory	Citral, Flavonoids, Phenolic acids	& INF- α , CRP, IFN- γ ; IL-1, IL-4, IL-10; NF-KB inhibition	DSS-induced colitis in rats, Ms patient serum, traditional anti-inflammatory use
Neuroprotective	Citral, Limonene, Verbascoside	Inhibition of B-amyloid and H ₂ O ₂ induced toxicity, Alzheimer's iron-chelating, GABA oxidative neurotoxicity modulation, enzyme assays inhibition	Alzheimer's disease models, oxidative neurotoxicity assays
Anticancer	Citral, EO, Polyphenols	Induction of apoptosis, anti-proliferation, inhibition of tumor growth and migration	Breast cancer, melanoma, colon cancer models <i>in vitro</i> and <i>in vivo</i>
Cardiovascular	Vitexin, Geraniol, Neral	& blood pressure, negative inotropy, α_1 -adrenergic receptor blockade	Normotensive rat models, vas deferens/heart tissue studies
Antibacterial / Antifungal	Citral, EO, Verbascoside	Membrane disruption, anti-biofilm, MIC reduction, synergism with antibiotics	MRSA, E. coli, C. albicans, Pseudomonas spp.
Metabolic / Antidiabetic	Verbascoside, Limonoids, Polyphenols	Inhibition of α -amylase/ α -glucosidase, insulin sensitivity, adiposity; lipid Metabolism regulation	Diabetic models, Molecular docking, metabolic cell line assays
Gut health modulator	Polyphenols, Verbascoside	Microbiota modulation, barrier protection	DSS-induced colitis, antioxidant/anti-inflammatory gut studies
Anxiolytic / Sedative	EO (Citral, Linalool, Limonene), Flavonoids	GABA-A receptor modulation, locomotor activity	Mouse open field tests, synergy with diazepam

Antioxidant effect of *Aloysia citrodora*: The natural antioxidants from plants are becoming increasingly important, not only in the nutritional area (food preservation and stability) but also in preventive medicine. Lemon verbena is a medicinal and aromatic plant long valued for its calming, digestive, and anti-inflammatory properties. Recent pharmacological investigations have increasingly highlighted its potent antioxidant effects, which are closely associated with its rich and diverse phytochemical profile [21, 22].

A study by Olivares-Vicente *et al.* explored the intracellular antioxidant mechanisms of Lemon Verbena metabolites in hypertrophic adipocytes exposed to glucotoxic conditions [23]. The study identified key plasma metabolites—such as isoverbascoside, caffeic acid, ferulic acid, and luteolin-7-diglucuronide—which were effectively taken up and metabolized by adipocytes through phase II reactions. Their intracellular accumulation was strongly correlated with reduced reactive oxygen species (ROS), demonstrating their role in long-term cellular antioxidant defense.

In a food science context, *A. citrodora* has demonstrated functional antioxidant applications. Mohamed Abdoul-Latif *et al.* reported that cookies enriched with lemon verbena EO and powder showed enhanced oxidative stability and improved sensory properties over a six-month storage period [13]. The plant's EO (rich in citral isomers such as geranial and neral) and polyphenol content (49.2 mg/g total phenolics) contributed to its antioxidant effects in food matrices. Evidence from in vivo studies also supports its antioxidant role. Rashid *et al.* evaluated different extracts of *A. citrodora* in both antioxidant and anticancer assays, finding that the ethanol extract showed the strongest radical scavenging activity, while the ethyl acetate extract produced a significant tumor size reduction in mouse models [2].

Comparative analysis by Polumackanycz *et al.* found that *A. citrodora* possesses higher phenolic content and

antioxidant activity than common verbena (*Verbena officinalis* L.) [12]. Notably, aqueous extracts (e.g., decoctions and infusions) exhibited stronger antioxidant properties than hydro-methanolic extracts, reinforcing the relevance of traditional preparation methods for maximizing bioactivity.

Additionally, Lenoir *et al.* reported that Lemon Verbena infusion conferred partial protection against dextran sulfate sodium (DSS)-induced colitis in rats [24]. Treated rats showed improved weight gain, reduced colonic shortening, and limited histological damage, likely due to the antioxidant activity of the infusion, despite no significant effect on myeloperoxidase levels.

In this study, the compound displayed strong free radical scavenging and mild neurosedative effects, underscoring the possibility of synergistic interactions among the plant's bioactive constituents [25].

These studies establish *Aloysia citrodora* as a robust source of natural antioxidants. Its phytochemical diversity demonstrated efficacy in both cellular and animal models, and applicability in food and health systems make it a valuable candidate for further development in nutraceutical and therapeutic contexts [26].

Anti-Inflammatory Effect: Most plants produce antimicrobial secondary metabolites, either as part of their normal growth and development, or in response to stress or pathogen attack. The use of EOs represents a new way to reduce the proliferation of microorganisms. Lemon verbena has also demonstrated significant anti-inflammatory properties in both preclinical and clinical settings. Pharmacological studies support its role in modulating inflammatory responses via both local tissue protection and systemic immune regulation.

In animal models of intestinal inflammation, lemon verbena infusion showed protective effects against colonic damage induced by DSS. Supplementation helped restore body weight, prevent colon shortening, and reduce histopathological signs of inflammation. These

effects are likely related to the plant's antioxidant properties and its ability to preserve mucosal integrity, even though changes in myeloperoxidase activity were not statistically significant [24].

In a clinical context, dietary supplementation with lemon verbena extracts significantly reduced levels of pro-inflammatory cytokines such as C-reactive protein and interferon-gamma (IFN- γ) in patients with multiple sclerosis. Simultaneously, anti-inflammatory cytokines like interleukin-4 (IL-4) and interleukin-10 (IL-10) were elevated, suggesting an immunomodulatory mechanism that favors an anti-inflammatory cytokine profile [27, 28].

These results highlight lemon verbena's promising role in managing chronic inflammatory conditions.

Neuroprotective Effect: EO derived from *Aloysia citrodora* has demonstrated significant neuroprotective activity in various *in vitro* models relevant to neurodegenerative diseases. In neuronal cell cultures, the EO effectively reduced cytotoxicity caused by hydrogen peroxide and β -amyloid exposure—two major neurotoxic agents implicated in the pathogenesis of Alzheimer's disease [29, 30]. Recent molecular docking and simulation studies have revealed that catechin, a phytochemical found in *Aloysia citrodora*, shows strong binding affinities to key proteins involved in Parkinson's disease. Catechin outperformed standard drugs in binding strength to multiple PD-related targets and demonstrated favorable pharmacokinetic and toxicity profiles. These findings highlight its potential as a neuroprotective agent, although experimental validation is still required [31].

These protective effects were attributed to the EO's strong antioxidant and iron-chelating properties, which counteract oxidative stress, a key driver of neuronal degeneration [32, 33]. A recent study showed that lemon verbena methanolic extract improved anxiety- and depression-like behaviors in diabetic rats, likely by reducing oxidative stress in the prefrontal cortex [34].

The article by Boukabache et al. explores the enzyme inhibition activity of *A. citrodora* essential oil and its main components, citral and limonene, for potential applications in metabolic and neurodegenerative diseases [35]. Natural bioactive compounds like polyphenols, essential oils, and carotenoids show promise in protecting the brain against oxidative stress linked to neurodegenerative diseases. Their antioxidant and anti-inflammatory properties may support neuroprotection, neurogenesis, and disease mitigation [36, 37]. These findings support the EO's role as a multifunctional agent capable of mitigating oxidative damage and preserving neuronal integrity.

Cardiovascular Effect: *Aloysia citrodora*, traditionally used for the management of anxiety, palpitations, and gastrointestinal spasms, exhibits notable sedative and cardiovascular properties, validated in both animal and *in vitro* models. These effects are closely tied to its phytochemical composition, particularly the presence of flavonoids such as vitexin, volatile monoterpenes like geranial and neral, and various polyphenolic compounds.

Cardiovascular evaluation in normotensive rats showed that intravenous administration of EO of *A. citrodora* induced a transient, dose-dependent hypotensive effect, not reversed by muscarinic blockade (atropine) or nitric oxide synthase inhibition (L-NAME), indicating that the mechanism does not involve cholinergic or NO-mediated pathways. Instead, non-competitive blockade of α 1-adrenergic receptor-mediated responses was observed in isolated rat vas deferens, suggesting an antiadrenergic mechanism [38]. In animal behavioral models, aqueous extracts exhibited dose-dependent sedative effects in mice, significantly reducing locomotion in the open-field test. These effects were potentiated by diazepam and antagonized by flumazenil, suggesting partial modulation of GABA-A receptors. Supporting this mechanism, recent phytochemical analysis confirmed the presence of GABA

in the ethanolic extract of *Aloysia citrodora*, providing a possible biochemical basis for its sedative and anxiolytic effects. Interestingly, melatonin was absent, indicating the hypnotic activity is likely independent of melatonergic pathways [39]. A recent study showed that lemon verbena extract improved sleep in mice by enhancing both rapid eye movement and non-rapid eye movement sleep, likely through increased expression of adenosine A1 receptors and gamma-aminobutyric acid type A receptors [40]. Additionally, in normotensive rats, it produced transient hypotensive responses, independent of cholinergic or nitric oxide pathways, and blocked α 1-adrenergic receptor-mediated contractions in vas deferens preparations. Isolated rat heart studies further demonstrated negative inotropic effects from *A. citrodora* and its constituent vitexin, indicating the plant's potential impact on cardiovascular regulation during states of agitation or stress-induced tachycardia [38].

In isolated perfused rat hearts, vitexin caused negative inotropic effects, reducing left ventricular pressure in a dose-dependent manner. Although vitexin contributed to these effects, it did not reproduce all cardiovascular actions of the extract, indicating synergism among multiple compounds [38]. These findings align with previous reviews that identify vitexin, verbascoside, and citral-rich EOs as contributors to both cardioprotective and anxiolytic activities [3].

These data offer a pharmacological justification for the ethnobotanical use of *A. citrodora* in managing cardiovascular symptoms. The observed effects support its potential as a natural cardiovascular modulator, warranting further clinical research.

Antibacterial Effect: *Aloysia citrodora* displays notable antibacterial activity attributed to its EO constituents such as citral (neral and geranial), verbascoside, and various monoterpenes and flavonoids. These components show synergistic and membrane-targeting effects that make the plant a promising candidate for

antimicrobial therapy, especially against drug-resistant strains.

The EO from Baqa al-Gharbiyye showed stronger antioxidant and antibacterial activity than that from Umm al-Fahm, with a notable inhibition of MRSA and *Proteus vulgaris* Hauser. Its performance was superior to ciprofloxacin and ampicillin, and its antifungal effect against *Candida albicans* Berkhout surpassed fluconazole. This EO also demonstrated potent cyclooxygenase inhibition, highlighting dual antimicrobial and anti-inflammatory potential [41, 42]. Fazly *et al.* further evaluated the synergistic antibacterial effects of lemon verbena aqueous extract, verbascoside, and caffeine in combination with gentamicin against drug-resistant *Staphylococcus aureus* Rosenbach and *Escherichia coli* Castellani and Chalmers. Although the natural agents alone showed limited direct antibacterial effects, they significantly reduced the minimum inhibitory concentration (MIC) of gentamicin. The combination of verbascoside and gentamicin had the most pronounced synergistic effect (FICI < 1), suggesting its role in re-sensitizing resistant bacterial strains to antibiotics [43, 44].

In a mechanistic study, Gao *et al.* reported that lemon verbena EO disrupts bacterial cell integrity and biofilm formation [45]. Treatment of *Pseudomonas* Migula strain D4 with EO led to increased membrane permeability, cytoplasmic leakage, and cell wall damage, verified by confocal microscopy and electron microscopy. EO also inhibited extracellular polysaccharide production, essential for biofilm development, reinforcing its role in combating chronic and biofilm-associated infections.

Scientists also investigated how the extract, when incorporated into lipid nanocapsules, could be effectively delivered for topical use to combat bacteria. The study aimed to create a stable and efficient system that could release the extract over time, thereby enhancing its ability to serve as a skin-applied antibacterial treatment.

[46]. In addition to nanoemulsion and lipid-based systems, cyclodextrin encapsulation has proven effective in stabilizing *A. citriodora* essential oil (EO) and controlling its release without compromising antimicrobial activity. A freeze-dried β -cyclodextrin/EO complex (β -CD/EO) showed stronger inhibition of *Listeria monocytogenes* than *E. coli*, extended beef shelf life by three days at $4 \pm 1^\circ\text{C}$, and received high sensory acceptance. TGA, SEM, and FT-IR confirmed successful complex formation. These results support the use of encapsulated *A. citriodora* EO as a natural food preservative [47].

This article investigated the antimicrobial potential of *Aloysia citrodora* hydrosol against various pathogens, including *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* (C.-P. Robin) Berkhout. Notably, *A. citrodora* hydrosol demonstrated significant inhibitory effects, particularly against *E. coli* and *C. albicans*, positioning it as a promising eco-friendly antimicrobial agent [48].

Anticancer Activity: The composition of the human diet can influence the risk of cancer, and its components can exert positive or negative influences. Chemoprevention is the long-term pharmacological control of the risk of cancer.

An aqueous extract of *Aloysia gratissima* demonstrated diverse biological activities, including antioxidant and cytotoxic effects against ovarian, glioblastoma, and colon cancer cell lines. However, it also induced DNA damage in neuroblastoma cells and exhibited mutagenic potential in bacterial strains, suggesting the need for cautious use [49]. This study investigated the antitumor effects of *A. citriodora* oil on breast cancer, demonstrating its ability to inhibit the growth of murine DA3 breast cancer cells *in vitro*, attenuate their migration, and induce apoptosis. Furthermore, oral administration of *Aloysia* in mice significantly reduced the size of developing tumors and

altered key apoptotic markers within the tumor tissue. These findings highlight *A. citriodora*'s potential as a source of bioactive compounds with nutraceutical properties for cancer management [50].

Another study investigated the potential of chitosan nanoparticles loaded with *A. citriodora* EO and citral for melanoma treatment. Researchers prepared and characterized these nanoparticles, then assessed their antioxidant properties and pro-apoptotic effects on A375 melanoma cells. Results showed that citral-loaded nanoparticles exhibited superior antioxidant activity and induced a higher percentage of apoptosis in melanoma cells compared to the EO-loaded nanoparticles and their free forms [51].

A. citrodora possesses potent anticancer properties through a combination of oxidative stress modulation, pro-apoptotic gene regulation, and EO-mediated cytotoxicity.

Antidiabetic and Hepatoprotective Activity: *Aloysia citrodora* presents a compelling natural agent with significant antidiabetic and hepatoprotective properties, addressing critical aspects of metabolic dysfunction through a multi-pronged approach. Its therapeutic potential stems from its ability to modulate inflammation, regulate enzymatic activity, and improve glucose and lipid metabolism, alongside providing crucial protection to the liver, an organ central to metabolic health.

Regarding antidiabetic activity, *A. citrodora* essential oil has shown significant inhibitory effects on enzymes such as α -amylase and α -glucosidase, which are crucial targets in managing metabolic disorders like diabetes. Information specifically on hepatoprotective activity was not explicitly detailed in the provided article summaries [52]. Beyond its anti-inflammatory effects, *A. citrodora* actively contributes to improved glucose and lipid metabolism. Another key antidiabetic mechanism involves the inhibition of carbohydrate-digesting enzymes. El Feky *et al.* demonstrated that plant-derived

limonoids, abundant in lemon verbena and its citrus relatives, exhibit potent inhibitory effects against α -amylase and α -glucosidase [53]. These enzymes are critical in carbohydrate metabolism, and their inhibition helps control postprandial glucose levels. Molecular docking and simulation studies further confirmed stable interactions between these limonoids and the active sites of the enzymes, validating their potential for glycemic control [54].

The safety profile of *A. citrodora* components also supports its pharmacological viability. Its dominant polyphenolic compound, verbascoside, has demonstrated excellent safety in toxicity studies. Verbascoside, a widely distributed phenylethanoid glycoside, is recognized for its extensive therapeutic properties, including antioxidant, antimicrobial, anti-inflammatory, neuroprotective, cardioprotective, skin-protective, and anti-cancer effects. Despite these benefits, verbascoside faces challenges like poor bioavailability, leading current research to focus on nanoformulations, particularly liposome-based systems, to improve its delivery for diverse applications such as wound healing and neuroprotection. While verbascoside has confirmed low acute and sub-acute toxicity, long-term toxicity studies and scalable production methods are still emphasized for its therapeutic advancement [55]. Furthermore, a comprehensive review by Bahramsoltani *et al.* highlighted the broad pharmacological activities of *A. citrodora*, citing both *in vitro* and *in vivo* studies showcasing its antioxidant, anti-inflammatory, and metabolic regulatory effects [3]. The presence of key constituents such as verbascoside, geraniol, neral, and flavonoids is understood to contribute to its efficacy in modulating glucose and lipid metabolism, as well as protecting liver function—mechanisms that are central to effective antidiabetic interventions [3].

Aloysia citrodora and its rich array of bioactive compounds hold considerable therapeutic promise in the

management of type 2 diabetes [56]. Its benefits arise from a synergistic combination of antioxidant, anti-inflammatory, and enzyme-inhibitory mechanisms, coupled with its direct positive effects on glucose and lipid metabolism, all underpinned by crucial hepatoprotective actions that support overall metabolic health.

Despite the promising preclinical findings, the integration of natural agents like *Aloysia citrodora* into functional food products necessitates clear regulatory frameworks and standardized guidelines, a topic actively addressed by organizations advocating for advanced functional food regulation [54].

CONCLUSION

Aloysia citrodora represents a valuable botanical source of bioactive compounds, particularly verbascoside, citral, and various terpenes and phenolic constituents. This review highlights its wide range of therapeutic effects, including antioxidant, anti-inflammatory, antimicrobial, anxiolytic, neuroprotective, and potential anticancer properties. Its ability to modulate oxidative stress, inflammation, and cellular signaling pathways positions it as a valuable candidate for managing chronic diseases [24, 25].

The plant also demonstrates promise in addressing metabolic disorders by improving insulin sensitivity, regulating lipid profiles, and reducing adiposity. Traditional uses for stress relief and insomnia are supported by studies showing mild sedative effects [55, 56]. Recent findings further suggest a role in gut health, including microbiota modulation and protection against intestinal pathogens [43].

Despite these promising results, most supporting evidence comes from *in vitro* and animal studies. The lack of robust human clinical trials, along with inconsistencies in extraction techniques and dosage, hinders the development of standardized therapeutic recommendations. Nonetheless, the therapeutic profile of *A. citrodora* aligns with the growing interest in

functional foods, which are increasingly recognized for promoting health and preventing chronic conditions [57, 58].

Future research should focus on high-quality clinical trials to confirm its efficacy, clarify mechanisms of action in human systems, and establish safe, evidence-based guidelines for its use in health promotion and disease prevention. Bridging this gap will be key to translating its traditional applications into modern clinical practice.

Importantly, *A. citrodora* and its essential oil are classified by the U.S. FDA as Generally Recognized as Safe for use as flavoring agents (21 CFR 172.510), reflecting a long history of safe use in food products [59]. While this supports its incorporation into functional foods, novel delivery forms or therapeutic dosing will require further regulatory evaluation.

In addition, *A. citrodora* is well-suited for sustainable cultivation. Practices such as biofertilization not only enhance crop yield but also support soil health and biodiversity, reinforcing its value as an environmentally responsible medicinal plant [60].

Abbreviations: National Academy of Sciences of the Republic of Armenia - NAS RA; ultraviolet B – UVB; reactive oxygen species - ROS; essential oil – EO; dextran sulfate sodium – DSS; interferon-gamma - IFN-γ; interleukin-4 - IL-4; interleukin-10 - IL-10; interleukin-12 - IL-12; Gamma-aminobutyric acid type A – GABA-A; Gas Chromatography – GC; Mass Spectrometry – MS; Methicillin-resistant *Staphylococcus aureus* – MRSA; minimum inhibitory concentration – MIC; Fractional Inhibitory Concentration Index – FICI. GA – conceptualization, supervision, critical revision of the manuscript, writing–review and editing; SS – literature search, data analysis, writing – review and editing; GM – literature review, data organization, writing – original draft preparation, writing – review and editing; MS – literature search, writing – review and editing; YM – validation, critical analysis, writing – review and editing;

IG – plant taxonomy and botanical background, writing – review and editing.

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