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Molecular and Translational Pharmacology of *Melissa officinalis*: Targeting Nrf2/ARE, NF-κB/MAPK, and Purinergic Receptors

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ABSTRACT

Melissa officinalis (lemon balm) (MO) is a medicinal herb traditionally used for neurological, metabolic, and infectious disorders. This review synthesizes evidence on its bioactive compounds and molecular mechanisms, with emphasis on antioxidant, anti-inflammatory, anticancer, metabolic, and neuroprotective effects. A structured literature search was conducted in PubMed, Scopus, and Web of Science (2010–2025) using terms related to MO, phytochemicals, oxidative stress, NF-κB/MAPK, Nrf2/ARE, and purinergic receptors. Eligible studies included in vitro, in vivo, and clinical trials. Bioactive compounds, particularly rosmarinic acid, consistently enhanced Nrf2–ARE–driven antioxidant defense, suppressed NF-κB/MAPK-mediated inflammation, and modulated immune responses via P2X7 inhibition and A2A activation. Flavonoids and essential oils contributed to anxiolytic, anticancer, and antimicrobial effects. Clinical studies confirmed efficacy in anxiety, insomnia, and mild cognitive impairment, although variability of extracts and poor bioavailability remain limitations. MO exhibits multi-target pharmacological potential through modulation of oxidative stress, inflammation, and purinergic signaling. Standardized preparations, bioavailability-enhancing formulations, and biomarker-guided clinical trials are needed to establish its therapeutic utility in neuropsychiatric, inflammatory, and metabolic disorders.

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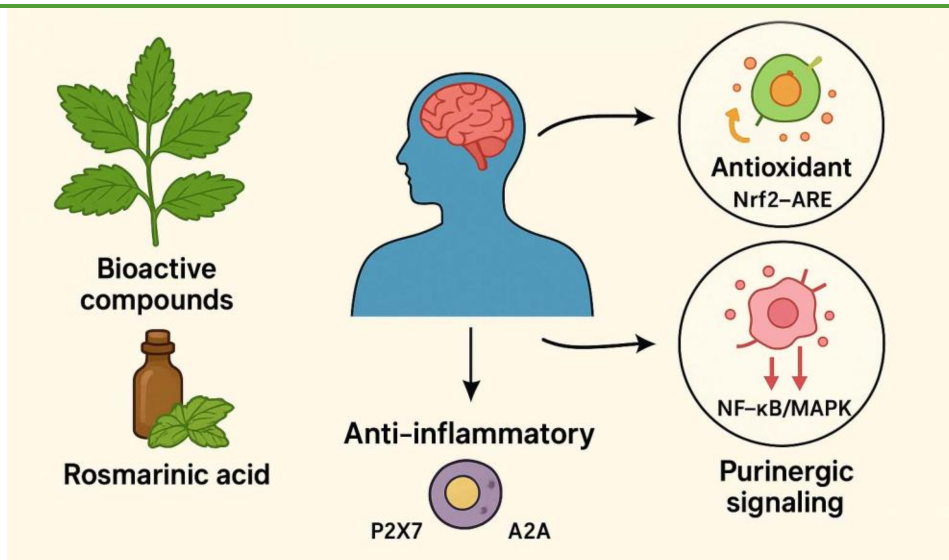
Graphical Abstract



Introduction

Melissa officinalis (MO), commonly known as lemon balm, is a perennial aromatic medicinal herb belonging to the Lamiaceae family that has been extensively used in traditional medical systems for over two millennia. In European, Middle Eastern, and Asian ethnomedicine, MO has traditionally been prescribed for managing a wide range of disorders, including anxiety, insomnia, headaches, gastrointestinal disturbances, cardiac palpitations, viral and bacterial infections, and inflammatory diseases [1–4]. Medieval Persian physicians such as Avicenna documented its use as a "strengthener of the heart and brain," highlighting its calming and restorative properties [5]. In modern phytotherapy and pharmacognosy, MO has attracted increasing scientific interest due to its anxiolytic, antidepressant, neuroprotective, antioxidant, anti-inflammatory, antiviral, and immunomodulatory activities, which have been demonstrated in numerous *in vitro*, *in vivo*, and clinical studies [6–9]. Clinical trials on mild to moderate anxiety and cognitive dysfunction have shown that standardized MO extracts significantly reduce stress markers, improve memory and attention, and restore sleep quality, without causing marked sedative effects or dependency [10–12].

Phytochemical characterization of MO reveals a unique and highly complex metabolic profile. It is particularly rich in phenolic acids, primarily rosmarinic acid, caffeic acid, chlorogenic acid, and ferulic acid, together with flavonoids such as luteolin, apigenin, quercetin, rutin, and kaempferol derivatives [13–15]. In addition, MO contains triterpenoids (ursolic acid and oleanolic acid), tannins, and a mixture of volatile essential oils, including citral (geranial and neral), citronellal, geraniol, β-caryophyllene, linalool, and limonene [16–18]. These secondary metabolites act synergistically, enhancing the plant's antioxidant, antimicrobial, antiviral, neuroprotective, and psychotropic potential [19,20].

Among these compounds, rosmarinic acid (RA) is considered a principal bioactive marker and a key contributor to the pharmacological profile of MO. RA exhibits strong free radical scavenging capacity, efficiently neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS), while protecting cellular lipids, proteins, and DNA from oxidative damage [21–23]. Moreover, RA has been reported to inhibit lipid peroxidation, prevent mitochondrial dysfunction, and stabilize cellular membranes under oxidative and inflammatory stress conditions [24,25]. At the molecular level, MO and its major phenolic constituents exert significant regulatory effects on major intracellular signaling pathways. Rosmarinic acid and related polyphenols have been shown to activate the Nrf2–ARE signaling pathway, leading to the transcriptional upregulation of critical antioxidant and detoxifying enzymes such as heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase-1 (NQO1), superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) [26–28]. Activation of this pathway significantly enhances cellular defense mechanisms and reduces oxidative damage in neurons, immune cells, and epithelial tissues [29].

Simultaneously, MO constituents suppress pro-inflammatory cascades by downregulating key signaling axes including NF-κB, MAPKs (ERK1/2, JNK, and p38), and STAT3. This results in a marked reduction in the expression of pro-inflammatory cytokines and mediators such as TNF-α, IL-1β, IL-6, IFN-γ, COX-2, and iNOS, thereby attenuating both acute and chronic inflammatory responses [30–33]. These properties make MO a promising candidate for the management of neuroinflammatory, autoimmune, metabolic, and degenerative disorders. Essential oil components of MO, particularly citral, linalool, and geraniol, have demonstrated central nervous system activity via modulation of GABAergic, serotonergic, cholinergic, and adenosinergic pathways. Experimental data suggest that these compounds bind to GABA_A receptors and enhance inhibitory neurotransmission, resulting in anxiolytic and mild sedative effects similar to benzodiazepines, but without their adverse effects or dependency potential [34–36]. Moreover, MO has been shown to inhibit acetylcholinesterase (AChE) activity, thereby increasing acetylcholine availability and improving cognitive functions, especially in neurodegenerative conditions such as Alzheimer's disease [37–39]. More recently, emerging evidence has highlighted the role of MO in the modulation of purinergic signaling, a highly important regulatory system in inflammation, immunity, cancer biology, and neurodegeneration. Bioactive compounds of MO, especially rosmarinic acid and flavonoids, have been shown to inhibit ATP-mediated activation of the P2X7 receptor, a key pro-inflammatory and pro-apoptotic receptor highly expressed on microglia, macrophages, and cancer cells [40–42]. This leads to suppression of NLRP3 inflammasome assembly, reduction of caspase-1 activation, and decreased secretion of IL-1β and IL-18, which are central mediators of neuroinflammation and tumor-associated inflammation [43–45].

Conversely, MO polyphenols may enhance A2A adenosine receptor signaling, which promotes anti-inflammatory and immunosuppressive pathways through cAMP/PKA activation and inhibition of pro-inflammatory cytokine production [46–48]. This dual effect — P2X7 inhibition + A2A activation — is particularly valuable in conditions associated with neuroinflammation, microglial overactivation, macrophage M2–M1 imbalance, and tumor-promoting immune environments [49–51]. Therefore, MO represents a promising natural modulator of immune homeostasis and neuroimmune crosstalk. Despite strong preclinical and preliminary clinical evidence, several critical limitations remain. Firstly, there is a high degree of phytochemical heterogeneity in MO extracts caused by differences in geographic origin, climate, soil composition, cultivation conditions, harvest time, and extraction techniques, which significantly affects reproducibility and standardization of results [52–54]. Secondly, major phenolic compounds such as rosmarinic acid suffer from limited oral bioavailability, extensive first-pass metabolism, and relatively poor blood–brain barrier penetration, which reduces their systemic and central efficacy [55–57]. Thirdly, the majority of clinical studies conducted so far have been limited by small sample sizes, short intervention periods, and a lack of molecular biomarkers for objective evaluation [58–60].

Therefore, future research should focus on standardization of high-rosmarinic-acid MO extracts, development of nanoformulations, liposomes and phytosomes to enhance bioavailability and CNS delivery, multi-omics approaches (genomics, proteomics, and metabolomics) to better understand MO's systemic action. Large-scale, double-blind, randomized, and placebo-controlled clinical trials should integrate molecular, immunological, and neurocognitive biomarkers. Such strategies will be crucial for establishing MO as a clinically validated phytotherapeutic agent in the treatment of anxiety disorders, neurodegenerative diseases, chronic inflammation, immune dysregulation, and tumor-associated neuroinflammation [61–65].

Phytochemical Composition

The pharmacological potential of MO is closely associated with its diverse phytochemical profile, which includes phenolic acids, flavonoids, tannins, terpenes, and essential oils. Among these, rosmarinic acid is the predominant compound, often considered a chemotaxonomic marker of the species, and is responsible for strong antioxidant and anti-inflammatory activity (Figure 1) [2,8].

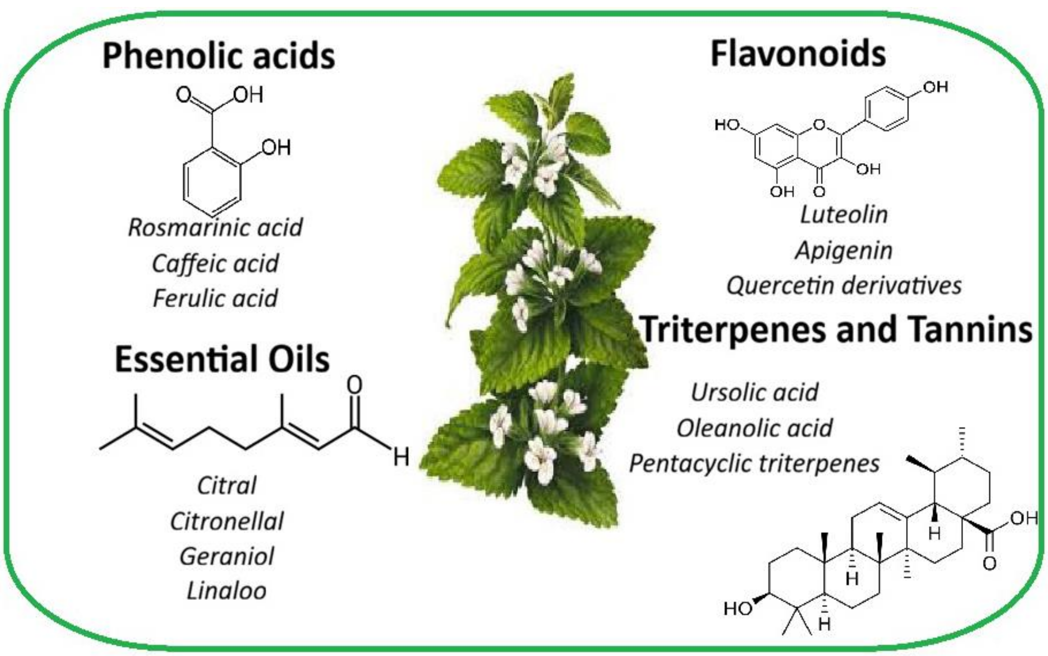


Figure 1. Phytochemical composition of MO, highlighting phenolic acids, flavonoids, essential oils, triterpenes, and tannins as major bioactive groups

Rosmarinic acid is the most abundant phenolic acid, accompanied by caffeic, chlorogenic, and ferulic acids. These compounds possess significant free radical scavenging capacity, promote Nrf2–ARE pathway activation, and protect biomolecules from oxidative stress [8]. The flavonoid fraction includes luteolin, apigenin, and quercetin derivatives, which contribute to both antioxidant and anti-inflammatory effects. These polyphenols modulate NF-κB and MAPK pathways, suppress cytokine release, and exhibit neuroprotective potential [2]. The essential oil composition is dominated by citral (geranial and neral isomers), citronellal, geraniol, and linalool, which are linked to anxiolytic, antimicrobial, and spasmolytic effects. Variability in essential oil content depends on geographical origin, harvest stage, and extraction method [1-3]. Additionally, pentacyclic triterpenes (ursolic acid and oleanolic acid) and condensed tannins contribute to the anti-inflammatory, hepatoprotective, and anticancer potential of MO [1]. Taken together, this diverse phytochemical spectrum underpins the pleiotropic biological activities of MO and supports its traditional and modern therapeutic applications.

Antioxidant Mechanisms

Oxidative stress, defined as the imbalance between ROS production and antioxidant defense, is a major contributor to the pathogenesis of chronic diseases, including cancer, diabetes, cardiovascular, and neurodegenerative disorders. MO exhibits strong antioxidant potential, largely due to its high content of phenolic acids, especially rosmarinic acid, and flavonoids such as luteolin and quercetin derivatives [1,5]. Rosmarinic acid activates the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, leading to dissociation from its repressor Keap1 and subsequent nuclear translocation. Inside the nucleus, Nrf2 binds to antioxidant response elements (ARE), inducing transcription of detoxifying and antioxidant enzymes such as HO-1, SOD, and GPx. This mechanism provides cellular protection against oxidative DNA damage and lipid peroxidation. Phenolic compounds in MO possess hydroxyl groups capable of donating hydrogen atoms or electrons to neutralize free radicals. *In vitro* studies have demonstrated strong scavenging activity against DPPH, superoxide, and hydroxyl radicals, confirming direct antioxidant action [3].

Flavonoids and rosmarinic acid can chelate redox-active transition metals such as Fe^{2+} and Cu^{2+}, thereby preventing Fenton reaction-mediated ROS generation. Additionally, extracts of MO inhibit lipid peroxidation in cellular membranes, protecting structural integrity under oxidative stress conditions [1]. Animal studies demonstrated that administration of MO extracts significantly reduced malondialdehyde (MDA) levels and restored glutathione content in oxidative stress models [9]. Clinical investigations further showed increased antioxidant enzyme activities and reduced oxidative biomarkers in volunteers consuming standardized MO preparations [5]. Collectively, these findings indicate that MO exerts its antioxidant actions through a dual mechanism: induction of endogenous antioxidant defenses via Nrf2–ARE signaling and direct scavenging/chelating activities, making it a promising candidate for prevention and management of oxidative stress–related disorders (Figure 2).

Anti-Inflammatory Effects

Chronic inflammation is a key pathological mechanism in many chronic diseases, including cancer, diabetes, cardiovascular and neurodegenerative disorders.

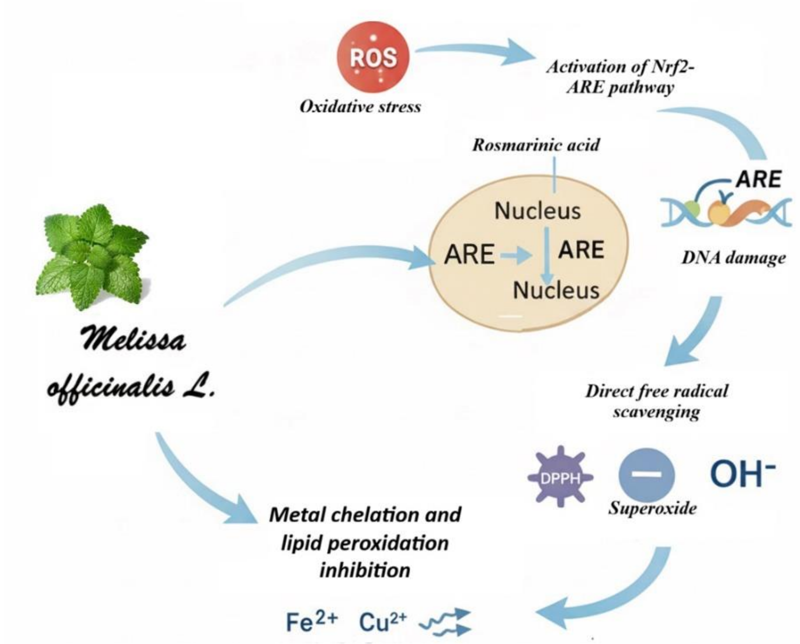


Figure 2. Antioxidant mechanisms of MO, including Nrf2–ARE pathway activation, free radical scavenging, metal chelation, and inhibition of lipid peroxidation

MO has been widely studied for its anti-inflammatory activity, largely attributed to rosmarinic acid, caffeic acid derivatives, flavonoids (luteolin, apigenin, and quercetin), and essential oils (citral, citronellal and geraniol). Experimental studies show that MO extracts suppress the nuclear factor kappa B (NF-κB) pathway, which controls transcription of pro-inflammatory mediators such as TNF-α, IL-1β, IL-6, COX-2, and iNOS [10,11]. Rosmarinic acid prevents IκBα degradation and NF-κB nuclear translocation, thereby attenuating inflammatory gene expression. Flavonoids also reduce phosphorylation of p38, JNK, and ERK1/2 MAPKs, which are upstream regulators of inflammatory cytokine release [1]. *In vitro* and *in vivo* studies revealed that MO reduces the secretion of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) and enhances anti-inflammatory cytokine IL-10, thereby restoring immune homeostasis [5]. Emerging data indicate that MO phenolic compounds can indirectly suppress NLRP3 inflammasome activation by reducing ROS and inhibiting purinergic P2X7 receptor signaling, leading to decreased IL-1β release [6,7]. Essential oils from MO also contribute to anti-inflammatory activity. Citral and citronellal inhibit cyclooxygenase and lipoxygenase pathways, reducing prostaglandin and leukotriene synthesis. Topical preparations of MO have shown significant reductions in erythema and edema in inflammatory skin models [3]. Animal models of colitis, arthritis, and neuroinflammation demonstrated significant reductions in inflammatory biomarkers following MO treatment [1]. Clinically, supplementation with standardized extracts improved symptoms of anxiety and insomnia, in part due to suppression of neuroinflammatory processes [5]. Taken together, these findings indicate that MO exerts multi-target anti-inflammatory effects through NF-κB/MAPK suppression, cytokine modulation, and purinergic receptor-linked inflammasome inhibition, supporting its therapeutic potential in chronic inflammation–related diseases (Figure 3).

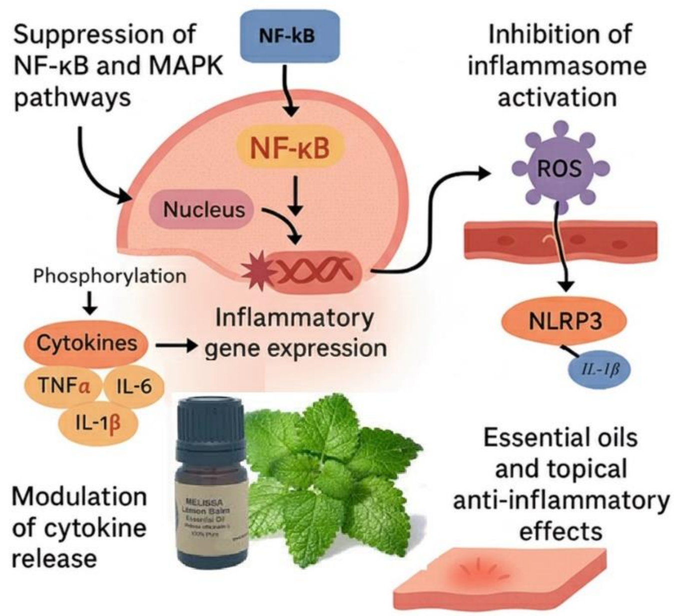


Figure 3. Anti-inflammatory effects of MO, showing NF-κB/MAPK suppression, cytokine modulation, inhibition of inflammasome activation, and COX/LOX blockade by essential oils

Anticancer Activities

A growing body of evidence indicates that MO exerts multimodal anticancer actions mediated by phenolic acids (notably rosmarinic acid), flavonoids, triterpenes such as ursolic acid, and essential-oil constituents like citral. Mechanistic themes include apoptosis induction, cell-cycle arrest, suppression of pro-survival signaling (NF-κB, PI3K/Akt, and MAPK/ERK), anti-angiogenesis, and anti-invasion [12-14]. MO leaf extracts inhibit proliferation and trigger apoptosis in human colon carcinoma cells via ROS-dependent mechanisms, confirming phenolics as major contributors [13]. Essential oil exhibits broad cytotoxicity against multiple cancer cell lines, including A549, MCF-7, and HL-60, alongside strong antioxidant capacity [14]. Comparative studies indicate both extracts and isolated rosmarinic acid display anticancer activity, though extracts often exert stronger effects due to synergism [12]. Rosmarinic acid suppresses hepatoma cell growth by downmodulating NF-κB and PI3K/Akt signaling, increasing pro-apoptotic markers, and reducing p-Akt and NF-κB p65 expression [15]. It also induces caspase activation and mitochondrial apoptosis in HepG2 and gastric cancer models [16]. Recent reviews emphasize RA's anti-proliferative, anti-metastatic, and pro-apoptotic profiles, while highlighting limitations in bioavailability and delivery [17].

Citral promotes apoptosis and growth suppression across stomach, breast, colorectal, and prostate cancers by modulating key survival pathways [18]. Importantly, MO essential oil and citral induce apoptosis even in multidrug-resistant cells, suggesting a role as chemosensitizers [19]. Ursolic acid, identified in MO, reduces MMP-9 expression and cell invasiveness [20]. Evidence shows UA induces G0/G1 arrest, promotes apoptosis, and inhibits angiogenesis, migration, invasion, and tumorsphere formation in lung and breast cancers. Transcriptomic studies implicate VEGF, JAK/STAT, PD-L1, and MMP pathways as major UA targets [21]. Since NF-κB plays a central role in oncogenesis and resistance to therapy, MO-derived actives that inhibit NF-κB/PI3K/Akt/MAPK signaling provide mechanistic plausibility for their antiproliferative and pro-apoptotic effects [22]. Preclinical evidence supports MO's anticancer potential through apoptosis induction, cell-cycle arrest, anti-angiogenesis, and anti-invasion, driven by rosmarinic acid, ursolic acid, and citral. Translation requires standardized extract fingerprints, enhanced RA delivery, and biomarker-guided *in vivo* studies and clinical trials (Figure 4) [12].

Antidiabetic Effects

Diabetes mellitus is characterized by hyperglycemia, oxidative stress, and chronic inflammation, leading to complications in the cardiovascular, renal, and nervous systems. Several studies indicate that MO and its major constituents, especially rosmarinic acid and flavonoids, exert significant antidiabetic effects through multiple mechanisms. Extracts of MO improve glucose tolerance and reduce blood glucose levels in experimental models of diabetes. In streptozotocin-induced diabetic rats, administration of MO extract significantly decreased fasting blood glucose and HbA1c, while enhancing insulin sensitivity [23]. These effects are partly mediated through the activation of AMPK, which improves glucose uptake in peripheral tissues [1]. Phenolic compounds in MO inhibit α-amylase and α-glucosidase, delaying carbohydrate digestion and glucose absorption, thereby reducing postprandial hyperglycemia [24]. This mechanism is comparable to standard antidiabetic drugs such as acarbose, but with fewer gastrointestinal side effects. Since oxidative stress contributes to pancreatic β-cell dysfunction, the strong antioxidant activity of rosmarinic acid and flavonoids in MO protects pancreatic tissue from ROS-induced damage [8].

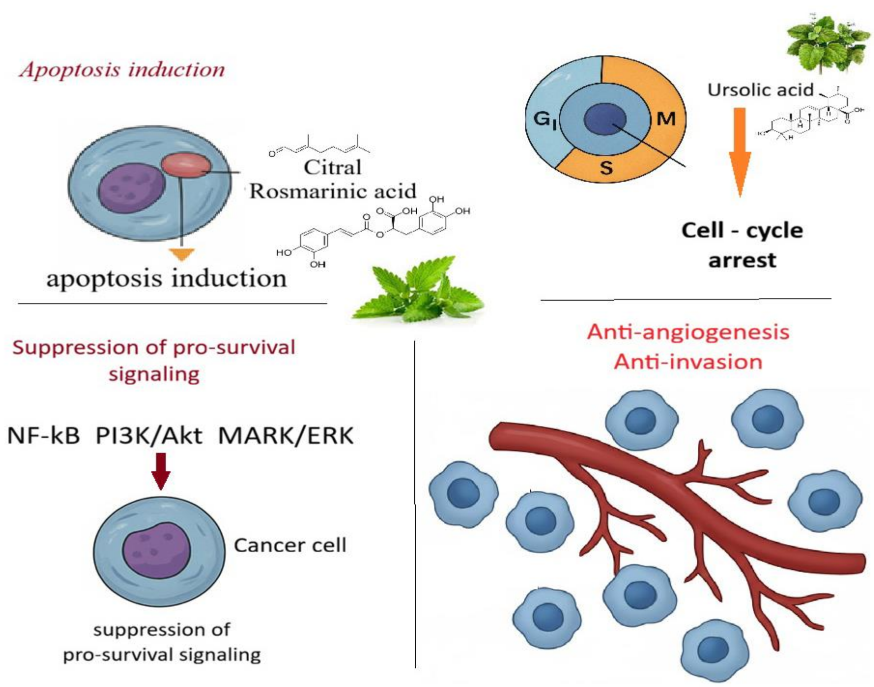


Figure 4. Anticancer activities of MO, including apoptosis induction, cell-cycle arrest, suppression of NF-κB/PI3K/Akt/MAPK signaling, anti-angiogenesis, and anti-invasion mediated by rosmarinic acid, citral, and ursolic acid

Furthermore, suppression of NF-κB–mediated cytokine production (TNF-α, IL-6, and IL-1β) reduces insulin resistance, linking the anti-inflammatory effects of MO with improved glucose homeostasis [25]. MO extracts have also been shown to improve dyslipidemia in diabetic animal models, with reductions in total cholesterol, triglycerides, and LDL-C, along with elevation of HDL-C [23]. Such effects suggest potential benefits in metabolic syndrome, where diabetes coexists with obesity and dyslipidemia. Although clinical data are limited, preliminary studies suggest that supplementation with standardized MO preparations may lower blood glucose and improve insulin sensitivity in prediabetic and type 2 diabetic patients. However, larger randomized clinical trials are necessary to validate these findings [1,25]. Evidence indicates that MO exerts antidiabetic effects via improvement of glucose metabolism, inhibition of carbohydrate-digesting enzymes, antioxidant/anti-inflammatory protection of β-cells, and improvement of lipid profiles. These mechanisms highlight MO as a promising adjunctive therapy for diabetes and metabolic syndrome (Figure 5).

Neuroprotective and Anxiolytic Activities

Neurological disorders such as Alzheimer's disease, Parkinson's disease, anxiety, and depression are strongly associated with oxidative stress, neuroinflammation, and neurotransmitter imbalance. MO has long been used in traditional medicine as a calming and cognitive-enhancing agent, and modern evidence confirms its neuroprotective and anxiolytic effects. Clinical studies have demonstrated that standardized MO extracts improve memory performance and attention in healthy volunteers, as well as in patients with mild to moderate Alzheimer's disease [5,26].

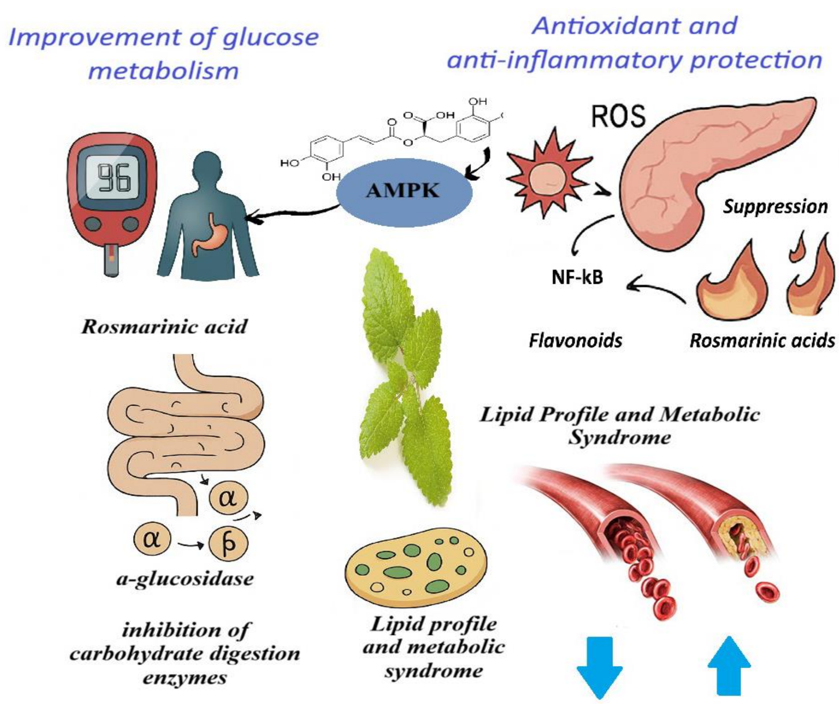


Figure 5. Antidiabetic effects of MO, showing AMPK-mediated glucose metabolism improvement, inhibition of carbohydrate-digesting enzymes, antioxidant and anti-inflammatory protection of β-cells, and regulation of lipid profile

The cognitive benefits are attributed to the inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), resulting in enhanced cholinergic neurotransmission [5]. Randomized controlled trials indicate that MO extracts reduce anxiety, agitation, and insomnia symptoms, partly mediated through GABAergic and adenosinergic mechanisms [5,27]. Essential oil constituents such as citral and linalool are also linked to anxiolysis through modulation of GABA-A receptors [3].

MO's phenolic compounds, especially rosmarinic acid, protect neurons against ROS-mediated injury, improve mitochondrial function, and suppress neuroinflammatory pathways, including NF-κB and MAPK. Animal studies show reduced lipid peroxidation and increased antioxidant enzyme activity in the brain following MO administration [1]. Emerging findings suggest that rosmarinic acid and related compounds modulate purinergic receptor activity, specifically inhibiting P2X7 receptor–mediated inflammasome activation and activating A2A adenosine receptors. This dual effect contributes to anti-inflammatory neuroprotection and anxiolysis [6,7]. Evidence from preclinical and clinical studies indicates that MO exerts neuroprotective and anxiolytic effects through cholinesterase inhibition, modulation of GABAergic and adenosinergic signaling, antioxidant and anti-inflammatory actions, and regulation of purinergic receptors. These mechanisms justify its potential use in treating anxiety, insomnia, and neurodegenerative disorders (Figure 6).

Regulation of Purinergic Signaling

Purinergic signaling, mediated by extracellular nucleotides (ATP and ADP) and nucleosides (adenosine), regulates immune responses, inflammation, and neurodegeneration. Dysregulation of purinergic receptors such as P2X7 and A2A contributes to chronic inflammation, autoimmunity, and neurological disorders [6,7]. Recent findings indicate that MO and its bioactive compounds modulate these pathways, thereby supporting their therapeutic potential.

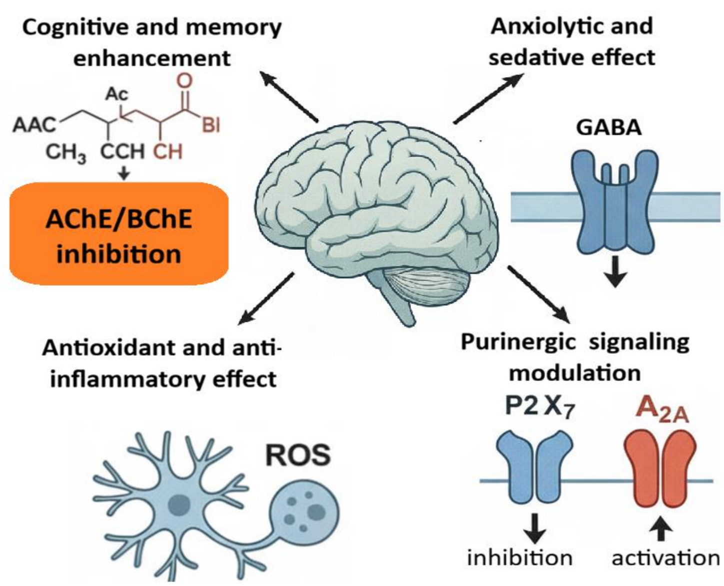


Figure 6. Neuroprotective and anxiolytic activities of MO, including cholinesterase inhibition, modulation of GABAergic and adenosinergic signaling, antioxidant and anti-inflammatory neuroprotection, and regulation of purinergic receptors

The P2X7 receptor is strongly implicated in inflammasome activation and IL-1β release. Rosmarinic acid, the dominant phenolic compound of MO, has been shown to reduce oxidative stress and neuroinflammation, partly by inhibiting ATP-induced P2X7 signaling. Through this mechanism, MO extracts suppress NLRP3 inflammasome activation, thereby limiting chronic neuroinflammation and tissue damage [1]. A2A receptors play dual roles in immunoregulation: activation of A2A promotes anti-inflammatory signaling and supports M2 macrophage polarization, while also exerting anxiolytic and neuroprotective effects [6]. MO extracts and essential oils, particularly rosmarinic acid and citral, enhance adenosinergic signaling, which contributes to their calming and immunomodulatory properties [5,27]. Since oxidative stress is a major upstream activator of purinergic receptor signaling, the strong antioxidant properties of MO indirectly regulate purinergic balance. By activating Nrf2–ARE and suppressing NF-κB, MO reduces extracellular ATP release and cytokine amplification, breaking the cycle of ROS–P2X7–inflammasome activation [1]. Evidence suggests that MO regulates purinergic signaling primarily through P2X7 inhibition and A2A receptor activation, linking its antioxidant, anti-inflammatory, and neuroprotective effects. These mechanisms may underlie its therapeutic potential in neurodegenerative disorders, anxiety, and immune-mediated conditions (Figure 7).

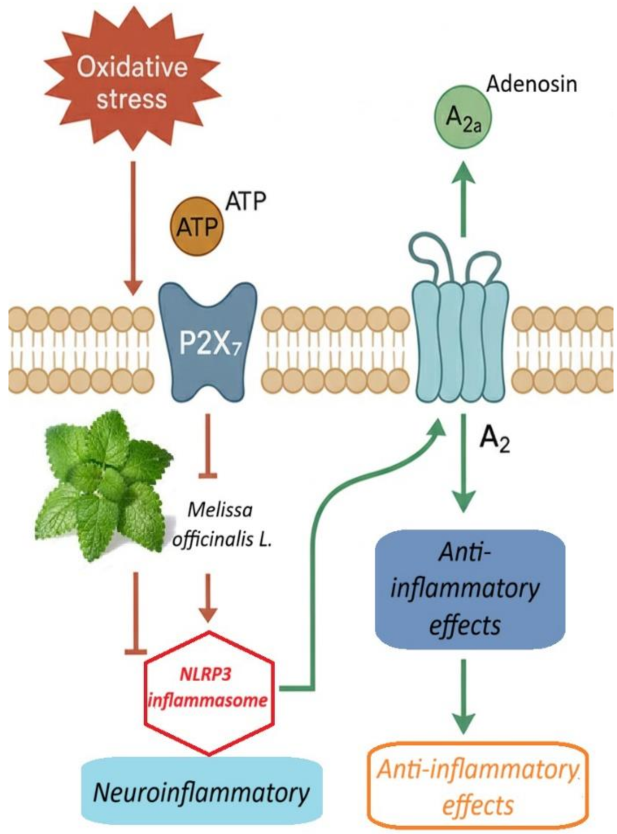


Figure 7. Regulation of purinergic signaling by MO, showing inhibition of P2X7 receptor–mediated inflammasome activation and activation of A2A adenosine receptors, leading to reduced neuroinflammation and enhanced anti-inflammatory effects

Challenges and Future Directions

Despite promising preclinical and clinical findings, several challenges remain before MO and its bioactive compounds can be integrated into evidence-based therapeutic strategies (Figure 8).

Extract Standardization. One of the main limitations is the variability in phytochemical composition depending on plant cultivar, geographical origin, harvest time, and extraction method [1]. Rosmarinic acid content, essential oil profile, and flavonoid levels fluctuate significantly, leading to inconsistent pharmacological outcomes across studies [8]. Standardized extracts with defined phytochemical fingerprints are urgently needed for reproducibility and clinical validation. Bioavailability and Pharmacokinetics.

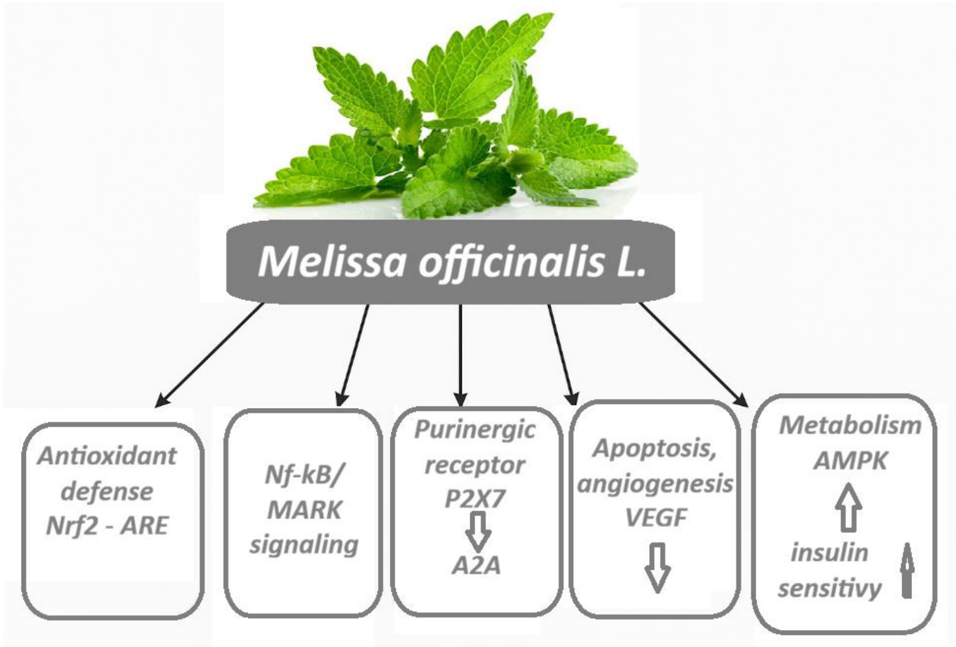


Figure 8. Graphical abstract of MO pharmacological actions. Bioactive compounds enhance antioxidant defenses (Nrf2–ARE), suppress inflammation (NF-κB/MAPK), modulate purinergic signaling (P2X7↓, A2A↑), induce apoptosis and inhibit angiogenesis (VEGF↓), and improve metabolism (AMPK↑, insulin sensitivity↑)

Although rosmarinic acid is considered the primary active compound, it suffers from low oral bioavailability due to poor absorption, rapid metabolism, and systemic. Novel drug delivery systems such as nanoparticles, liposomes, and phytosomes are being investigated to enhance stability and bioavailability, but their clinical relevance has not yet been established. Mechanistic Insights. While antioxidant, anti-inflammatory, and purinergic pathways have been implicated, many molecular targets remain underexplored. For example, detailed interactions of MO bioactives with purinergic receptors (P2X7, A2A), MAPK sub-pathways, and epigenetic regulators warrant deeper mechanistic studies [6]. Clinical Evidence Gaps. Although small randomized controlled trials have suggested benefits in anxiety, insomnia, and cognitive impairment [26,27], robust phase II–III clinical trials with larger sample sizes and biomarker endpoints are lacking. Long-term safety data are also scarce, especially for high-dose or chronic use. Integrative and Translational Research. Future research should aim to develop standardized phytopharmaceutical preparations with consistent bioactive profiles; conduct clinical studies in diabetes, cancer, and neurodegenerative diseases using biomarker-driven outcomes; explore synergistic effects of MO with conventional drugs, particularly in inflammation, oncology, and psychiatry; and apply systems pharmacology and network analysis to unravel multi-target actions and predict herb–drug interactions. While MO demonstrates broad pharmacological potential through antioxidant, anti-inflammatory, neuroprotective, and purinergic mechanisms, clinical translation requires overcoming challenges related to extract standardization, bioavailability, and limited high-quality trials. Addressing these gaps will determine whether MO progresses from traditional medicine to modern therapeutic applications.

Conclusion

MO is a medicinal plant with a rich phytochemical composition, dominated by rosmarinic acid, flavonoids, and essential oils. Evidence from *in vitro*, *in vivo*, and preliminary clinical studies demonstrates its multi-target pharmacological potential across antioxidant, anti-inflammatory, anticancer, antidiabetic, neuroprotective, and anxiolytic domains. Mechanistic investigations highlight modulation of Nrf2–ARE, NF-κB/MAPK, and purinergic receptors (P2X7 inhibition and A2A activation) as central pathways through which MO exerts protective and therapeutic effects. These molecular actions explain its benefits in oxidative stress–related diseases, chronic inflammation, metabolic disorders, cancer, and neuropsychiatric conditions. However, translation into modern therapy faces several challenges, including variability in extract composition, poor oral bioavailability of rosmarinic acid, and the lack of large, biomarker-guided randomized clinical trials. Addressing these issues through extract standardization, advanced delivery systems, and robust clinical research will be crucial to establishing its efficacy and safety in clinical practice. In conclusion, MO represents a promising candidate for integrative medicine, bridging traditional use with modern molecular pharmacology. Future efforts must focus on standardized preparations, mechanistic biomarker validation, and well-designed clinical trials to fully unlock its therapeutic potential.

Abbreviations

MO – *Melissa officinalis*
RA – Rosmarinic acid
Nrf2 –Nuclear factor erythroid 2–related factor 2
ARE – Antioxidant response elements
HO-1 – Heme oxygenase-1
SOD – Superoxide dismutase
GPx – Glutathione peroxidase
NF-κB–Nuclear factor kappa-light-chain-enhancer of activated B cells
MAPK – Mitogen-activated protein kinase
AMPK – AMP-activated protein kinase
TNF-α – Tumor necrosis factor alpha
IL-6, IL-1β, IL-10 – Interleukin-6, Interleukin-1 beta, Interleukin-10
COX-2 – Cyclooxygenase-2
iNOS – Inducible nitric oxide synthase
P2X7 – P2X7 purinergic receptor
A2A – Adenosine A2A receptor
MDA – Malondialdehyde
ROS – Reactive oxygen species
AChE – Acetylcholinesterase
BChE – Butyrylcholinesterase
MMP-9 – Matrix metalloproteinase-9
PD-L1 – Programmed death-ligand 1
VEGF – Vascular endothelial growth factor
JAK/STAT – Janus kinase/signal transducer and activator of transcription

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Competing Interests

The authors declared no competing interests.

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Ethics Approval

Not applicable. This is a review article and did not involve human participants, identifiable human data, or animal experiments.

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Data Availability

No datasets were generated or analyzed for this review; therefore, data sharing was not applicable. All information discussed was drawn from published sources cited in the References.

Authors' Contributions

Zafar Abdujalilovich Mamajonov – Conceptualization, methodology design, literature search, and manuscript drafting. Irodakhon Yusupovna Mamatova – Data collection, analysis of phytochemical and pharmacological evidence, visualization, and writing—review and editing. Gulrukh Juraevna Ulugbekova– Validation, visualization (figures and graphical abstract), reference management, and formatting according to journal style. Ibragim Rakhmonovich Askarov – Supervision, critical revision of the manuscript, and final approval of the version to be published. All authors have read and agreed to the published version of the manuscript.

Use of AI Tools

During manuscript preparation, the authors used a large language model tool for language polishing and formatting assistance. After using this tool, the authors reviewed and edited the content and take full responsibility for the integrity and accuracy of the text.

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