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Exploring the Chemical Composition, Therapeutic Properties, and Innovative Delivery Methods of Melissa officinalis

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Abstract

Melissa officinalis L., colloquially termed lemon balm, stands as a preeminent medicinal herb lauded for its intricate phytochemical matrix and diverse therapeutic applications. This comprehensive review synthesizes contemporary research on its chemical constituents, pharmacological efficacy, and advancements in nanotechnology-driven delivery platforms. The plant's bioactive arsenal—encompassing flavonoids, terpenoids, phenolic acids, and volatile oils—exerts antioxidant, antimicrobial, anti-inflammatory, and neuroprotective effects. Innovations in drug delivery, such as nanoemulsions, lipid nanoparticles, and polymeric films, aim to enhance bioavailability and therapeutic precision. By integrating multidisciplinary insights, this article underscores the imperative for continued exploration of Melissa officinalis in modern pharmacotherapy.

Introduction

The utilization of botanical resources for therapeutic purposes has been a cornerstone of human healthcare since antiquity, with evidence of herbal medicine practices documented across ancient civilizations such as Mesopotamia, Egypt, and China (Heinrich et al., 2021). These traditions evolved into sophisticated systems, including Ayurveda and Traditional Chinese Medicine, which continue to influence modern phytotherapy (Yuan et al., 2016). The 19th century heralded a transformative era with the isolation of bioactive alkaloids like morphine from Papaver somniferum and quinine from Cinchona bark, marking the dawn of pharmacognosy (Sneader, 2005). Subsequent advancements in synthetic chemistry during the 20th century led to the proliferation of industrially produced

pharmaceuticals, yet natural compounds remain indispensable, particularly in low- and middle-income nations where access to synthetic drugs is limited (Newman & Cragg, 2020). According to the World Health Organization (WHO, 2023), approximately 80% of populations in developing regions depend on plant-based remedies for primary healthcare, underscoring their enduring relevance.

Medicinal flora are revered not only for their therapeutic efficacy but also for their role as reservoirs of bioactive molecules, which serve as precursors for semi-synthetic drug development (Veeresham, 2012). For instance, the antimalarial drug artemisinin, derived from Artemisia annua, exemplifies the synergy between traditional knowledge and modern pharmacology (Tu, 2011). Bioactive constituents, including alkaloids, terpenoids, and polyphenols, are heterogeneously distributed across plant organs—seeds, roots, leaves, and flowers—each contributing unique pharmacological activities (Pan et al., 2014). These compounds often exhibit pleiotropic effects, modulating multiple biological pathways to confer health benefits (Hussain et al., 2012).

Melissa officinalis L. (Lamiaceae), commonly termed lemon balm, epitomizes the intersection of traditional herbalism and contemporary scientific inquiry. Indigenous to the Mediterranean Basin and Western Asia, this perennial herb has been cultivated across Europe for centuries, prized for its nervine, digestive, and antiviral properties (Moradkhani et al., 2010). Morphologically, M. officinalis is characterized by a robust, erect habit (60–100 cm height), with cordate, serrated leaves (2–8 cm length) adorned with glandular trichomes that secrete volatile oils (Miraj & Kiani, 2016). Its rhizomatous root system enhances drought resilience, enabling adaptation to diverse agroclimatic conditions (Zhishen et al., 2019). Despite its horticultural vigor—often leading to invasive growth in gardens—the plant's leaves remain a focal point for phytochemical extraction due to their high concentration of bioactive metabolites (Kennedy & Wightman, 2011).

This review delineates the phytochemical complexity of M. officinalis, emphasizing its volatile oils, triterpenes, and polyphenolic fractions, which underpin its broad-spectrum pharmacological activities. Contemporary research has increasingly focused on nanotechnology-driven delivery systems, such as nanoemulsions and lipid-based carriers, to overcome limitations associated with traditional formulations, including poor bioavailability and chemical instability (Jafari et al., 2017). By synthesizing recent advancements, this work aims to elucidate the potential of M. officinalis in modern therapeutics, particularly through optimized drug delivery platforms.

Phytochemical Composition

The pharmacological efficacy of Melissa officinalis is inextricably linked to its intricate phytochemical matrix, which has been extensively characterized using chromatographic and spectroscopic techniques (Dastmalchi et al., 2008).

Volatile Constituents

Steam distillation of aerial parts yields an essential oil (0.1–0.3% w/w) dominated by oxygenated monoterpenes, notably citral—a

racemic blend of geranial (trans-citral) and neral (cis-citral)—which constitutes 50–70% of the oil (Kowalski et al., 2015). Minor constituents include citronellal (3–8%), geraniol (2–5%), and sesquiterpenes such as β-caryophyllene (Nurzynska-Wierdak et al., 2013). Regional variations significantly influence oil composition; for example, Jordanian M. officinalis essential oil exhibits elevated β-caryophyllene levels (12.4%) compared to Polish cultivars (Barakat et al., 2019). Seasonal dynamics also modulate yield, with maximal citral concentrations observed during flowering stages (Ghasemi Pirbalouti et al., 2014).

Triterpenes and Saponins

Non-volatile fractions of M. officinalis are enriched with pentacyclic triterpenes, including ursolic acid and oleanolic acid, which demonstrate anti-inflammatory and pro-apoptotic activities (Mencherini et al., 2007). Sulfated derivatives, such as ursene glycosides isolated from stem extracts, exhibit unique bioactivity, though their pharmacokinetic profiles remain under investigation (Mencherini et al., 2012). Triterpenoid saponins, though less studied, contribute to the plant's adaptogenic properties, potentially enhancing stress resilience (Ghosh et al., 2010).

Polyphenolic Profile

Phenolic acids and flavonoids constitute the cornerstone of M. officinalis's antioxidant capacity. Rosmarinic acid, a caffeic acid ester, dominates the phenolic profile (86,637 µg/g in methanolic extracts), followed by chlorogenic and caffeic acids (Ghiulai et al., 2020). Flavonoids such as luteolin, quercetin, and apigenin glycosides further augment radical-scavenging activity (Zheng & Wang, 2001). Ultrasonication-assisted extraction with polar solvents (e.g., 80% ethanol) enhances phenolic recovery by disrupting cell walls, achieving yields 30% higher than conventional maceration (Azwanida, 2015).

Volatile Compounds: Extraction and Variability

The pharmacodynamic potency of M. officinalis essential oil is contingent upon extraction methodology and plant provenance. Hydrodistillation, while traditional, often degrades thermolabile compounds; conversely, supercritical CO_2 extraction preserves delicate monoterpenes but requires costly infrastructure (Pourmortazavi & Hajimirsadeghi, 2007). GC-MS analyses of Polish cultivars identified geranial (45.2%) and neral (33.8%) as predominant monoterpenes, with trace amounts of linalool (<1%) contributing to olfactory complexity (Nurzynska-Wierdak et al., 2013). Comparative phytochemical studies underscore ecotypic divergence: Mediterranean accessions yield higher citral concentrations, whereas Central Asian variants are richer in sesquiterpene hydrocarbons (Barra et al., 2010).

Triterpenes and Polyphenols: Structural and Functional Insights

Triterpenes, classified into ursane, oleanane, and lupane groups, interact with cellular membranes and signaling pathways to exert anti-proliferative effects (Liby et al., 2007). Ursolic acid, for instance, inhibits NF-κB and COX-2 pathways, attenuating inflammation in murine colitis models (Jang

et al., 2014). Polyphenols, particularly rosmarinic acid, chelate transition metals and scavenge ROS, mitigating oxidative stress in neuronal cells (Petersen & Simmonds, 2003). Structure-activity relationships reveal that ortho-dihydroxy groups in phenolic acids enhance free radical neutralization, a property exploited in nutraceutical formulations (Rice-Evans et al., 1996).

Methodological Advancements in Phytochemical Analysis

Modern techniques such as UPLC-QTOF-MS and NMR metabolomics have revolutionized the characterization of M. officinalis's secondary metabolites (Farag et al., 2012). For instance, SPME-GC-MS has enabled non-destructive profiling of volatile emissions from live plants, revealing diurnal fluctuations in terpene synthesis (Rohloff et al., 2005). Such innovations not only refine extraction protocols but also facilitate the discovery of novel bioactive compounds with therapeutic potential.

Pharmacological Investigations and Therapeutic Applications

Extensive empirical research has established that botanical extracts and volatile oils derived from medicinal plants, including Melissa officinalis L., exhibit a broad spectrum of bioactivities with significant therapeutic implications (Sánchez-Camargo et al., 2019). The pharmacological prominence of M. officinalis is predominantly attributed to its polyphenolic constituents—notably phenolic acids (e.g., rosmarinic acid) and flavonoids (e.g., luteolin)—which mediate antioxidant, antiproliferative, and antimicrobial effects through multifaceted molecular mechanisms (Miraj & Kiani, 2016). Contemporary studies have prioritized leaf-derived extracts due to their enriched phenolic profiles, which correlate with diverse biological activities such as antiangiogenic, antiviral, and neuroprotective actions (Shakeri et al., 2017).

Antioxidant and Anticancer Properties

A seminal comparative analysis by Moaca et al. (2018) evaluated the bioactivity of stem and leaf ethanolic extracts, revealing that leaf extracts exhibited superior antioxidant capacity (32.76 mg gallic acid equivalents/g) compared to seed extracts (8.4 mg GAE/g). This disparity was attributed to the higher polyphenol density in foliar tissues. Furthermore, in vitro assays using MDA-MB-231 breast cancer cells demonstrated dose-dependent cytotoxicity, suggesting potential antitumor applications. Ghiulai et al. (2020) expanded these findings by investigating the chemopreventive efficacy of M. officinalis extracts in breast cancer models. Utilizing the chorioallantoic membrane (CAM) assay, they identified 96% ethanolic extracts as the most potent inhibitors of angiogenesis, a critical process in tumor metastasis. Additionally, ethanolic extracts exhibited marked antiproliferative effects against human colon adenocarcinoma (HCT-116) and gastric carcinoma (AGS) cell lines, underscoring their broad-spectrum

anticancer potential (Kowalczyk et al., 2020).

Antimicrobial and Antiviral Mechanisms

The essential oil of M. officinalis, rich in citral isomers, has demonstrated robust antimicrobial activity against pathogens such as Staphylococcus aureus and Escherichia coli (Usach et al., 2021). In a comparative study, phospholipid vesicles loaded with citral exhibited enhanced bactericidal efficacy compared to those containing Citrus limon essential oil, likely due to citral's ability to disrupt microbial cell membranes (Usach et al., 2021). Antiviral applications were explored by Vanti et al. (2021), who engineered glycerosomes—nanoscale vesicles composed of phosphatidylcholine and glycerol—to encapsulate M. officinalis essential oil. These glycerosomes inhibited herpes simplex virus type 1 (HSV-1) replication in vitro without inducing cytotoxicity, highlighting their potential for topical antiviral therapies. Complementary research by Rechia et al. (2022) developed starch-glycerol polymeric films infused with hydroalcoholic extracts, which improved drug retention and patient compliance in labial herpes treatment.

Neuroprotective and Anxiolytic Effects

In vivo studies have elucidated the neuropharmacological benefits of M. officinalis extracts. Rosmarinic acid, a dominant phenolic compound, modulates γ-aminobutyric acid (GABA) transmission, alleviating anxiety-like behaviors in rodent models (Awad et al., 2009). Clinical trials further corroborate these findings, with lemon balm supplementation improving cognitive function in Alzheimer's patients, likely via acetylcholine esterase inhibition and oxidative stress mitigation (Akhondzadeh et al., 2003).

Innovative Delivery Systems

Advances in nanotechnology have revolutionized the delivery of M. officinalis bioactives, addressing challenges such as poor solubility and rapid degradation. Sguizzato et al. (2021) pioneered the encapsulation of caffeic acid into solid lipid nanoparticles (SLNs) using poloxamer surfactants, achieving enhanced dermal penetration and oxidative stability. Comparative studies by Hallan et al. (2020) demonstrated that ethosomal vesicles outperformed SLNs in transdermal caffeic acid delivery, attributed to their flexibility and improved skin permeation. For oncological applications, Nordin et al. (2022) developed citral-loaded nanostructured lipid carriers (NLCs), which exhibited selective cytotoxicity against triple-negative breast cancer cells (MDA-MB-231) while sparing healthy tissues.

Dosage Translation and Safety Considerations

Translating efficacious animal doses to human equivalents (HED) remains a critical challenge in herbal drug development. The FDA's body surface area (BSA) normalization method is widely employed, where

$$HED = \text{Animal Dose} \times (\text{Animal Km} / \text{Human Km})$$

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, ensuring safety and minimizing toxicity risks (Reagan-Shaw et al., 2008).

Conclusion and Future Perspectives

Melissa officinalis stands as a pharmacognostic treasure, its phytochemical richness underpinning applications ranging from oncology to dermatology. Nanoengineered delivery systems—such as lipid nanoparticles, polymeric films, and glycerosomes—augment bioavailability and therapeutic precision, bridging traditional herbalism with modern medicine. Future research must prioritize clinical validation, dose optimization, and sustainable cultivation practices to fully harness this plant's potential. As nanotechnology evolves, M. officinalis may emerge as a cornerstone in personalized and targeted therapies, redefining its role in global healthcare paradigms.

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