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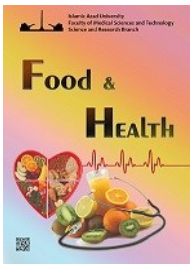

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The Multifunctional Potential of Nepeta crispa Willd. (Lamiaceae): A Comprehensive Review of its Phytochemistry, Bioactivities, and Transition to a Bioactive Material in Green Food Technology

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ABSTRACT

Nepeta crispa Willd., a native Iranian species of Lamiaceae, has been found to be a promising lead in the identification of natural bio-preservatives and functional food components. As a member of one of the abundant genera of the mint family, Nepeta species are traditionally used for their carminative, sedative, and anti-inflammatory properties, which are now increasingly being confirmed by modern pharmacological research. The medicinal efficacy of N. crispa is attributed primarily to its essential oil with high content of oxygenated monoterpenes 1,8-cineole and nepetalactone isomers, and phenolic compound-rich polar extracts, both of which are responsible for good antimicrobial and antioxidant activities. While 1,8-cineole gives antiseptic and anti-inflammatory effects, nepetalactones are responsible for good antimicrobial and repellent effects against insects, all of which together provide a good biochemical foundation for food preservation. While these advantages exist, immediate application of N. crispa essential oil is restricted by volatility, oxidative instability, and intense fragrance. Improvements in recent nanoencapsulation technologies, particularly with the pectin–WPC complexes, have introduced a promising method to address these limitations by improving stability, release regulation, and acceptability by senses. Application in fermented milk products such as doogh, N. crispa oil had greater antioxidant activity, antimicrobial inhibition, and consumer acceptability compared with the free form. Contributing complementary studies through N. crispa powder fortified yogurt further verify its application as a functional additive.
This review consolidates the phytochemical composition, bioactivities, and new technology applications of N. crispa, promoting its changing status from a traditional medicinal plant to a scientifically proven bioactive material for the clean-label systems of the food industry. Directions for the future point to standardization of extracts, determination of active ingredients, optimization for sensory properties, and industrial-scale validation to finally realize the potential of this precious indigenous species in green food technology.

1. Introduction

The flowering plant genus Nepeta L. (Lamiaceae), or catmint and catnip, is among the largest and most diverse of the mint family with approximately 250–300 species distributed throughout Europe, Asia, the Middle East, and Africa (1-3). Iran and Turkey have been recognized as major diversity hotspots of this genus, with nearly 79 species recorded in Iran itself, of which a few are endemic and being widely used in folk and traditional medicine. The species of Nepeta are aromatic perennial or annual herbs with characteristic glandular trichomes that release essential oils with high concentrations of bioactive constituents, a feature that is the basis of both their taxonomic importance and pharmacological utility (1-3).

2. Ethnobotanical and Traditional Uses

Nepeta species have traditionally been utilized for centuries in traditional medicine as anti-inflammatory, sedative,

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carminative, and antispasmodic substances (1, 2, 4). N. cataria L., for instance, has been traditionally utilized to cure colic, asthma, common cold, cough, diarrhea, and bronchial conditions and has also been utilized as a naturally occurring food and beverage flavoring agent (1-4). Other species belonging to the genus like N. glomerulosa, N. binaludensis, N. bracteata, N. pogonosperma, and N. pungens, are also well known in Iranian ethnomedicine for their aromatic and medicinal features (1,2). Of these, N. crispa Willd., "Mofarrah" locally known, has a special position as a sedative and carminative, traditionally applied to disorders of the respiratory and nervous systems (1). These ethnobotanical uses have close correlates with recent pharmacological data for diverse biological activities across the genus including antimicrobial, antioxidant, anti-inflammatory, and anticancer activity (2, 3, 5).

3. Phytochemistry and Chemotaxonomy

Phytochemical investigations have revealed that Nepeta essential oils are primarily composed of nepetalactones, unsaturated iridoid lactones that are the cause for the characteristic smell and the majority of the biological activities of the genus (2,5). Chemically, Nepeta species are generally two major chemotypes: high nepetalactones and isomers, and high in other terpenoid constituents such as 1,8-cineole, β-caryophyllene, caryophyllene oxide, β-farnesene, and α-citral (2,3). Along with terpenoids, the other groups of compounds, flavonoids, diterpenes, triterpenes, and phenolic acids, are varied and collectively account for the pharmacological and ecological variability of the genus (3,6).

4. Morphology

Morphologically, Nepeta species are characterized by a high number of trichomes, which are uni- or multicellular epidermal outgrowths that have fundamental structural and physiological functions (1). Non-glandular trichomes primarily serve the purpose of physical defense, protecting leaves against herbivory, UV radiation, and water loss, while glandular trichomes are highly specialized secretory organs with functions in essential oil biosynthesis and accumulation. Indeed, variations in trichome type, density, and distribution directly affect the yield and chemical composition of essential oils, therefore relating micromorphological features to phytochemical profile (1,3). These morphological parameters then provide both adaptive and taxonomic indicators for the genus.

5. Biological Activities and Pharmacological Potential

Recent pharmacological works have validated many of the traditional claims about Nepeta species, and a wide range of biological activities has been highlighted for the species. Essential oils and different solvent extracts have shown to possess antibacterial, antifungal, antioxidant, analgesic, antidepressant, insecticidal, and anti-inflammatory activities (2-4). For example, N. binaludensis and N. satureioides have demonstrated notable melanogenesis-inhibitory and antioxidant effects, highlighting potential applications in cosmetic formulations. Moreover, extracts of N. binaludensis demonstrated dose- and time-dependent cytotoxicity against human breast cancer cell lines (MCF-7 and MDA-MB-231), which could be attributed to the existence of iridoids, triterpenes, and sterols such as ursolic acid and nepetolide. The application of N. betonicifolia in Turkish folk medicine as a traditional cure for cancer also unifies the therapeutic promise of the genus. The traditional use of N. betonicifolia in Turkish folk medicine for cancer treatment further supports the therapeutic promise of the genus (3).

6. Focus on Nepeta crispa Willd

Besides its ethnomedicinal background, N. crispa Willd., an endemic Iranian representative of Lamiaceae, has gained increasing scientific attention due to its peculiar phytochemical profile and outstanding bioactivities (7,8). It usually steamdistilled essential oil, yielded at about 1.02 % (w/w), comprises 23 identified compounds accounting for almost 99.8 % of the total oil composition (8). Its oil is particularly rich in oxygenated monoterpenes, dominated by 1,8-cineole (eucalyptol, 47.9–71 %) and 4aα, 7α, 7aβ-nepetalactone (up to 20.3 %), thus mirroring the chemotypes reported for N. ispahanica and N. binaludensis (8,9). These prevailing compounds exert a wide spectrum of biological activity; the former compound, 1,8-cineole, is a well-known antiseptic and anti-inflammatory agent, while nepetalactones show potent antimicrobial and insect-repellent activities (8). Polar methanolic extracts of the plant exhibit high phenolic and flavonoid contents, hence showing strong antioxidant capacity. Whereas antimicrobial activity is more related to the essential-oil fraction, antioxidant potential is largely attributed to these phenolic-rich polar fractions (10).

7. Food Applications and Nanoencapsulation Advances

Besides medicinal applications, Nepeta species also possess excellent potential for innovation in the food industry. Increasing consumer pressure for clean-label products and mounting safety concerns regarding synthetic preservatives and antioxidants have triggered a paradigm shift towards natural alternatives (11). In this context, medicinal and aromatic plants endemic to specific regions have been found to be treasure troves of bioactive molecules. Among them, Nepeta crispa Willd., an Iranian endemic plant from the family Lamiaceae, is notable due to its profound ethnopharmacological background and its remarkable biological activities (7,8). On the other hand, the volatility, oxidative instability, and strong aroma of essential oils make their practical incorporation into food systems difficult. Recent innovations have overcome such limitations with the use of nanoencapsulation technology. Nanoencapsulation of N. crispa essential oil within a complex coacervate matrix made of pectin and whey-protein concentrate (WPC) produced semi-spherical nanoparticles, with a mean diameter of ~400 nm, while a pectin-to-WPC ratio of 75:25 gave the highest

encapsulation efficiency. Fourier-transform infrared spectroscopy showed that oil entrapment was successfully achieved through hydroxyl-phenolic interactions, giving a cohesive polymeric network linked by hydrogen bonding. Practical application of this system in fermented dairy beverages such as doogh demonstrated notable technological benefits: nanoencapsulated oil enhanced antioxidant capacity, reduced IC_{50} values, and improved microbial safety, while moderating the strong aroma of the free oil.

Table1. Example of the most relevant studies conducted on N. crispa.

No	Type of Source	Research Focus	Author(s)	Year	Purpose / Use in the Study	Summary or Key Findings
1	Experimental Research	The benefits and effectiveness of the nanoencapsulated form of the essential oil *N. crispa* compared to its free (non-encapsulated) form.	A.Haseli, et al.	2023	Develop an effective natural preservative for the yogurt drink "doogh" by using nanoencapsulated *Nepeta crispa* (Mofarrah) essential oil	The study successfully nanoencapsulated *N. crispa* essential oil using a 75:25 pectin:whey protein blend. When added to doogh (yogurt drink) at 0.20 mg/mL, this nanoencapsulated oil significantly improved the product's sensory properties, enhanced its antioxidant activity, and effectively inhibited the growth of harmful bacteria like *E. coli* and *S. aureus* (8).
2	Research Article	To perform a quality control analysis of *Nepeta crispa* from Hamadan province, Iran	M.Bahramloo, et al.	2023	A comprehensive evaluation including the chemical composition of its essential oil and commercial distillates, its antioxidant properties, total phenolic and flavonoid content, and its micromorphological characteristics	The study confirmed that *N. crispa* has significant antioxidant potential, linked to its high phenolic and flavonoid content, with 1,8-cineole as the major component. It also highlighted a critical quality issue: commercial distillates are often adulterated due to the plant's rarity. The methanol extract showed stronger antioxidant activity than the essential oil (9).
3	Research Article	To investigate the antioxidant potential of *Nepeta crispa willd*	M. Motaghed et al.	2022	Comparing the antioxidant effectiveness of the plant's methanol extract versus its essential oil using multiple laboratory assays and testing its ability to prevent oxidation in sunflower oil.	The methanol extract demonstrated significantly stronger antioxidant activity than the essential oil in all tests and was effective at preventing oil oxidation. The study concludes that the methanol extract is a promising novel bio-resource of natural antioxidants for potential use in the food and pharmaceutical industries (13).
4	Experimental research	To investigate the antibacterial effects of the medicinal plant *Nepeta crispa* (Mofarrah) against Escherichia coli, specifically by determining the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of its extracts.	Sh. Emadi, et al.	2021	Extracting both alcoholic and aqueous extracts from *Nepeta crispa* and evaluating their antibacterial activity using the disk diffusion and well diffusion methods against *E. coli*.	The results demonstrated that the alcoholic extract exhibited superior efficacy in inhibiting the growth of *E. coli* compared to the aqueous extract, showing stronger potential as a natural antibacterial agent (10).
5	Experimental research	To examine the effects of adding different levels of dried Nepeta crispa on the physicochemical and sensory properties of yogurt.	R.Reyahi-Khoram, et al.	2018	Enrich yogurt with different concentrations of dry Nepeta crispa (Mofarrah) and to evaluate its impact on the product's key quality parameters and overall sensory characteristics to determine its feasibility and acceptability as a functional food ingredient.	The study concluded that enriching yogurt with dry Mofarrah (*Nepeta crispa*) was successful. The addition significantly altered the yogurt's physicochemical properties (acidity, moisture, pH, fat, and salt) and, most importantly, resulted in a product with acceptable sensory characteristics. This success is significant because it suggests that Mofarrah can be used to create a potentially important enriched food product, leveraging its known antioxidant and antimicrobial properties without compromising taste and consumer acceptance (11).
6	Experimental research	To study the antioxidant potential of two native Iranian plants, Senjed and Mofarrah.	Badrhadad, A. and Piri, Kh.	2014	Measuring total phenols, flavonoids, and DPPH free radical scavenging activity in their extracts.	The study concluded that the methanolic extracts of both Mofarrah and Senjed exhibited superior antioxidant properties. The methanolic extract of Mofarrah demonstrated the highest free radical scavenging activity (IC50: 0.137 mg/mL), closely followed by the Methanolic extract of Senjed (IC50: 0.142 mg/mL). A strong positive correlation was established between the high levels of total phenolic and flavonoid compounds in these extracts and their potent antioxidant activity. These findings suggest that these native plants, particularly their methanolic extracts, are promising natural reservoirs of antioxidants for potential applications in food and health industries (14).
7	Experimental research	Chemical composition and antimicrobial activity of the essential oil of *Nepeta crispa* Willd	A. Sonbolia,et al.	2004	Identify the major chemical constituents of the essential oil using GC and GC/MS and to evaluate its antibacterial and antifungal properties against selected microorganisms.	This study successfully identified and characterized the essential oil of *Nepeta crispa*, establishing its significant potential as a natural antimicrobial agent. The oil, obtained in a 1.02% yield, was primarily composed of 1,8-cineole (47.9%) and nepetalactone (20.3%). Bioassays confirmed its potent, broad-spectrum antibacterial and antifungal activity against a range of microorganisms. These results not only validate the traditional ethnopharmacological uses of the plant but also provide a strong scientific foundation for its future application. The research conclusively suggests that *N. crispa* essential oil is a promising natural alternative for use as a preservative in the food, pharmaceutical, and cosmetic industries (7).

At concentrations of 0.20 mg/mL, encapsulated oil achieved optimal sensory acceptability and functional performance, supporting its role as a viable natural preservative. Comparable effects have also been observed when N. crispa powder was directly fortified into yogurt, where it influenced acidity, pH, and sensory parameters by stimulating lactic-acid-bacteria activity (10). Together, these findings emphasize that N. crispa represents not only a pharmacologically potent medicinal plant but also a promising candidate for development of natural food stabilizers and functional additives (8,12). A summary of the most relevant studies evaluating the antimicrobial and antioxidant effects of N. crispa and its applications in food systems is presented in Table 1.

8. Discussion

The efficacy of any nanoencapsulation strategy is inherently dependent on the intrinsic bioactivity of the core material being encapsulated. In the case of Nepeta crispa Willd., an endemic Iranian species, its essential oil possesses a compelling chemical profile that justifies its selection for such advanced delivery systems. The oil is characterized by a high concentration of 1,8-cineol (47.9%) and 4aα,7α,7aβ-nepetalactone (20.3%), compounds renowned for their potent antimicrobial and antifungal properties (10). This chemical richness translates into significant broad-spectrum biological activity, particularly against Gram-positive bacteria like Staphylococcus aureus, likely due to the ability of its lipophilic monoterpenes to disrupt microbial cell membranes (10). Given this robust yet volatile bioactive profile, the application of a protective nanoencapsulation system becomes crucial for its practical application in complex food matrices like doogh. As demonstrated by (9), encapsulating N. crispa essential oil within a pectin-whey protein complex effectively addressed the challenges of stability and controlled release. The optimized 75:25 pectin-to-whey protein formulation created a dense polymeric network that successfully entrapped the sensitive phenolic compounds, as confirmed by FT-IR analysis, and minimized their premature degradation (9). This synergistic approach, leveraging the inherent antimicrobial power of the oil (10) and enhancing its stability through nanoencapsulation (9), proved highly effective. The result was a doogh formulation with significantly enhanced antioxidant capacity, strong inhibitory effects on pathogens such as E. coli and S. aureus, and, critically, maintained sensory acceptability (9). Together, these findings underscore a powerful paradigm: the combination of a botanically-derived bioactive agent with a tailored biopolymer-based delivery system can successfully bridge the gap between laboratory-proven efficacy and real-world application in functional food development. The application of Nepeta crispa is not limited to advanced delivery systems; its direct use as a functional food ingredient also shows significant potential. This aromatic plant, has been successfully incorporated directly into yogurt to develop a novel fermented dairy product (11). The fortification of yogurt with N. crispa powder significantly influenced the product's physicochemical properties, notably increasing acidity and lowering pH, which suggests a stimulatory effect on lactic acid bacteria, a beneficial outcome for a probiotic food matrix. Importantly, sensory evaluations revealed that samples containing 0.25% and 0.50% Mofarrah received higher acceptability scores, indicating that its distinctive herbal aroma and bioactive compounds can be successfully integrated without compromising palatability (11). This successful application in yogurt, alongside the advanced nanoencapsulation approach in doogh, solidifies the role of N. crispa as a multifunctional natural additive. It demonstrates that whether through advanced delivery systems or direct incorporation, this endemic herb holds significant potential for innovating functional dairy products with enhanced preservative, nutritional, and sensory qualities. The rationale for employing Nepeta crispa as a natural food preservative extends beyond its established antimicrobial activity to encompass its considerable antioxidant potential. In an era marked by growing safety concerns regarding synthetic additives, the search for effective natural alternatives has intensified (12). Nepeta crispa demonstrates notable free radical-scavenging capacity and reducing power, as evidenced by its performance in DPPH and FRAP assays. While the potency of its crude methanol extract may be lower than that of synthetic benchmarks, its proven efficacy in inhibiting lipid peroxidation underscores its promise for stabilizing lipid-rich food matrices (12). This inherent antioxidant capability, coupled with its antimicrobial properties, positions N. crispa as a multi-functional natural agent. The multifunctionality of Nepeta crispa lies organically within its distinct phytochemical profile, which has been comprehensively defined through detailed phytochemical profiling. As a native representative of Iran's richly diverse Nepeta flora, N. crispa possesses a complex chemical profile dominated by oxygenated monoterpenes, particularly 1,8-cineole and the various nepetalactone isomers, although their relative abundances are impressively variable from study to study due to environmental factors, geographic range, and extraction procedures (13). This chemical variability is particularly expressed when contrasting traditional hydro-distillation with modern methods like microwave-assisted extraction, which can significantly alter both the yield and bioactive composition of compounds. Surprisingly, such a chemical composition possesses a clear-cut structure-activity relationship directly related to its documented bioactivities. While the polar fractions of the plant, the principal being methanol extracts, exhibit significant antioxidant activity due to their phenolic acids and flavonoids, antimicrobial activity of the essential oil appears more concerned with its dominant monoterpene components (13). This relative bioactivity emphasizes the importance of selective extraction and formulation rules according to desired functional attributes for specific food system applications. Furthermore, quality control and authentication become paramount in the commercial application of this botanical ingredient. Market-sourced chromatographic analysis has revealed alarming inconsistencies in authenticity and adulteration procedures, highlighting the importance of uniformly standardized production processes and rigorous quality control to achieve

reproducible efficacy and safety in food, cosmetic, and pharmaceutical applications (13). The integration of advanced analytical technologies with traditional knowledge thus becomes imperative to formulate consistent standardization parameters for N. crispa based products. This integrative phytochemical understanding then makes a foundational groundwork for maximizing the applications strategies listed above - from nanoencapsulation techniques providing protection to the volatile antimicrobial components (9) to explicit fortification utilizing the plant's phenolic antioxidant profile (11) - towards ultimately enabling the complete potential of N. crispa as a useful bio-preservative and functional food ingredient. Medicinal herbs are increasingly recognized as important natural sources of bioactive compounds, i.e., antioxidant phytochemicals. Two such plants, Nepeta crispa and Elaeagnus angustifolia, which are traditionally employed in the Hamedan Province in Iran, have in this study been assessed for their radical-scavenging activity, content of total phenolic substances, and flavonoids. These are well-documented contributors to the plant extracts' antioxidant activity, protecting biomolecules from oxidative stress, and of potential worth in foods, pharmaceuticals, and cosmetics. Besides its preservative and antimicrobial activities, N. crispa is also demonstrated to exhibit excellent antioxidant activity. In accordance with the established phytochemical fingerprint of Nepeta crispa, comparative studies provide quantitative confirmation of its robust antioxidant activity. Methanolic extract of N. crispa has been revealed to exhibit excellent free radical-scavenging activity compared to other medicinal herbs like E. angustifolia (14), with an IC_{50} value of 0.137 mg/mL in the DPPH assay. This valuable activity is linearly related to its high content of phenolic and flavonoids, thus highlighting the importance of the selection of solvent in achieving maximum extraction of bioactive compounds. The recurrent observations of concentration dependent inhibition of radicals not only confirm the dose-dependent nature of N. crispa extracts but also warrant their use as good natural alternatives to synthetic antioxidants for food and pharmaceutical applications.

9. Conclusion

This review of Nepeta crispa emphasizes its excellent potential as a natural multifunctional agent for food preservation and the formulation of functional products. The plant's essential oil, which is dominated by the oxygenated monoterpenes 1,8-cineole and nepetalactone isomers, exhibits potent antimicrobial and antifungal properties, while its methanolic extract possesses great antioxidant activity due to its rich content of phenolic and flavonoid derivatives. These two bioactivities render N. crispa as a candidate for the replacement of synthetic additives in traditional and functional foods. Encapsulation of N. crispa essential oil into pectin–whey protein complexes is a promising method to enhance the stability, bioavailability, and controlled release of its volatile bioactive componds, making it easier for their effective application in complicated food matrices such as doogh. Meanwhile, direct incorporation of N. crispa powder in yogurt demonstrates the feasibility of developing naturally fortified fermented dairy products without sensory compromise. Together, these synergistic approaches present a compelling paradigm for N. crispa application across various food systems, from laboratory-scale efficacy to industrial feasibility. Future research is warranted to optimize the parameters for encapsulation to attain maximum bioactive retention, examine synergistic effects with probiotic cultures, and establish standardized quality control protocols for ensuring batch-to-batch consistency of N. crispa based products. By coupling phytochemical characterization with contemporary delivery technologies, it is possible to successfully upscale this Iranian endemic herb as a sustainable and safe bio-preservative to meet growing demands for clean-label and health-promoting food products.

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