Pharmacological and chemical features of *Nepeta* L. genus: Its importance as a therapeutic agent

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Medicinal plants have always had great value for the human population due to their valuable constituents and potential bioactivities. The objective of this review is to present an updated overview of an important medicinal plant genus *Nepeta* L., from the family Lamiaceae, revealing its traditional utilization, biological activity, phytoconstituents, and mechanisms of action. For this purpose, a literature survey was carried out by using SciFinder, ScienceDirect, Scopus, PubMed, and Web of Science followed by a revision of the bibliographies of the related articles. We have described and analyzed the role of plants in drug discovery and the importance of *Nepeta* species. Information on the utilization purposes of *Nepeta* species in folk medicine has been emphasized, and scientific studies on the biological effects and secondary metabolites are addressed. *Nepeta* species are characterized by terpenoid-type compounds and phenolic constituents, which exert several activities such as an antimicrobial, repellent against major pathogen vector mosquitoes, insecticide, larvicide against *Anopheles stephensi*, cytotoxic anticarcinogen, antioxidant, anticonvulsant, analgesic, anti-inflammatory agent, and antidepressant, revealing its importance in medicinal and agricultural fields. On the basis of numerous studies, the *Nepeta* genus demonstrates remarkable therapeutic effects against various diseases. However, clinical studies are warranted to confirm preclinical findings.

KEYWORDS
biological activity, folk medicine, Lamiaceae, *Nepeta*, phytochemistry

1 | INTRODUCTION

Since time immemorial, natural products have been widely used for the treatment of human diseases (Suppakul, Miltz, Sonneveld, & Bigger, 2003). In particular, plants possess economically and therapeutically valuable metabolites; therefore, plant products gained extensive importance to be used for medicinal purposes (Balandrin, Klocke, Wurtele, & Bollinger, 1985; Yildirim, Karakas, & Turker, 2013). One of the most important plant families that have great economic value as medicinal, cosmetic, and food products is the family Lamiaceae, which is composed of about 252 genera and more than 6,700 species and commonly distributed in temperate regions (Hedge, 1992; Kumar, Mathela, Tewari, & Bisht, 2014; Lawrence, 1992).

The genus *Nepeta* L. (catmint), a large genus of the family Lamiaceae, is named after the ancient Italian City of Nephi (J. Hussain, Rehman, & Hussain, 2010; J. Hussain, Ullah, Hussain, Hussain, & Shah, 2008). It is also known as *Glechoma* and *Catania* and it contains about 280 annual and perennial species, the majority of which are aromatic plants native to temperate Europe, Asia, North Africa, and North America (Jamila et al., 2011; Naghibi, Mosaddegh, Mohammad Motamed, & Ghorbani, 2005; Shakeri et al., 2014). Nevertheless, the greatest diversity of *Nepeta* species has been reported for two areas, Iran and the Western Himalayas (Jamzad et al., 2003; Pojarkova, 1954). In Iran, the *Nepeta* genus is represented by 75 species, of which, 54% are endemic. The species used as medicinal herbs in Iran are *Nepeta ispanahica* Bois., *Nepeta binaloudensis* Jamzad, *Nepeta bracteata* Benth., *Nepeta pogonosperma* Jamzad et Assad, and *Nepeta purgens* (Bunge) Benth. Approximately 30 species have been recorded in India, mostly in the temperate Himalaya (J. Hussain,
Rehman, Hussain, Al-Harrasi, et al., 2012), and 58 species have been found in Pakistan (J. Hussain et al., 2010). On the other hand, the Nepeta genus is represented by 33 species in Turkey, 17 of which have been reported to be endemic (Kaya, Demirci, & Baser, 2007). The wide variety and high content of terpenoid, flavonoid, and phenolic compounds of Nepeta species provide diverse pharmacological effects, justifying its traditional utilization for medicinal purposes. Several species are known for their medicinal properties and are used in folk medicine for their diuretic, diaphoretic, antitussive, antispasmodic, antiasthmatic, febrifuge, emmenagogue, and sedative activities (FormisANO, Rigano, & Senatore, 2011; Nestorović et al., 2010; Shakeri et al., 2014). Nepeta species have been assessed mainly for their potential antimutum, anti-inflammatory, and antimicrobial effects (Afshar, Nematpour, Meshkani, & Khafi, 2017; J. Hussain, Rehman, Hussain, Ali, & Al-Harrasi, 2012; Kumar, Mathela, Tewari, & Singh, 2014; Nestorović et al., 2010; Nostro, Cannatelli, Crisafi, & Alonzo, 2001). The leaves of Nepeto species are also prepared and consumed as herbal tea, and the essential oils are used as perfumes or fragrances and for food flavoring (Khajeh, Yamini, & Shariati, 2010). The feline and canine attractant, insect repellent, arthropod defense, antibacterial, antifungal, and antiviral effects and other biological activity features are generally attributed to the terpenoid constituents found in Nepeta species (Kumar, Mathela, Tewari, & Singh, 2014; Nestorović et al., 2010; Tucker & Tucker, 1988; Wagner & Wolf, 1977). Besides the terpenoid-type compounds including monoterpenes, sesquiterpenes, cyclopentanoid iridoid derivatives, and nepetalactones, the presence of other secondary metabolites including phenolics and flavonoids was shown for Nepeta species according to phytochemical analyses (Bicchi, Mashaly, & Sandra, 1984; Formisano et al., 2011; Kaya et al., 2007; Khalil, Gedara, Lahloub, Halim, & Voehler, 1997; Rapisarda, Galati, Tzakou, Flores, & Miceli, 2001; Shakeri et al., 2014). Essential oils containing an iridoid or lactone skeleton were found to be more effective than those having regular terpene constituents with regard to their antimicrobial potential, which might be attributed to their higher hydrogen bonding capacity (Bisht et al., 2010; Kumar, Mathela, Tewari, & Singh, 2014). Among the Nepeta species, Nepeta cataria L. is the most intensively studied species. On the other hand, it was seen that researches also have focused on many other Nepeta species besides N. cataria. Therefore, the aim of the present study is to overview the biological activity and phytochemical features of Nepeta species, as well as their phytoconstituents’ activity mechanisms. This review is based on the available literatures on the folkloric uses of and phytochemical, pharmacological, and clinical studies on the species of Nepeta L. genus, which were collected from electronic databases such as SciFinder, PubMed, ScienceDirect, and Web of Science, as well as library searches of journals and books.

2 TRADITIONAL USE OF Nepeta sp.

According to the ethnobotanical investigations carried out in Turkey, infusion prepared from Nepeta italicana was reported to be used as a tonic and to treat bronchitis (Yesilada et al., 1995, 1993). Nepeta betonicifolia C.A. Mey. was demonstrated to be used against cancers, cough, rheumatism, and wound healing (Mükemre, Behçet, & Çakıcıoğlu, 2015). In Serbia, infusion prepared from the herb of N. cataria L. was utilized to relieve menstrual difficulties and treat ovarian cysts (Zlatkovic, Bogosavljevic, Radojevic, & Pavlovic, 2014). The extract and smoke of the whole plant of Nepeta lagopsis Bentham. was reported to be used to heal wounds (Rehman, Mashwani, Khan, Ullah, & Chaudhary, 2015), and a decoction prepared from aerial parts of Nepeta praetervisa Rech. f. was used against helmhnt infections in Pakistan (Bibi et al., 2016). On the other hand, in China, N. cataria was used with several other plants in medicinal plant formulations for the treatment of mastitis, measles, dermatitis, dysentery, chronic rhinitis, chronic tonsillitis, and swollen sore throat (Zhang et al., 2015).

3 BIOLOGICAL ACTIVITY STUDIES ON Nepeta L. GENUS

3.1 In vitro and in vivo studies

3.1.1 Antimicrobial activity

In the study conducted by Nostro et al. (2001), the effect of N. cataria extract on 44 Staphylococcus aureus strains was studied. In doing so, the effect of subminimum inhibitory concentrations on coagulase, deoxyribonuclease, thermonuclease, and lipase production and on in vitro adherence was assessed. The enzymes, deoxyribonuclease, thermonuclease, and lipase were found to be inhibited by one-half and one-fourth minimum inhibitory concentrations (MICs), and a reduction of adherence was demonstrated (Nostro et al., 2001). A varying degree of growth inhibitory activity against some Sclerotium, Macrophomina, and Fusarium species was indicated by former reports on the antifungal characteristics of the essential oils of some Nepeta species (Saxena & Mathela, 1996). The objective of the study by Kumar, Mathela, Tewari, and Singh (2014) was not only to identify the antifungal constituents of Nepeta elliptica Royle ex Benth. but also to evaluate the growth of mycelium and spore germination inhibition potential of the oil and its almost exclusive constituent (7R)-trans, trans-nepetalactone (>85% in the oil) against five plant pathogenic fungi. Considerable inhibition effect against Helminthosporium maydis, Fusarium oxysporum, and Rhizoctonia solani with half-maximal inhibitory concentration (IC₅₀) values of 115.00, 122.67, and 153.30 μg/ml was revealed by the data on mycelium growth inhibition of the oil. However, (7R)-trans,trans-nepetalactone displayed antifungal activity against H. maydis and F. oxysporum with IC₅₀ values of 182.74 and 191.68 μg/ml, respectively. An inhibitory effect against spore germination of five fungi, namely, F. oxysporum, H. maydis, Alternaria solani, Curvularia lunata, and Albugo candida, with IC₅₀ values of 571.78, 449.35, 739.67, 471.61, and 822.41 μg/ml, respectively, was exhibited. Both the oil and (7R)-trans,trans-nepetalactone possess the potential for the development of new antifungal agents so as to restrain common plant diseases (Kumar, Mathela, Tewari, & Singh, 2014). Another study for the assessment of the antimicrobial activity of methanol extracts of three Nepeta species, namely, Nepeta ranjensis Diklić & Milojević, Nepeta sibirica L., and Nepeta nervosa Royle & Bentham., against eight bacterial and eight fungal species, was carried out by Nestorović et al. (2010). These plants differ in their qualitative...
and quantitative nepetalactone content. N. rutanjensis, which is an endemic and critically endangered perennial in Serbia, contains much higher amounts of trans,cis-nepetalactone than cis,trans-nepetalactone (Chalchat, Gorunović, Petrović, & Maksimović, 2000; Stojanović, Radulović, Lazarević, Miladinović, & Doković, 2005). N. sibirica is an endemic plant to Central Asia, Mongolia, and Southern Siberia and contains a high quantity of cis,trans-nepetalactone (de Pooter et al., 2006; Letchamo, Korolyuk, & Tkachev, 2005). Nepetalactones in N. nervosa Royle & Bentham, being a species endemic to Kashmir, exist only in trace amounts (Lawrence, 1992; Nestorović et al., 2010), demonstrating that all of the extracts were 10 to 30 times better than commercial antifungal agents at inhibiting fungal growth. MICs were found to be varied between 50 and 100 μg/ml for N. nervosa, 25 and 75 μg/ml for N. rutanjensis, and 25 and 100 μg/ml for N. sibirica. Although all extracts tested displayed significant antibacterial and strong antifungal activity, the N. rutanjensis extract displayed the best antimicrobial potential. Reverse-phase high-performance liquid chromatography coupled with ultraviolet and mass spectroscopy detection was used in examining the nepetalactone content in methanol extracts of micropropagated plants. In N. rutanjensis shoots, trans,cis-nepetalactone was identified, whereas in N. sibirica, cis,trans-nepetalactone stereoisomer was detected. On the other hand, nepetalactone was not detected in the shoots of N. nervosa (Nestorović et al., 2010).

In addition to their conventional uses, it has been found that Nepeta essential oils are active towards various Gram-negative and Gram-positive bacteria and fungi, which specifically contain food. Nepeta essential oils also possess good antioxidant potential. These properties of Nepeta essential oils make them valuable in preserving food (H. Hussain, Al-Harrasi, & Green, 2016). Investigations report that Nepeta oils are quite effective in controlling the decay of food crops. In a study by Kumar, Mathela, Tewari, and Bisht (2014), the antifungal activities of essential oils of Nepeta leucophylla Bentham., Nepeta ciliaris Bentham., and Nepeta clarkei against F. oxysporum, H. maydis, A. solani, R. solani, Sclerotonia sclerotiorum, C. lunata, and A. candida were investigated. The most effective ones were found to be the oils consisting of oxygenated terpenoids. The essential oils were shown to be active against the spore germination of all plant pathogens. The essential oils of N. leucophyllo and N. ciliaris were effective against H. maydis with an IC50 value of 43.6 μg/ml and against F. oxysporum with an IC50 value of 219.2 μg/ml, respectively (Kumar, Mathela, Tewari, & Bisht, 2014). Nepeta ucrainica L. ssp. kopetdagensis is found only in the northeast part of Iran. In a study by Shakeri et al. (2014), antibacterial characteristics of the essential oil obtained from the aerial parts of N. ucrainica ssp. kopetdagensis were examined. A serial dilution method was used in analyzing the antibacterial activity of the essential oil of Nepeta sintenisii Bornm. against six bacterial strains. The essential oil demonstrated a significant antibacterial effect against Gram-positive bacteria, particularly S. aureus with an MIC value of 14 μg/ml and minimum bactericidal concentration value of 14 μg/ml (Shakeri et al., 2014). The antimicrobial effect of N. sintenisii essential oil was examined by Shakeri et al. (2016). According to the results of the study on the antimicrobial activity of the essential oil against 11 bacterial strains and one fungus, the essential oil not only exhibited effective and broad-spectrum antibacterial effects against both Gram-positive and Gram-negative bacteria but also had antifungal effect against Candida albicans.

### 3.1.2 Repellent and insecticide activity

The insecticidal activity of the essential oil obtained from N. cataria was assessed against Spodoptera littoralis larvae, and it was found out that the essential oil was highly toxic, with the value of lethal concentration, 50% (LC50) ≤10.0 ml/m³ (Pavela, 2005). In another research, N. cataria essential oil and the main iridoid compounds were investigated against major pathogen vector mosquitoes Anopheles gambiae and Culex quinquefasciatus, the brown ear tick Rhipicephalus appendiculatus, and the red poultry mite Demanysus gallinae in terms of repellent effect. Gas chromatography (GC) and GC–mass spectroscopy analysis on N. cataria Chemotypes A and B demonstrated that (4aS,7S,7aR)-nepetalactone was the major compound in Chemotype A, whereas (4aS,7S,7aS)-nepetalactone was major in Chemotype B. Within the oils, the sesquiterpene hydrocarbon (E)-(1R,9S)-caryophyllene was found out to be the only main component. In spite of the fact that the oils showed high repellent activity (Chemotype A median repellent dose value (RD50) = 0.081 mg/cm² and Chemotype B RD50 = 0.091 mg/cm²) for A. gambiae, which is analogous with the synthetic repellent N,N-diethyl-meta-toluamide (RD50 = 0.12 mg/cm²), lower repellent activity was recorded for C. quinquefasciatus (Chemotype A RD50 = 0.34 mg/cm² and Chemotype B RD50 = 0.074 mg/cm²). In proportion to the Chemotype A and Chemotype B oils, overall lower repellent activity was unveiled by additional repellency testing against A. gambiae, which employed the purified (4aS,7S,7aR)- and (4aS,7S,7aS)-nepetalactone isomers. In addition to its disclosure of a synergistic effect between (4aS,7S,7aR) and (4aS,7S,7aS) isomers, testing of binary mixtures of these two isomers along an array of ratios, being at the same dose, revealed an astounding ratio-dependent effect in which pure isomers and equivalent or near-equivalent mixtures have a lower effect but nonequivalent ratios have a higher effect. The compound (E)-(1R,9S)-caryophyllene in Chemotype B oil exerted a similar effect as the essential oil. In conclusion, because both nepetalactone isomers and other components such as (E)-(1R,9S)-caryophyllene exist, unfraccionated essential oils of Nepeta sp. provide a conceivably greater protection for humans and livestock against major pathogen vectors when compared to nepetalactone isomers (Birkett, Hassanali, Hoglund, Pettersson, & Pickett, 2011). Nepetalactones extracted from Nepeta faassenii Bergmans ex Steam showed a wide variety of pharmacological uses at low cytotoxicity rates. In behavioral tests, Ghaninia, Larsson, Hansson, and Ignell (2008) demonstrated the repellent effect of nepetalactone, lowering the landing rate of Aedes aegypti and other mosquito species. This effect even exceeded the effect of the synthetic compound, N,N-diethyl-meta-toluamide (Bernier, Furman, Kline, Allan, & Barnard, 2005). The underlying mechanism of nepetalactone was related to the response in STB1 sensilla, as shown by GC-coupled single-sensillum recording (Ghaninia et al., 2008).

### 3.1.3 Larvicidal activity

The larvicidal effect of the essential oil and methanol extract of Nepeta menthoides Boiss. & Buhse against Anopheles stephensi, being the major
malaria vector, was examined by Mahnaz et al. (2012). A Clevenger-type apparatus was used to obtain the essential oil, and a percolation method was applied in attaining the methanol extract. In addition to these, the larvicidal effect was tested by World Health Organization (WHO) method. So as to calculate LC$_{50}$ and LC$_{90}$ values, five different concentrations of the oil and extract were analyzed. LC$_{50}$ was 69.5 and 243.3 ppm, and LC$_{90}$ was calculated as 175.5 and 419.9 ppm for the extract and essential oil, respectively. The findings of the study suggest that methanolic extract showed a greater effect than the essential oil (Mahnaz et al., 2012).

### 3.1.4 Cytotoxic activity

The essential oil of N. sintenisii demonstrated a significant antiproliferative effect in an in vitro cytotoxicity evaluation test against four cell lines of human ovarian carcinoma (A2780), cervical cancer (Hela), human colon adenocarcinoma (LS180), human breast adenocarcinoma (MCF-7), and human umbilical vein endothelial cells, with an IC$_{50}$ value of 20.37 μg/ml belonging to the Hela cells (Shakeri et al., 2016). A 3-(4,5-dimethylthiazole-2-yl)-2,5-biphenyl tetrazolium bromide (MTT) test was used for the assessment of cytotoxic activity of the essential oil of N. ucrainica ssp. kopetdaghensis on human ovarian carcinoma A2780 cell line and human breast adenocarcinoma MCF-7 cell line. The cytotoxic effect of the essential oil was demonstrated against the cell lines with IC$_{50}$ values of <50 μg/ml (Shakeri et al., 2014).

In a study by Afshar et al. (2017), the activities of 70% ethanol, n-hexane, and aqueous extracts prepared from N. binaloudensis, an endemic species of Iran, were evaluated in breast cancer cell lines including MCF-7 and MDA-MB-231 by comparing them to MCF-10A, a noncancer line on the cell proliferation and expression of adenosine deaminase and ornithine decarboxylase 1 genes. Ten to 320 μg/ml of extract concentrations was applied to the cell lines. Cell viability was measured by using an MTS assay. Gene expression was analyzed by real-time polymerase chain reaction. N. binaloudensis was found to have the capacity to inhibit the growth of malignant cells in a time- and dose-dependent manner. In comparison to other extracts, the n-hexane extract was more toxic among the extracts of N. binaloudensis. According to the results, ornithine decarboxylase 1 and adenosine deaminase genes are less expressed in cancer cell lines. When compared to the control group, it was seen that ornithine decarboxylase 1 and adenosine deaminase messenger RNA expression were reduced 4.9-fold and 3.5-fold in the MCF-7 cell line and 3.6-fold and 2.6-fold in the MDA-MB-231 cell line at 60 μg/ml of n-hexane extract concentration of N. binaloudensis. In conclusion, the study has shown that the n-hexane extract of N. binaloudensis displays an inhibitory action on the gene expression of ornithine decarboxylase 1 and adenosine deaminase in the breast cancer cell line (Afshar et al., 2017).

### 3.1.5 Genotoxic activity

Nepetalactone and epinepetalactone are the major compounds of the essential oil extracted from the aerial parts of Nepeta meyeri Benth. A comparison of the germination percentage and random amplified polymorphic deoxyribonucleic acid (RAPD) of Brassica napus and Zea mays treated with essential oil of N. meyeri showed strong inhibitory effects on germination. A change in RAPD profiles such as differing band intensity, loss of bands, and the appearance of new bands compared with the control group, indicating a genotoxic effect of N. meyeri on weed and crop plants, has been observed (Kekeç, Mutlu, Alpsoy, Sakçi, & Atici, 2013). Bozari, Agar, Aksakal, Erturk, and Yannis (2013) demonstrated genotoxic effects of the essential oil obtained from Nepeta nuda L. containing mainly nepetalactone, germacrene, and elemol. Increasing concentrations of essential oil led to inhibition of root and stem cell growth and differing RAPD profiles in germinated seeds (Bozari et al., 2013).

### 3.1.6 Induction of apoptosis

Apoptosis was induced by N. cataria extracts in human prostatic PC3 and DU-145 as well as MCF-7 breast cancer cell lines. The extracts (methanol, n-hexane, dichloromethane, ethyl acetate, n-butanol, water, and essential oil) containing different nepetalactone stereoisomers (97.7%) showed higher cytotoxicity towards estrogen-receptor-positive PC3 cells compared to low-hormone-receptor-expressing DU-145 cells, indicating phytoestrogenic effects possibly due to β-sitosterol. Additionally, treated cells induced apoptosis in PC3 cells in a concentration-dependent manner. An increase of the proapoptotic protein Bax and cleavage of poly(adenosine diphosphate ribose) polymerase was observed (Emami et al., 2016). Apoptosis induction has been also found in Hela cervical carcinoma cells treated with SiO$_2$-antisense molecules covered by nepetalactone extracted from Nepeta gloeocephala Rech. f. The compound decreased phosphorylation of the integrin-linked kinase at Thr-173 and Ser-246 without influencing integrin-linked kinase levels and caused cell arrest in G2/M. Additionally, a decline in downstream AKT-Ser473 and AKT-Thr308 phosphorylation caused by the application of SiO$_2$-antisense covered by nepetalactone without affecting the total amount of protein kinase B/AKT has been observed (Figure 1; Dehghany Ashkezary, Aboee-Mehrizi, & Moradi, 2017).

![FIGURE 1](https://example.com/figure1.png)
3.1.7 Effects on immune response

Nepeta compounds modulate immune responses in various manners. Verbascoside, a phenylpropanoid from N. ucrainica, deployed immunomodulatory activity in vitro (Akbay, Calis, Undegek, Basaran, & Basaran, 2002). The authors demonstrated positive chemotactic activities at all doses of verbascoside applied and concluded immunosuppressive and antioxidant effects elucidated by the decreasing intracellular activity of neutrophils with increased doses (Akbay et al., 2002). An immunomodulatory effect in vitro has been observed by caffeoyl phenylethanoid glycoside verbascoside extracted by N. cataria. Verbascoside inhibited calcineurin in the absence of calmodulin, implicating a direct interaction. The caffeoyl phenylethanoid glycoside lamiuside A (teucrioside) extracted in the same way showed inhibitory effects of calcineurin only in the presence of calmodulin, suggesting an interaction with calmodulin or the calmodulin–calcineurin complex, thus reducing proinflammatory gene expression regarding interleukin 2 and tumor necrosis factor α (Prescott, Veitch, & Simmonds, 2011).

3.1.8 Antimelanogenesis activity

Different extracts of Nepeta binaludensis revealed inhibitory effects on melanogenesis in murine B16F10 melanoma cells. Decreased melatonin levels at constant tyrosinase activity and reactive oxygen species levels were accompanied with a decrease of the microphthalmia-associated transcription factor (MITF) protein expression levels. MITF is one of the most important nuclear transcription factors regulating melanogenesis by activating tyrosinase transcription (Otreba, Rok, Buszman, & Wrzesniok, 2012). It plays an important role in melanocyte development and survival and is associated with tumorigenesis and progression of melanoma (Tayarani-Najaran, Akberi, Vatani, & Emami, 2016).

3.1.9 Antioxidant activity

In a study, in vitro antioxidant activity of the essential oil and extracts of Nepeta flavida Hub.-Mor., namely, hexane, dichloromethane, and methanol, were examined. The samples were evaluated for their antioxidant effects by a 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay and β-carotene-linoleic acid test. In the DPPH assay, the IC50 value of the essential oil of N. flavida was determined as 42.8 ± 2.19 μg/ml. The polar subfraction of the methanol extract showed the strongest activity among the extracts with an IC50 value of 63.2 ± 1.75 μg/ml. Moreover, the N. flavida essential oil exhibited 86.3% ± 1.69 inhibitory effect against linoleic acid oxidation, in the β-carotene-linoleic acid system. A correlation was found between the polarity and antioxidant effect. The extracts exhibited the same activity pattern in this system; the most active one is the polar subfraction, 79.7% ± 0.89. On the other hand, being a main constituent of the essential oil, 1,8-cineole exhibited a marked antioxidant effect in both systems, whereas linalool, the other constituent, did not exhibit any activity (Tepe, Daferera, Tepe, Polissiou, & Sokmen, 2007). Besides, DPPH and ferric reducing antioxidant power methods were used in assessing the antioxidant effect of the essential oil of N. sintenisii. A weak antioxidant effect in the DPPH test was found with the IC50 value of 7.16 mg/ml and in the ferric reducing antioxidant power assay with the value of IC50 0.82 mM Fe2+/mg essential oil (Shakeri et al., 2016).

3.1.10 Anticonvulsant and myorelaxant activities

Galati, Miceli, Galluzzo, Taviano, and Tzakou (2004) studied the neuropharmacological effect of the essential oil, methanol extract, and its fraction obtained from Nepeta sibthorpii Bentham in rodents. N. sibthorpii preparations improved general behavior pattern and provided protection against pentyleneetetrazol-induced convulsions. The number of convulsions was found to be remarkably decreased by the application of methanol extract (0.6 ± 0.5), fraction I (0.6 ± 0.9), and essential oil (0.7 ± 0.9) in comparison with the pentyleneetetrazol group (3.0 ± 0.5). The activity was attributed to epinepetalactone through GABAergic mediation (Galati et al., 2004). In the treatment of gastrointestinal and respiratory hyperactive illnesses such as colic, diarrhea, cough, asthma, and bronchitis, N. cataria has been used (Baranauskiene, Venskutonis, & Demytenaere, 2003; Duke, 2002). So as to examine the curative usage of N. cataria for hyperactive gut and respiratory disorders, the study by Gilani et al. (2009) was conducted. It was found that spontaneous and high-K+ (80 mM) precontractions were impeded by the essential oil, papaverine, and verapamil in isolated rabbit jejunum. The essential oil and papaverine also inhibited carbachol and K+ precontractions in isolated guinea-pig trachea. Similar to papaverine, the essential oil led to cardiodepression at such higher concentrations as 25–80 times in isolated guinea-pig atria. In conclusion, it was found that N. cataria has spasmylostatic and myorelaxant activities. Explaining its being administered conventionally in diseases such as colic, diarrhea, cough, and asthma, these activities seem to be mediated through the dual inhibition of calcium channels and phosphodiesterase (Gilani et al., 2009). An aqueous methanolic extract of Nepeta ruderális Buch.-Ham. ex Benth. on rabbit jejunum revealed a complete relaxation of spontaneously contracting high K+ (80 mM), and carbachol (1 μM) induced contraction of jejunum with half-maximal effective concentration values of 5.85, 4.0, and 2.86 mg/ml (comparable to verapamil as the control drug). Similar results have been observed in rabbit tracheal tissue. Antidiarrheal activity have been found in vivo in castor-oil-induced diarrhea at doses of 300 and 500 mg/kg. Mice did not show acute toxicity at doses up to 5 g/kg. Broncho-relaxant and spasmylostatic effects were mediated by calcium channel blocking activity caused by rightward displacement of higher concentrations of concentration–response curves of calcium (Mahmood, Chaudhry, Masood, Saeed, & Adnan, 2017).

3.1.11 Analgesic and anti-inflammatory activities

N. cataria is a plant having conventional uses associated with the treatment of inflammation. Calcineurin, which is an important regulator of T-cell-mediated inflammation, was found to be inhibited by N. cataria extract. Bioactivity-guided extraction and fractionation methods were used to isolate the active constituents of N. cataria, namely, caffeoyl phenylethanoid glycosides teucriside, verbascoside, and lamiuside A (teucrioside). Regardless of the presence or absence of calmodulin, the three compounds inhibited calcineurin, which is indicative of a direct interaction with calcineurin. In the analysis of the immunomodulatory activity of caffeoyl-phenylethanoid-glycoside-comprising
species, the inhibition of calcineurin should be regarded as a conceivable mode of action (Prescott et al., 2011). Kirmanoic acid and kurrmanoic acid, being two new pentacyclic triterpenes, were isolated from the chloroform extract of N. clarkii Hook. Kirmanoic acid was analyzed for its effects such as analgesic, anti-inflammatory, and central nervous system (CNS) depressant; and it showed significant analgesic activity compared to standard drug in acetic-induced writhing and formalin assays. Furthermore, kirmanoic acid also exhibited stronger anti-inflammatory activity than standard drug. According to a behavioral study of kirmanoic acid, it exhibited mild CNS stimulant and muscle relaxant in mice. Besides, a slight increase in locomotor activity was identified owing to kirmanoic acid (J. Hussain, Rehman, Hussain, Al-Harrasi, et al., 2012). The extracts of Nepeta atlantica Ball and Nepeta tuberosa L. ssp. reticulata (Desf.) Maire have a great many secondary metabolites such as iridoid lactonione and glucosidique and lupane triterpine type. The methanol extracts were prepared from the aerial parts of each species. In vivo peripheral analgesic activity was assessed according to the test of Koster in mice; central analgesic activity was evaluated by using the tail flick test in rats. LD₅₀ was determined as 1672 ± 232 mg/kg for N. atlantica and 1,401 ± 97.29 mg/kg for N. tuberosa ssp. reticulata. The bioactivity assays demonstrated a marked protection against abdominal cramp at a 60 mg/kg (intraperitoneal) dose with values of 67.91% and 75.53% and at a 120 mg/kg (intraperitoneal) dose with values of 90.10% and 92.89% for N. atlantica and N. tuberosa ssp. reticulata, respectively (Bouidida, Alaoui, Cherrah, Fkh-Tetouani, & Idrissi, 2006).

Nepetolate B from N. clarkii exerted CNS-depressing activity. By performing formalin tests, J. Hussain et al. (2015) showed analgesic and anti-inflammatory effects. Pain inhibition was tested at nepetolate B concentrations of 0.1, 0.2, and 0.4 mg/kg, respectively, reaching pain inhibition of 68.0%, 25.5%, and 75.5% in the early phase and 63.0%, 66.7%, and 48.1% in the late phase. These effects were even higher than acetyl salicylic acid (66.7%, and 48.1% in the late phase. These effects were even higher in inhibition of 68.0%, 25.5%, and 75.5% in the early phase and 63.0%, 66.7%, and 48.1% in the late phase. These effects were even higher in inhibition of 68.0%, 25.5%, and 75.5% in the early phase and 63.0%, 66.7%, and 48.1% in the late phase. These effects were even higher in inhibition of prostaglandin synthesis has been described (Santos & Martínez, González, 2005). Only one Nepeta species, namely, N. menthoideae, was reported to exert larvicidal potential against A. stephensi (Mahnaz et al., 2012). Cytotoxic activity researches have shown that three Nepeta species, namely, N. sintenisii, N. ucrainica ssp. kopetdagensis, and N. gloeocephala, displayed cytotoxic effect (Afshar et al., 2017; Shakeri et al., 2014, 2016). N. meyeri and N. nuda caused genotoxic effects (Bozari et al., 2013; Kekeç et al., 2013). N. gloeocephala was demonstrated to possess apoptotic potential (Dehghany Ashkezary et al., 2017). N. ucrainica and N. cataria displayed immunomodulatory activity in vitro (Akbay et al., 2002; Prescott et al., 2011). One Nepeta species, N. binaludensis,
exerted inhibitory effects on melanogenesis in murine B16F10 melanoma cells (Otreba et al., 2012; Tayarani-Najaran et al., 2016). *N. flavida* and *N. sintenisii* revealed antioxidant capacity in two previous in vitro studies (Shakeri et al., 2016; Tepe et al., 2007). Anticonvulsant and myorelaxant activity researches on *N. sibthorpii*, *N. cataria*, and *N. ruderalis* have shown that these three species possess anticonvulsant and myorelaxant effects (Galati et al., 2004; Gilani et al., 2009; Mahmood et al., 2017). *N. menthoides* attenuated the development of morphine dependence and potentiated morphine analgesia (Rahmati & Beik, 2017). *N. cataria* enhanced penile erection and improved the sexual behavior of male rats (Bernardi et al., 2011). The main findings were summarized in Table 1.

### 3.2 | Clinical studies

Two clinical studies were conducted on *N. menthoides* evaluating its ameliorative effects on premenstrual syndrome (PMS) and antidepressant activities (Table 2).

### 3.2.1 | Ameliorative effects on premenstrual syndrome

Mirghafourvand et al. (2016) investigated the effectiveness of *M. officinalis* L., both alone and in combination with *N. menthoides*, on PMS. The study was composed of a total of 93 female students from Tabriz University of Medical Sciences, Iran. So as to give information about the presence and severity of PMS symptoms, the participants completed the Daily Record of Severity of Problems questionnaire for two consecutive menstrual cycles. Later, they were randomly divided into three groups, two of which were intervention groups and one of which was a placebo group. Each group contained 31 subjects. The participants in the experimental groups received either a capsule of *M. officinalis* (500 mg) or a capsule containing a combination of *M. officinalis* (250 mg) and *N. menthoides* (250 mg); on the other hand, the participants in the placebo group received a capsule of starch powder (500 mg). The subjects took capsules twice on a daily basis during the luteal phase of two consecutive menstrual cycles. Two months after the treatment, PMS symptoms significantly decreased in the *M. officinalis* and *M. officinalis–N. menthoides* groups if compared to the placebo group (Mirghafourvand et al., 2016).

### 3.2.2 | Antidepressant activity

The freeze-dried aqueous extract of *N. menthoides* was assessed for the treatment of major depression. Seventy-two patients participated in a two-armed double-blind randomized controlled trial, which was carried out between April and September 2015. These patients were from the two psychiatry clinics of Shiraz University of Medical Sciences. On the basis of a structured clinical interview as defined by
the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, these patients fulfilled the criteria for major depression. Patients were grouped randomly, to be given N. menthoides or sertraline for 4 weeks. When compared to that of the control group, the average changes in the Beck Depression Inventory scores in the N. menthoides group were significantly higher ($p \leq .001$). A lower recurrence rate in the N. menthoides group was observed in the 2 weeks of follow-up after the intervention ($p \leq .001$). In patients with major depression, N. menthoides may be useful in controlling the mood. As this herb causes sustention of antidepressant effect and delay in the recurrence of depression, it could be considered worthwhile (Kolouri et al., 2016).

4 | CHEMICAL CONSTITUENTS OF THE GENUS Nepeta L.

The phytochemical composition of species belonging to the Nepeta genus is characterized by the presence of different classes of secondary metabolites, especially terpenes (monoterpene, diterpene, triterpene, and sesquiterpene derivatives), phenol and polyphenol compounds (mainly flavonoids), and steroids ($\beta$-sitosterol, stigmasterol, and stigmasteryl glucoside).

4.1 | Terpenes

Terpenes, including terpenoid lactones and iridoid monoterpene nepetalactones, are the main constituents in Nepeta essential oils. The phytochemical analysis of oil composition reveals the presence of monoterpens, diterpenes, triterpenes, and sesquiterpenes (Baser, Demirci, Kirimer, & Kurkcuglu, 2000; Formisano et al., 2011; Sattar et al., 1995; Topçu, Kökdil, & Yalçın, 2000). Nepetalactones (Figure 2) are the most frequent constituents determined among monoterpens, along with dehydroabietanetetraenes, 1,8-cineole, $\alpha$-terpineol, $\alpha$-citral, geraniol, and their derivatives (Clark, Hamilton, Chapman, Rhodes, & Hallahan, 1997; Formisano et al., 2011; Inouye, 1991). 4aa,7a,7aa-Nepetalactone has been the first nepetalactone (a cyclopentanoid monoterpene) isolated and characterized from N. cataria (Regnier, Waller, & Eisenbraun, 1967). Nepetalactones can originate four diastereoisomers, due to the presence of three chiral centers, with the predominance, in nature, of 7S stereochemistry (Clark et al., 1997). The identified and characterized nepetalactones (Figure 2) in the Nepeta genus are 4aa,7a,7aa-nepetalactone; 4aa,7a,7aa-nepetalactone; 4aa,7a,7aa-nepetalactone; 4aa,7a,7aa-nepetalactone; and 4aa,7b,7aa-nepetalactone (Bellesia et al., 1979; Eisenbraun et al., 1981; Formisano et al., 2011; Heuskin et al., 2009; McElvain & Eisenbraun, 1957). The stereoisomers are not equally distributed in the Nepeta genus; the cis,cis-isomer, for instance, predominated in Nepeta racemosa Lam. and the cis,trans-isomer in N. cataria, whereas the trans,trans-isomer predominated in N. elliptica and N. nuda (Clark et al., 1997). Nepetalactones (Figure 2) are also present as hydrogenated derivatives such as $\alpha$-dihydronepetalactone, $\beta$-dihydronepetalactone, 5,9-dehydrodihydronepetalactone, nepetalic acid, iridomyrmecin, and isoiridomyrmecin (Eom, Yang, & Weston, 2006; Heuskin et al., 2009; Javidnia, Miri, Safavi, Azarpia, & Shafiee, 2002; Kalpoutzakis, Aliagnis, Mentis, Mitaku, & Charvala, 2001; Moghaddam & Hosseini, 1996; Suschke, Sporer, Schnee, Geiss, & Reichling, 2007). Other monoterpenes identified in the Nepeta genus are iridoid glucosides (Figure 3), such as 1,5,9-epideoxyloganic acid, nepetarioside, nepetaside, velpetin, ixoroside, ajugol, aucubin, nepetanudosides A-D, monoterpenic $\gamma$-lactones, cyclopentanomonomoterpene enol acetates (such as iridodial $\beta$-monoenoil acetate, dihydroidiododial diacetate, and iridodial dienol diacetate), monoterpene alkaloids (such as actinidine), and cyclopentanemonoterpenes (such as argolic acid A and argolic methyl ester B; Formisano et al., 2011; Saxena & Mathela, 1996; Suschke et al., 2007; Takeda et al., 1996; Figure 4). Abietane-type and dehydroabietane diterpenes are diterpenes isolated in Nepeta tedyca Webb & Berthel. and N. tuberosa spp. reticulate, whereas pimarane- and isopimarane-type diterpenes are molecules isolated from Nepeta pratii H. Lév., Nepeta septemcrenata Ehrenb. ex Benth., N. tuberosa spp. reticulate, and Nepeta parnasica Heldr. & Sart. (Fraga, Hernández, Mestres, & Arteaga, 1998; Fraga, Mestres, Diaz, & Arteaga, 1994; Hou, Tu, & Li, 2002; Hussein, 2006).
Rodríguez, de la Paz, & Cano, 1999; Khalil et al., 1997; Urones, Sanchez Marcos, Fernandez Ferreras, & Basabe, 1988). Other types of diterpenes derive from dimerization of dehydronepetalactone or nepetalactone derivatives, such as nepetanudone and nepetaparnone (Fraga et al., 1998; Urones et al., 1988). Ursolic acid (Figure 5) is the most common triterpene identified in the* Nepeta* genus present in several plants, followed by lupane-type and oleanane-type skeleton, such as nepeticin, oleanolic acid, lupeol, betulin, nepehinol, and triterpene nepetalic acids, such as dihydro-3α-(β-sitosteryl-3β-oxy) nepetalactone, dihydro-3β-(5α-stigmaster-7-en-3β-oxy) nepetalactone, and dihydro-3α-(olean-12-en-28-oyl-3β-oxy) nepetalactone (Figure 6; Ahmad, Bano, & Bano, 1986; Bhandari, Garg, Agrawal, & Bhakuni, 1990; Hou et al., 2002; Janicsak, Veres, Zoltan Kakasy, & Mathe, 2006; Klimek & Modnicki, 2005; von Carstenn-Lichterfelde, Rodriguez, & Valverde, 1973). In addition to the already known nehipetol, nehipediol, β-farnesene, α-bisabolene, β-caryophyllene, and α-humulene (Rather et al., 2012), the presence of sesquiterpene derivatives has been reported by Hanlidou, Karousou, and Lazari (2012) in *Nepeta argolica* Bory & Chaub. (caryophyllene oxide) and in *Nepeta ciliarica* Boiss. ex Benth. from Lebanon, mainly sesquiterpene hydrocarbons and oxygenated sesquiterpenes (Formisano, Rigano, Arnold, Piozzi, & Senatore, 2013).

**4.2 | Flavonoid and phenol compounds**

Different kinds of flavonoids have been isolated from *Nepeta* species, including flavones, flavonols, flavanols, and flavanone (El-Moaty, 2009; Formisano et al., 2011; J. Hussain, Rehman, Hussain, Ali, & Al-Harrasi, 2012; Jamzad et al., 2003; Miceli et al., 2005; Modnicki, Tokar, & Klimek, 2007; Proestos, Boziaris, Nychas, & Komaitis, 2006; Tomás-Barberán, Gil, Ivanceva, & Tomás-Lorente, 1992). Moreover, *Nepeta* flavones (such as cirsimaritin, 8-hydroxycirsimaritin, salvigenin, 8-hydroxysalvigenin, and 8-hydroxycirsilol) are typically used as a characteristic chemotaxonomic feature of the genus.
Some flavonoids are present only in few species and seem to be randomly distributed, whereas others are much more common and have been isolated in a lot of species belonging to the Nepeta genus such as cirsimaritin, isothymusin, and genkwatin (Jamzad et al., 2003). Other frequently identified flavones (Figure 8) are, for instance, apigenin, luteolin, salvigenin, 8-hydroxysalvigenin, xanthomicrol, ladanein, cirsiol, scutellaran A, and nepetrocin, whereas luteolin 7-O-β-D-glucuronide, luteolin 7-O-glucurono-(1→6)-glucoside, nornepetin, nepetin, nepetin 7-glucuronide, nepetin, hispidulin 7-glucoside, hispidulin 7-O-β-D-glucuronide, ladanein, gardenin B, thymosin, acacetin, and salvitin have been identified only in few or single species of the Nepeta genus (Jamzad et al., 2003; Tomás-Barberán et al., 1992). The flavonols (Figure 9) are characterized by the presence of the aglycons kaempferol and quercetin and their derivatives (kaempferol 3-O-β-D-glucopyranoside, kaempferol 3-O-α-rhamnoside, kaempferol 3-O-β-D-rutinoside, kaempferol 3-O-rhamnoside-4′-O-glucoside, quercetin 3-O-β-D-rutinoside, 3,6,3′-trimethylquercetagetin, and 3,6,7,3′,4′-pentamethylquercetagetin). Epicatechin and eriodictyol (Figure 9) are the flavanol and flavanone, respectively, identified only in N. cataria (Proestos et al., 2006). Also, the phenol components are well represented in the Nepeta genus with the identification of over 20 derivatives (El-Moaty, 2009; Formisano et al., 2011; Grayer et al., 2003; Modnicki et al., 2007; Mouhajir, Pedersen, Rejdali, & Towers, 2001; Proestos et al., 2006; Snook et al., 1993). Among them, some of the most representative compounds (Figure 10) are gallic acid, ferulic acid, p-coumaric acid, 4-hydroxybenzoic acid, caffeic acid,
5 | CONCLUSION

In the present review, Nepeta species were overviewed with aspects of their phytochemical features and activity potential. Mainly terpenoids and phenolic compounds were determined and identified by using chromatographic and spectroscopic techniques. It was also shown that plants of Nepeta genus have various traditional utilization worldwide and possess diverse biological effects including antimicrobial, repellent, insecticidal, larvicidal, cytotoxic, anticarcinogenic, antioxidant, anticonvulsant, and anti-inflammatory, and antidepressant activities with regard to the wide range of secondary metabolites. It was concluded that, for the discovery and development of novel biologically active constituents to be used in several applications in medicinal and agricultural fields, Nepeta species could represent promising candidates.

CONFLICT OF INTEREST

None of the authors have any conflicts of interest to declare.

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