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REVIEW

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

Ipek Süntar[1] | **Seyed Mohammad Nabavi**[2] | **Davide Barreca**[3] | **Nicolas Fischer**[4] | **Thomas Efferth**[4]

[1] Department of Pharmacognosy, Faculty of Pharmacy, Gazi University, Etiler, 06330 Ankara, Turkey

[2] Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, 1435916471 Tehran, Iran

[3] Department of Chemical, Biological, Pharmaceutical, and Environmental Sciences, University of Messina, Italy

[4] Institute of Pharmacy and Biochemistry, Johannes Gutenberg University of Mainz, Staudinger Weg 5, 55128 Mainz, Germany

Correspondence
Ipek Süntar, Department of Pharmacognosy, Faculty of Pharmacy, Gazi University, Etiler, 06330 Ankara, Turkey.
Email: ipesin@gazi.edu.tr
Davide Barreca, Department of Chemical, Biological, Pharmaceutical, and Environmental Sciences, University of Messina, Italy.
Email: dbarreca@unime.it

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 *Cataria* 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, Mohammadi 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 ispahanica* Boiss., *Nepeta binaloudensis* Jamzad, *Nepeta bracteata* Benth., *Nepeta pogonosperma* Jamzad et Assadi, and *Nepeta pungens* (Bunge) Benth. Approximately 30 species have been recorded in India, mostly in the temperate Himalaya (J. Hussain,

Abbreviations: CNS, central nervous system; DPPH, 2,2-diphenyl-1-picrylhydrazyl; GC, gas chromatography; IC_{50}, half-maximal inhibitory concentration; ILK, integrin-linked kinase; LC_{50}, lethal concentration, 50%; LD_{50}, lethal dose, 50%; MIC, minimum inhibitory concentration; MITF, microphthalmia-associated transcription factor; PKB/AKT, protein kinase B/AKT; PMS, premenstrual syndrome; RD_{50}, median repellent dose value; WHO, World Health Organization

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 antitumor, 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 *Nepeta* 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 repellant, 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 italica* L. was reported to be used as tonic and to treat bronchitis (Yeşilada et al., 1995, 1993). *Nepeta betonicifolia* C.A. Mey. was demonstrated to be used against cancers, cough, rheumatism, and wound healing (Mükemre, Behçet, & Çakılcıoğlu, 2015). In Serbia, infusion prepared from the herb of *N. cataria* L. was utilized to relieve menstrual difficulties and treat ovarian cysts (Zlatkovic, Bogosavljevic, Radivojevic, & Pavlovic, 2014). The extract and smoke of the whole plant of *Nepeta lagopsis* Benth. 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 helminth 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 (7*R*)-*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 (IC_{50}) values of 115.00, 122.67, and 153.30 μg/ml was revealed by the data on mycelium growth inhibition of the oil. However, (7*R*)-*trans*,*trans*-nepetalactone displayed antifungal activity against *H. maydis* and *F. oxysporum* with IC_{50} 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 IC_{50} values of 571.78, 449.35, 739.67, 471.61, and 822.41 μg/ml, respectively, was exhibited. Both the oil and (7*R*)-*trans*,*trans*-nepetalactone possess the potential for the development of new antifungal agents so as to restrain common plant diseases (Kumar, Mathela, Tewari, and Singh, 2014). Another study for the assessment of the antimicrobial activity of methanol extracts of three *Nepeta* species, namely, *Nepeta rtanjensis* 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. rtanjensis*, 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. rtanjensis*, and 25 and 100 μg/ml for *N. sibirica*. Although all extracts tested displayed significant antibacterial and strong antifungal activity, the *N. rtanjensis* 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. rtanjensis* 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 contaminate 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* Benth., *Nepeta ciliaris* Benth., 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. leucophylla* and *N. ciliaris* were effective against *H. maydis* with an IC_{50} value of 43.6 μg/ml and against *F. oxysporum* with an IC_{50} value of 219.2 μg/ml, respectively (Kumar, Mathela, Tewari, & Bisht, 2014). *Nepeta ucrainica* L. ssp. *kopetdaghensis* 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. *kopetdaghensis* 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% (LC_{50}) ≤10.0 ml/m^3 (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 *Dermanyssus gallinae* in terms of repellent effect. Gas chromatography (GC) and GC–mass spectroscopy analysis on *N. cataria* Chemotypes A and B demonstrated that (4a*S*,7*S*,7a*R*)-nepetalactone was the major compound in Chemotype A, whereas (4a*S*,7*S*,7a*S*)-nepetalactone was major in Chemotype B. Within the oils, the sesquiterpene hydrocarbon (*E*)-(1*R*,9*S*)-caryophyllene was found out to be the only other main component. In spite of the fact that the oils showed high repellent activity (Chemotype A median repellent dose value (RD_{50}) = 0.081 mg/cm^2 and Chemotype B RD_{50} = 0.091 mg/cm^2) for *A. gambiae*, which is analogous with the synthetic repellent *N*,*N*-diethyl-*meta*-toluamide (RD_{50} = 0.12 mg/cm^2), lower repellent activity was recorded for *C. quinquefasciatus* (Chemotype A RD_{50} = 0.34 mg/cm^2 and Chemotype B RD_{50} = 0.074 mg/cm^2). 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 (4a*S*,7*S*,7a*R*)- and (4a*S*,7*S*,7a*S*)-nepetalactone isomers. In addition to its disclosure of a synergistic effect between (4a*S*,7*S*,7a*R*) and (4a*S*,7*S*,7a*S*) 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*)-(1*R*,9*S*)-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*)-(1*R*,9*S*)-caryophyllene exist, unfractionated 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 Stearn 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, Sakçali, & Atici, 2013). Bozari, Agar, Aksakal, Erturk, and Yanmis (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 OC3 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).

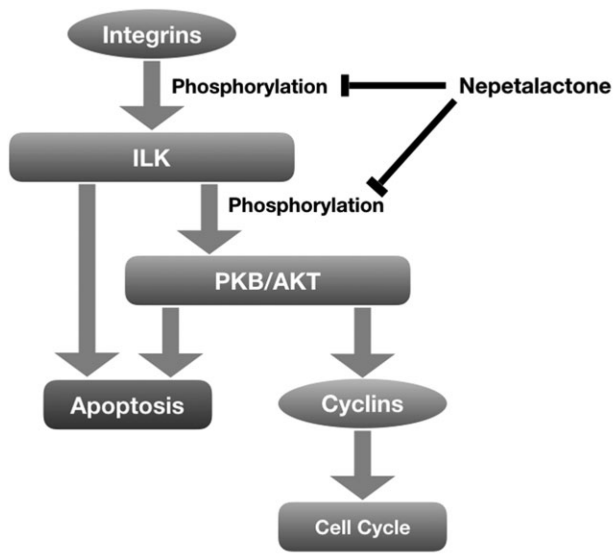

FIGURE 1 Schematic representation of nepetalactone effects on biological processes. ILK = integrin-linked kinase; PKB/AKT = protein kinase B/AKT

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, Undeger, 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 (teupolioside) 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, & Wrześniok, 2012). It plays an important role in melanocyte development and survival and is associated with tumorigenesis and progression of melanoma (Tayarani-Najaran, Akaberi, 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 IC_{50} 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 IC_{50} 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 IC_{50} value of 7.16 mg/ml and in the ferric reducing antioxidant power assay with the value of IC_{50} 0.82 mM Fe^{2+}/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 pentylenetetrazol-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 pentylenetetrazol 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, & Demyttenaere, 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 spasmolytic 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 ruderalis* 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 spasmolytic 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 teucrioside, verbascoside, and lamiuside A (teupolioside). 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 kurramanoic acid, being two new pentacyclic triterpenes, were isolated from the chloroform extract of *N. clarkei* 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 lactonique 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. LD_{50} 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, Fkih-Tetouani, & Idrissi, 2006).

Nepetalate B from *N. clarkei* exerted CNS-depressing activity. By performing formalin tests, J. Hussain et al. (2015) showed analgesic and anti-inflammatory effects. Pain inhibition was tested at nepetalate 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 ($p < .01$). Another anti-inflammatory compound is 1,8-cineole, which is the main compound of the essential oil of *Nepeta parmiriensis* (98%). Its cyclooxygenase 1 inhibitory effect (IC_{50}: 0.7 μg/ml) was described by Jeppesen, Soelberg, and Jäger (2012). 1,8-Cineole is present in a wide variety of plants, and its inhibition of prostaglandin synthesis has been described (Santos & Rao, 2000). Besides the anti-inflammatory effect, 1,8-cineole exerted antinociceptive effects by modulating CNS pain transmission (Martinez, González-Trujano, Pellicer, López-Muñoz, & Navarrete, 2009). Antinociceptive effects in rats were also found by Ali et al. in *N. pogonosperma*, attributed to the compounds epinepetalactone and 1,8-cineole. The effective components of the essential oil exert their antinociceptive effects by modulating CNS pain transmission. A specific opioid receptor subtype agonist activity of epinepetalactone (Aydin, Beis, Oztürk, & Baser, 1998) has been discussed as an additional principle for the significant analgesic activity (Ali, Javan, Sonboli, & Semnanian, 2012).

3.1.12 | Chronic morphine dependence

Pretreatment with ethanolic *N. menthoides* extract attenuated the development of chronic morphine dependence. Parvardeh, Moghimi, Eslami, and Masoudi (2016) showed that pretreatment of chronic morphine-treated mice with *N. menthoides* extract or methadone or a combination of both attenuated the development of morphine dependence (not expression) and potentiated morphine analgesia. This effect may be mediated by a reduction of brain nitric oxide and malondialdehyde overproduction. -Terpineol, a main constituent of *N. menthoides*, considerably attenuated morphine dependence through affecting nitric oxide production (Parvardeh et al., 2016). On the other hand, linalool, another main compound of this plant, inhibited *N*-methyl-D-aspartate receptors (Hosseinzadeh, Imenshahidi, Hosseini, & Razavi, 2012). Thus, *N. menthoides* may be a promising candidate plant against morphine addiction (Rahmati & Beik, 2017).

3.1.13 | Effects on sexual behavior

As a popular medicine, *N. cataria* has been a part of North American culture for quite a long time and has been used within the formulations of daily life things such as teas, dyes, and infusions. In male rats that were potently fed with chow rich in *N. cataria* leaves, the effect of *N. cataria* on sexual behavior and penile erection was assessed. The fact that *N. cataria* changes behaviors related to dopamine and that sexual behavior is closely linked with the dopaminergic system was indicated earlier; as a matter of fact, yawning was observed. So as to analyze the prospective motor and emotional interferences of the sexual performance, the general activity and the motor coordination were studied. Whereas male rats in the *N. cataria* group were fed with chow rich in *N. cataria* leaves (10%) for 4 hr, the rats of the control group were fed with regular chow. The sexual behavior, apomorphine-induced penile erection, and motor coordination were monitored 15 min later, following the end of the 4-hr period of *N. cataria* feeding. The general effect in the open field was evaluated 0, 15, 30, and 60 min after the treatment, and it was seen that *N. cataria* treatment increased the penile erection of male rats. As it affects dopaminergic systems, *N. cataria* enhances penile erection and improves the sexual behavior of male rats to a degree (Bernardi, Kirsten, Lago, Giovani, & Massoco, 2011).

The studies have demonstrated that 24 *Nepeta* species were investigated for their in vitro and in vivo bioactivities. Among them, 10 *Nepeta* species, namely, *N. cataria*, *N. elliptica*, *N. rtanjensis*, *N. sibirica*, *N. nervosa*, *N. leucophylla*, *N. ciliaris*, *N. clarkei*, *N. ucrainica* ssp. *kopetdaghensis*, and *N. sintenisii*, were demonstrated to have an antimicrobial effect against different strains (Kumar, Mathela, Tewari, & Bisht, 2014; Kumar, Mathela, Tewari, & Singh, 2014; Nestorović et al., 2010; Nostro et al., 2001; Shakeri et al., 2014, 2016). The abovementioned studies also revealed that nepetalactones from both *N. cataria* and *N. faassenii* exerted repellent and insecticide activities (Birkett et al., 2011; Ghaninia et al., 2008; Pavela, 2005). Only one *Nepeta* species, namely, *N. menthoides*, 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. *kopetdaghensis*, 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 *Melissa 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

TABLE 1 In vitro and in vivo bioactivity studies on *Nepeta* genus

Activity	*Nepeta* species	References
Antimicrobial	*Nepeta cataria* *Nepeta elliptica* *Nepeta rtanjensis* *Nepeta sibirica* *Nepeta nervosa* *Nepeta leucophylla* *Nepeta ciliaris* *Nepeta clarkei* *Nepeta ucrainica* ssp. *kopetdaghensis* *Nepeta sintenisii*	Nostro et al. (2001) Kumar, Mathela, Tewari, and Singh (2014) Nestorović et al. (2010) Kumar, Mathela, Tewari, and Bisht (2014) Shakeri et al. (2014) Shakeri et al. (2016)
Repellent and insecticide	*N. cataria* *Nepeta faassenii*	Pavela (2005) and Birkett et al. (2011) Ghaninia et al. (2008)
Larvicidal	*Nepeta menthoides*	Mahnaz et al. (2012)
Cytotoxic	*N. sintenisii* *N. ucrainica* ssp. *kopetdaghensis* *Nepeta binaloudensis*	Shakeri et al. (2014) Afshar et al. (2017)
Genotoxic	*Nepeta meyeri* *Nepeta nuda*	Kekeç et al. (2013) Bozari et al. (2013)
Apoptotic	*Nepeta gloeocephala*	Dehghany Ashkezary et al. (2017)
Immunomodulatory	*N. ucrainica* *N. cataria*	Akbay et al. (2002) Prescott et al. (2011)
Antimelanogenesis	*Nepeta binaludensis*	Otreba et al. (2012) and Tayarani-Najaran et al. (2016)
Antioxidant	*Nepeta flavida* *N. sintenisii*	Tepe et al. (2007) Shakeri et al. (2016)
Anticonvulsant and myorelaxant	*Nepeta sibthorpii* *N. cataria* *Nepeta ruderalis*	Galati et al. (2004) Gilani et al. (2009) Mahmood et al. (2017)
Analgesic and anti-inflammatory	*N. cataria* *N. clarkei* *Nepeta atlantica* *Nepeta tuberosa* ssp. *reticulata* *Nepeta parmiriensis* *Nepeta pogonosperma*	Prescott et al. (2011) J. Hussain, Rehman, Hussain, Al-Harrasi, et al. (2012) and Ali et al. (2012) Bouidida et al. (2006) Jeppesen et al. (2012) Ali et al. (2012)
Chronic morphine dependence	*N. menthoides*	Rahmati & Beik (2017)
Effects on sexual behavior	*N. cataria*	Bernardi et al. (2011)

TABLE 2 Clinical studies on *Nepeta* genus

Type of the study	Disease	No. of participants	Plant species	Main outcome	References
A randomized controlled trial	Premenstrual syndrome	93	*Nepeta menthoides* and *Melissa officinalis*	Premenstrual syndrome symptoms significantly decreased	Mirghafourvand, Malakouti, Charandabi, Khalili, and Homayi (2016)
A double-blind randomized controlled trial	Depression	72	*N. menthoides*	Changes in Beck Depression Inventory scores were significantly higher	Kolouri et al. (2016)

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 (β-sitosterol, stigmasterol, and stigmasterol 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 monoterpenes, diterpenes, triterpenes, and sesquiterpenes (Baser, Demirci, Kirimer, & Kurkcuoglu, 2000; Formisano et al., 2011; Sattar et al., 1995; Topçu, Kökdil, & Yalçın, 2000). Nepetalactones (Figure 2) are the most frequent constituents determined among monoterpenes, along with dehydronepetalactones, 1,8-cineole, α-terpineol, α-citral, geraniol, and their derivatives (Clark, Hamilton, Chapman, Rhodes, & Hallahan, 1997; Formisano et al., 2011; Inouye, 1991). 4aα,7α,7aα-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 7*S* stereochemistry (Clark et al., 1997). The identified and characterized nepetalactones (Figure 2) in the *Nepeta* genus are 4aα,7α,7aα-nepetalactone; 4aα,7α,7aβ-nepetalactone; 4aβ,7α,7aβ-nepetalactone; 4aβ,7α,7aα-nepetalactone; 4aα,7β,7aβ-nepetalactone; and 4aα,7β,7aα-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 α-dihydronepetalactone, β-dihydronepetalactone, 5,9-dehydronepetalactone, nepetalic acid, iridomyrmecin, and isoiridomyrmecin (Eom, Yang, & Weston, 2006; Heuskin et al., 2009; Javidnia, Miri, Safavi, Azarpira, & Shafiee, 2002; Kalpoutzakis, Aligiannis, Mentis, Mitaku, & Charvala, 2001; Moghaddam & Hosseini, 1996; Suschke, Sporer, Schneele, Geiss, & Reichling, 2007). Other monoterpenes identified in the *Nepeta* genus are iridoid glucosides (Figure 3), such as 1,5,9-epideoxyloganic acid, nepetariaside, nepetaside, velpetin, ixoroside, ajugol, aucubin, nepetanudosides A–D, monoterpenic γ-lactones, cyclopentanemonoterpene enol acetates (such as iridodial β-monoenol acetate, dihydroiridodial diacetate, and iridodial dienol diacetate), monoterpene alkaloid (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 teydea* Webb & Berthel. and *N. tuberosa* ssp. *reticulate*, whereas pimarane- and isopimarane-type diterpenes are molecules isolated from *Nepeta prattii* H. Lév., *Nepeta septemcrenata* Ehrenb. ex Benth., *N. tuberosa* ssp. *reticulate*, and *Nepeta parnassica* Heldr. & Sart. (Fraga, Hernàndez, Mestres, & Arteaga, 1998; Fraga, Mestres, Dìaz, & Arteaga, 1994; Hou, Tu, & Li, 2002; Hussein,

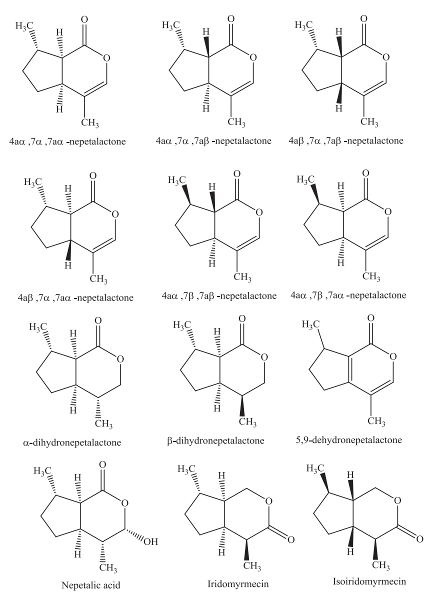

FIGURE 2 Chemical structure of several nepetalactones identified in *Nepeta* genus

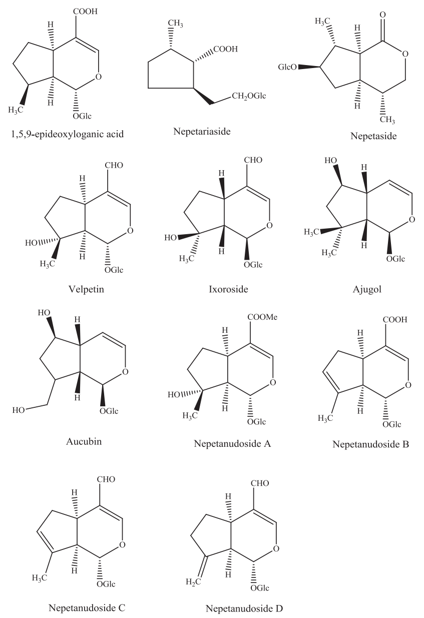

FIGURE 3 Chemical structure of several iridoid glucosides identified in *Nepeta* genus

Rodrìguez, 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-stigmast-7-ene-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, Rodrìguez, & 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 cilicica* Boiss. ex Benth. from Lebanon, mainly sesquiterpene hydrocarbons and oxygenated sesquiterpenes (Formisano, Rigano, Arnold, Piozzi, & Senatore, 2013).

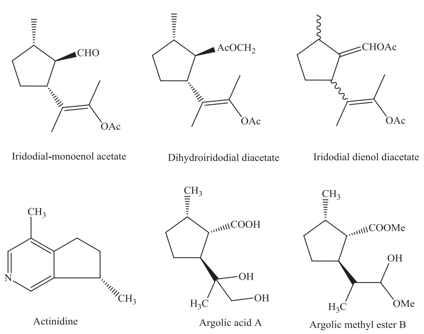

FIGURE 4 Chemical structure of several cyclopentanemonoterpene enol acetates, monoterpene alkaloid, and cyclopentanemonoterpenes identified in *Nepeta* genus

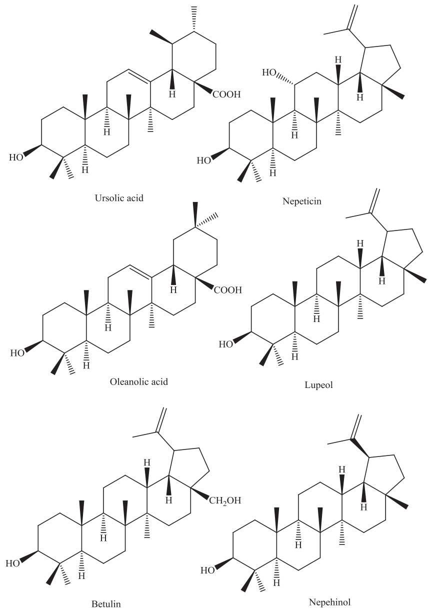

FIGURE 5 Chemical structure of several triterpenes identified in *Nepeta* genus

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, Ivancheva, & Tomás-Lorente, 1992). Moreover, *Nepeta* flavones (such as cirsimaritin, 8-hydroxycirsimaritin, salvigenin, 8-hydroxysalvigenin, and 8-hydroxycirsiliol) are typically used as a characteristic chemotaxonomic feature of the genus

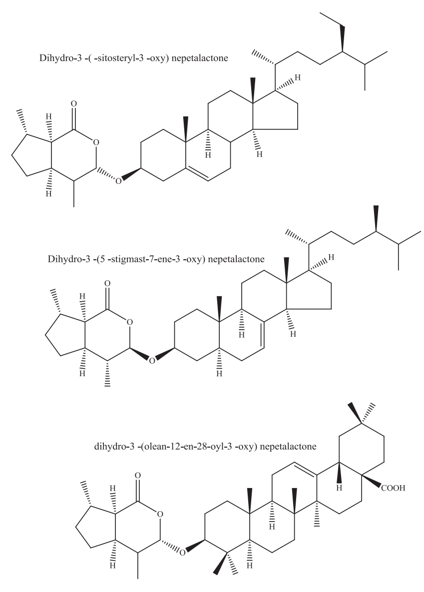

FIGURE 6 Chemical structure of several triterpene nepetalic acids identified in *Nepeta* genus

(Figure 7). 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 genkwanin (Jamzad et al., 2003). Other frequently identified flavones (Figure 8) are, for instance, apigenin, luteolin, salvigenin, 8-hydroxysalvigenin, xanthomicrol, ladanein, cirsiliol, scutellarin A, and nephrocizine, whereas luteolin 7-*O*-β-D-glucuronide, luteolin 7-*O*-glucurono-(1→6)-glucoside, nornepetin, nepetin, nepetin 7-glucuronide, nepetrin, 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,

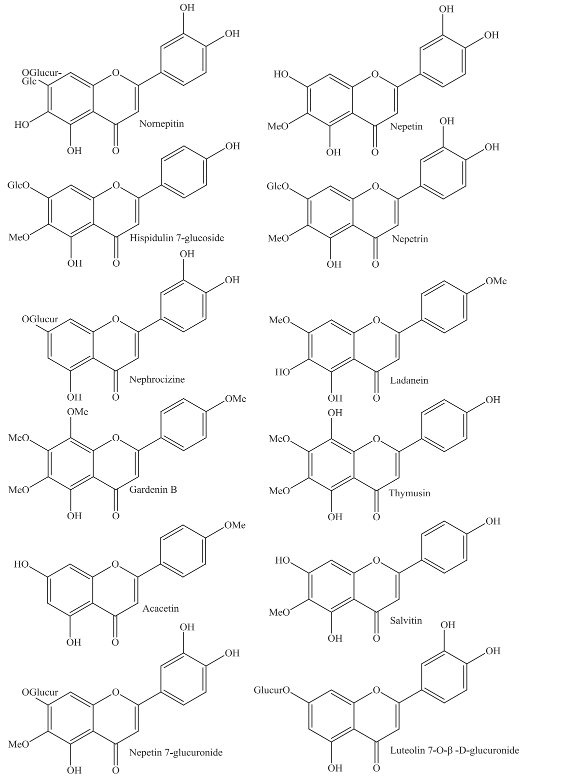

FIGURE 8 Chemical structure of other flavones identified in *Nepeta* genus. O-Glucur = *O*-glucuronide; O-Me = *O*-methoxy group; O-Rha = *O*-rhamnoside; OGlc= *O*-glucoside

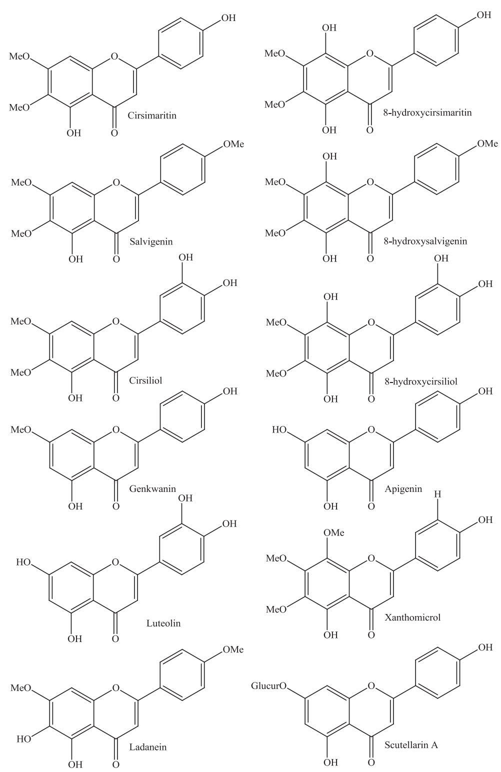

FIGURE 7 Chemical structure of typical flavones used as a characteristic chemotaxonomic feature of the *Nepeta* genus. O-Glucur = *O*-glucuronide; O-Me = *O*-methoxy group; OGlc = *O*-glucoside

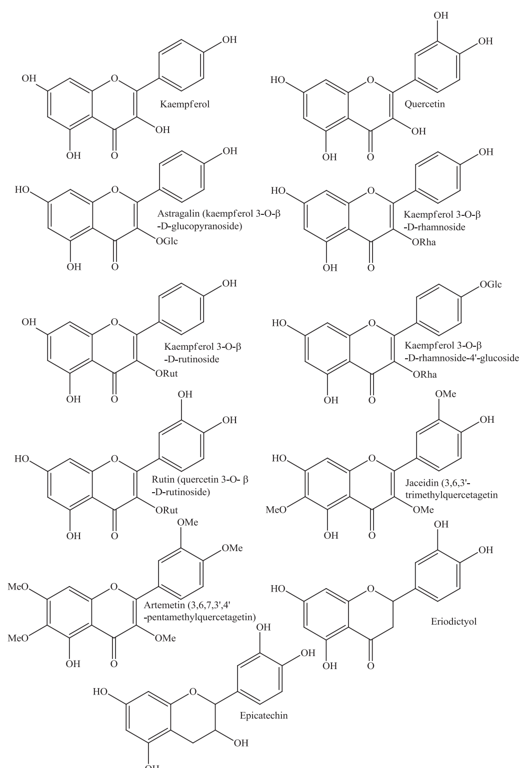

FIGURE 9 Chemical structure of several flavonols, flavanols, and flavanones identified in *Nepeta* genus. O-Me = *O*-methoxy group; O-Rha = *O*-rhamnoside; OGlc = *O*-glucoside

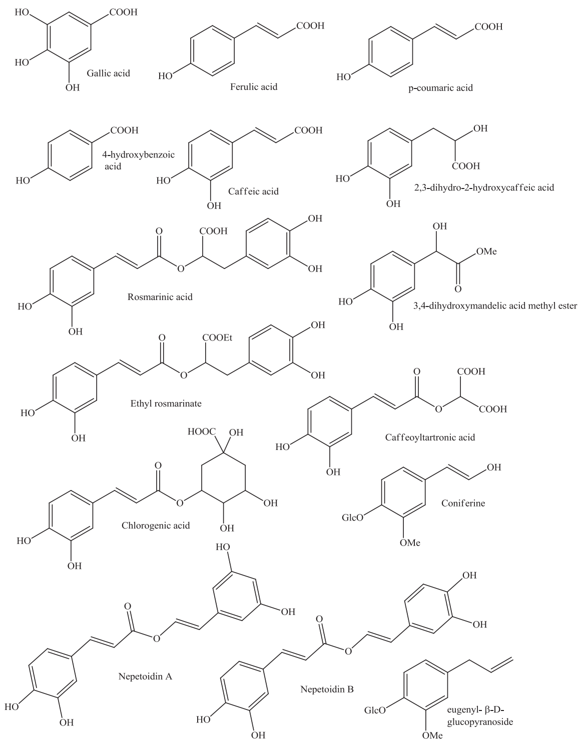

FIGURE 10 Chemical structure of several phenols identified in *Nepeta* genus. O-Me = *O*-methoxy group; OGlc = *O*-glucoside

rosmarinic acid, 2,3-dihydro-2-hydroxycaffeic acid, 3,4-dihydroxymandelic acid methyl ester, ethyl rosmarinate, caffeoyltartronic acid, chlorogenic acid, coniferin, eugenyl β-D-glucopyranoside, eugenyl-*O*-β-apiofuranosyl-(1→6)-*O*-β-glucopyranoside, lariciresinol 4′-*O*-β-D-glucopyranoside, nepetoidin A, and nepetoidin B. A higher number of phenol derivatives have been identified in *N. cataria* and *N. prattii* (Formisano et al., 2011; Grayer et al., 2003).

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, insecticide, larvicidal, cytotoxic, anticarcinogenic, antioxidant, anticonvulsant, myorelaxant, analgesic, 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.

ORCID

Ipek Süntar http://orcid.org/0000-0003-4201-1325
Davide Barreca http://orcid.org/0000-0002-1463-4069

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