J Plant Biotechnol (2022) 49:3-14
DOI:https://doi.org/10.5010/JPB.2022.49.1.003

ISSN 1229-2818 (Print)
ISSN 2384-1397 (Online)

Review

Botanical features and ethnopharmacological potential of *Leonotis nepetifolia* (L.) R. Br: a review

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Received: 6 November 2021 / Revised: 7 January 2022 / Accepted: 7 January 2022

Abstract *Leonotis nepetifolia* (L.) R. Br, commonly called dagga, klip dagga, or lion's ear, has been used to effectively treat various diseases and other health problems for a long time because of its antimicrobial, anti-inflammatory, antioxidant, and analgesic activities. Several studies have attributed these biological activities to *L. nepetifolia's* constituent secondary metabolites, such as alkaloids, phenolics, flavonoids, tannins, steroids, glycosides, coumarins, anthocyanins, and saponins. This review aims to examine the evidence-based ethnopharmacological uses of *L. nepetifolia* in the treatment of bronchial asthma, diarrhea, skin diseases, malaria, burns, cancer, diabetes mellitus, and rheumatism. However, although *L. nepetifolia* has great potential to treat these diseases, further isolation and identification of its therapeutic phytochemical constituents are required. In addition, the performance of its extracts and phytochemicals should be thoroughly tested in preclinical and clinical trials in order to ascertain their safety and efficacy, which will prove valuable in developing new medicines.

Keywords ethnopharmacological, *Leonotis nepetifolia*, klip dagga, lion's ear, phytochemicals, secondary metabolites, biological activity

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Introduction

Medicinal plants are major components of indigenous medical systems worldwide. For several years, medicinal plants have been used to treat diseases (da Silva Almeida et al. 2018). As reported by the World Health Organization (WHO), 80% of people in the world use herbal medicines in the management of their primary healthcare needs (Bhardwaj et al. 2018; Majeed 2017). In addition to their use in traditional medicine, medicinal plants are sources of new drugs; indeed, more than 25% of prescribed drugs in developed countries are wild plant species derived (Chen et al. 2016). Furthermore, approximately 70%-80% of the people in the developing world rely on conventional plant-derived remedies (Rankoana 2016). Given the growing demand for herbal drugs, natural health products, and plant secondary metabolites, the use of medicinal plants is rapidly increasing globally (Chen et al. 2016).

Leonotis nepetifolia (L.) R. Br (family Lamiaceae, genus *Leonotis*) (Damasceno et al. 2019), also called 'dagga', 'klip dagga', or 'lion's ear', is a plant species native to South Africa with significant medicinal value (Dhawan et al. 2013). The plant has become widespread in many tropical regions around the world (Pushpan and Karra 2016). In many traditional health practices, *L. nepetifolia* is used to treat bronchial asthma, diarrhea, fever, influenza, malaria, cough, epilepsy, womb prolapse, skin ailments, and rheumatism (da Silva Almeida et al. 2018; Oliveira et al. 2015). The therapeutic power of *L. nepetifolia* has been attributed to its phytochemical contents, including alkaloids, tannins, saponins, flavonoids, steroids, and terpenoids (Li et al. 2012; Ngoci et al. 2013; Powder-George 2018; Sobolewska et al. 2012). Several studies have confirmed that these phytochemicals protect humans against disease-causing organisms (Njeru et al. 2013). The phytochemical compounds present in the plant are associated with a variety of bioactivities, such as antimicrobial, immunomodulatory, anti-cancer, antioxidant,

Stage 1: Data Search	
Key words, screening, and selection	*"Leonotis nepetifolia* (L.) R. Br" OR "dagga - klip dagga" OR "lion's ear") AND ("botany" OR "distribution" OR "phytochemicals" OR "phytochemical compounds" OR "phytochemical contents" OR "ethnopharmacological uses" OR "ethno-medicinal uses" OR "disease treatment" OR "safety and toxicity" OR "traditional medicine" OR "medicine"

↓

Stage 2: Data Analysis
Comparison and verification of data obtained on the botanical features, distribution, traditional medicinal uses, and ethnopharmacological potential of *L. nepetifolia*

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Stage 3: Summary
Botanical features, distribution, traditional medicinal uses, parts used, mode of preparation, and ethnopharmacological potential of *L. nepetifolia*

Fig. 1 Summary of the review methodology followed in this study

analgesic, and anti-inflammatory (Ngocu et al. 2012; Oliveira et al. 2015).

However, the literature on evidence-based ethnopharmacological uses of *L. nepetifolia* is currently limited and scattered. This review aimed to examine evidence-based ethnopharmacological uses of *L. nepetifolia* in the treatment of bronchial asthma, diarrhea, diabetes, cancer, malaria, skin diseases, burns, and rheumatism, to provide consolidated medicinal information about the plant and to facilitate further research and its medicinal applications.

Materials and Methods

The literature was searched as in Komakech et al. (2017) after modifications to find information about *L. nepetifolia* from peer-reviewed articles published in scientific journals (**Figure 1**) with a focus on botany, distribution, and ethnopharmacological and traditional medicinal uses of *L. nepetifolia*. Google Scholar, PubMed, Scopus, AMED, and Science Direct databases were searched in order to acquire relevant and reliable data. The key search terms used included ("*Leonotis nepetifolia* (L.) R. Br" OR "Dagga - Klip dagga" OR "Lion's ear") AND ("Botany" OR "Distribution" OR "Phytochemicals" OR "Phytochemical compounds" OR "Phytochemical contents" OR "Ethnopharmacological uses" OR "Ethno-medicinal uses" OR "Disease treatment" OR "Safety and Toxicity" OR "Traditional medicine" OR "Medicine"). Search results were verified for accuracy and reliability, then summarized, analyzed, and compared; finally, appropriate conclusions were drawn.

Botany and Distribution of *L. nepetifolia*

L. nepetifolia is an erect annual herb that grows 2.5 m high, occasionally reaching up to 3 m (**Figure 2a**). The stem is unbranched at the base and loosely branched towards the apex with strongly angled stems having appressed retrose hairs that are longer at the nodes (**Figure 2b**) (Dhawan et al. 2013). The leaves are smooth with a toothed margin; they are large, ovate, lobed, acute, and winged in the upper part (**Figure 2d and 2e**). The inflorescence comprises axillary dense, globose multi-flowered verticillasters (Tiwari 2019). Flowers are orange and borne in spiny clusters. Floral leaves are lanceolate and deflexed; bracts are linear, highly spinous-pointed, and deflexed (**Figure 2c**). Calyxes are tubular, incurved, and hairy with 8-9 sharp pointed teeth. The plant typically has a bilabiate, orange-scarlet and hairy corolla with the upper lip densely woody, and the lower lip made up of three lobes. Stamens are four and didynamous; the ovary has four lobes and the fruit contains four ovoid nutlets (Tiwari 2019).

Genus *Leonotis* consists of 30 species found mostly in the tropics. Among them, *L. nepetifolia* is the only species distributed out of Africa (Iwarsson and Harvey 2003). Indeed, the species has a pantropical global distribution, and can be found in Africa, Southeast Asia, Australia, the Pacific islands, Southern USA, Central and South America, the Caribbean islands, and Mexico (Pushpan and Karra 2016).

Ethnopharmacological Uses of *L. nepetifolia*

In traditional medicine, *L. nepetifolia* is used to treat many diseases including bronchial asthma, diarrhea, fever, influ

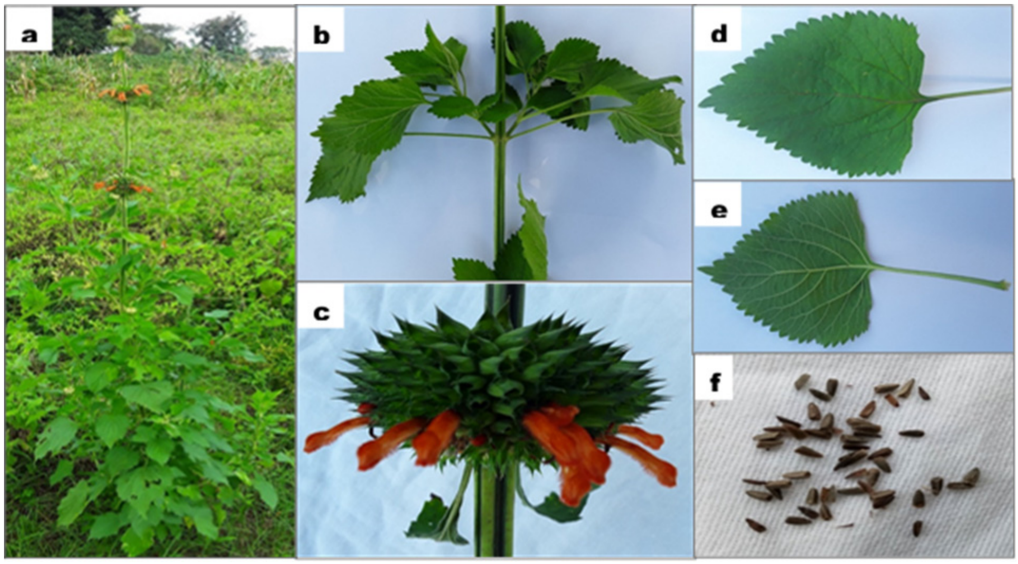

Fig. 2 Botanical features of *L. nepetifolia*: (a) plant growing in the wild, (b) stem characteristics and leaf arrangement, (c) inflorescence, (d) features of the upper leaf surface, (e) features of the lower leaf surface, and (f) seeds

enza, malaria, cough, womb prolapse, epilepsy, burns, skin ailments, and rheumatism (**Table 1**). Constituent phytochemicals such as tannins, alkaloids, flavonoids, saponins, steroids, phenolics, glycosides, anthocyanins, and coumarins have been implicated to account for the usefulness of the plant to treat the abovementioned diseases (Ngoci et al. 2013) (**Table 2**). Importantly, the antimicrobial, immunomodulatory, anti-cancer, antioxidant, analgesic, and anti-inflammatory activities of these phytochemicals have been confirmed both *in vitro* and *in vivo* (Ngocu et al. 2012; Oliveira et al. 2015), as discussed below.

Ethnopharmacological Uses of *L. nepetifolia* for Treatment of Malaria

Malaria is among the top causes of morbidity and mortality in the world. Approximately 219 million cases of malaria and 435,000 associated deaths were registered in 2017 (Ghosh and Rahi 2019). Several ethnomedicinal studies have reported that the whole *L. nepetifolia* plant is widely used to treat malaria in many communities worldwide (Adia et al. 2014; Anywar et al. 2014; Ferreira et al. 2015; Wagh 2016). In this case, either the decoction, leaf tea, or leaf infusion, is given for treatment (Anywar et al. 2014; Ferreira et al. 2015; Wagh 2016). The effective use of *L. nepetifolia* in the traditional treatment of malaria is linked to the presence of secondary metabolites including tannins, alkaloids, flavonoids, glycosides, and saponins, which are the active constituents responsible for the antimalarial activity (Musila et al. 2013). *In vitro* and *in vivo* studies on *Plasmodium falciparum* 3D7 strain and on mice infected with *Plasmodium berghei* revealed that plant extracts with these secondary metabolites showed strong antiplasmodial activity (Abdillah et al. 2015). Alkaloids exhibit antimalarial effects by blocking protein synthesis in malarial parasites (Abdulelah and Zainal-Abidin 2007). In turn, steroids and saponins have been confirmed to be damaging to many pathogenic protozoans, including *P. falciparum, P. ovale,* and *P. vivax* (Delmas et al. 2000). Additionally, an *in vitro* antiplasmodial study showed that tannins have antiplasmodial activity (Adia et al. 2014). Further, another study showed that methanol and ethyl acetate extracts of *L. nepetifolia* leaf had moderate antiplasmodial activity with 27% inhibition of *P. falciparum* and low cytotoxic effects on the MRC5 cell line (Lacroix et al. 2011). These findings vindicate the use of *L. nepetifolia* in traditional medicine for the treatment of malaria.

Ethnopharmacological Uses of *L. nepetifolia* for Treatment of Diarrhea

Diarrhea is very common in countries of the developing world, and in Southeast Asia and Africa alone, it causes 8.5% and 7.7%, respectively, of all deaths (Dairo et al. 2017). In fact, diarrheal diseases rank second on the list of major causes of death among children under the age of five, worldwide (Fenta et al. 2020). To manage the disease, *L. nepetifolia* has traditionally been used in the treatment of diarrhea across Africa, where *L. nepetifolia* powdered flowers or leaf ashes are added to porridge or tea, and in some cases decoction of *L. nepetifolia* is consumed (Kingo and Maregesi 2020; Omwenga et al. 2015; Tugume et al. 2019). In an *in vitro* test, *L. nepetifolia* leaf, flower, and stem methanolic extracts

Table 1 Diseases treated using *L. nepetifolia*, plant parts used, and modes of administration

Diseases treated	Plant part (s) used	Mode of administration	References
Malaria	Whole plant or leaves	Decoction; infusion; leaf tea	Adia et al. (2014), Anywar et al. (2014), Ferreira et al. (2015), Kumar and Dash (2012), Wagh (2016)
Diarrhea	Flowers and leaves	Decoction; powder taken in porridge or tea	Kingo and Maregesi (2020), Omwenga et al. (2015), Tugume et al. (2019)
Asthma	Stem, leaves, and flowers	Decoction; powder of the flower taken in porridge or tea	Clement et al. (2005), Kingo and Maregesi (2020), Maregesi et al. (2007), Olanda et al. (2020)
Skin infections	Leaves, seeds, inflorescence, root, and whole plant	Paste applied topically	Anbarashan et al. (2011), Kalaichelvi et al. (2017), Li et al. (2012), Maurya and Seth (2014), Nadu (2019), Prashantkumar and Vidyasagar (2008), Rao et al. (2006), Sharma et al. (2014), Singh and Shahi (2017), Van Andel and Van't Klooster (2007)
Wounds, burns, and scalds	Flowers and leaves	Powder or ash applied topically	Kalaichelvi et al. (2017), Krishna et al. (2014), Maregesi et al. (2007), Mudaiya et al. (2016), Pingale et al. (2013), Rao et al. (2006)
Rheumatism	Leaves, whole plant, flowers, and seeds	Infusion; decoction; paste applied locally	Kalaichelvi et al. (2017), Li et al. (2012), Mallick and Acharya (2013), Nayak et al. (2004), Pandey and Tripathi (2010), Pereira et al. (2012), Pingale et al. (2013), Pushpan et al. (2013), Reddy et al. (2019), Singh and Shahi (2017), Ssegawa and Kasenene (2007), Tiwari et al. (2018)
Cancer	Whole plant or leaves	Decoction	Kalaichelvi et al. (2017), Kingo and Maregesi (2020), Nadu (2019)
Diabetes	Whole plant or leaves	Decoction	Kumar and Jnanesha (2017), Maobe (2014), Pingale et al. (2013)
Fever	Whole plant or leaves	Brewed as a tea	Kalaichelvi et al. (2017), Li et al. (2012), Veerabadran et al. (2013)
Cough	Leaves and inflorescence	Brewed as a tea; boiled to a viscous paste and orally administered	Li et al. (2012), Pandey and Tripathi (2010), Veerabadran et al. (2013)
Uterine prolapse	Leaves	Brewed as a tea	Veerabadran et al. (2013)
Menstrual pains and period dysregulation	Whole plant	—[a]	Jain and Srivastava (2005), Lans (2007)
Jaundice	Stem, leaves, and flowers	Infusion	Jain and Srivastava (2005), Pingale et al. (2013)
Parasitic worm infections	Leaves	Decoction	Jain and Srivastava (2005)
Convulsions	Leaves	Boiled in water and drunk; decoction	Maregesi et al. (2007)
Postnatal breast pain	Inflorescence	Ash mixed with mustard oil and applied topically	Tiwari et al. (2018)
Pneumonia	Whole plant	—[a]	EL-Kamali (2009), Nadu (2019)
Syphilis	Whole plant	—[a]	Nadu (2019)
Labor pains	Leaves	Chewed; boiled in water and drunk	Catherine et al. (2020)
Paralysis	Whole plant	Ash applied topically	Mallick and Acharya (2013), Nayak et al. (2004), Singh and Shahi (2017)
Hepatitis	Whole plant	Decoction	EL-Kamali (2009), Mukazayire et al. (2011), Pingale et al. (2013)
Hernia	Leaves	—[a]	Pingale et al. (2013)

[a]Not specified.
Source: adapted from Kang et al. (2013).

showed antibacterial activity against *Shigella dysenteriae, Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa, Micrococcus luteus, Shigella flexneri, Vibrio cholerae,* and *Staphylococcus aureus*, which are some of the main bacterial pathogens that cause diarrhea (Narayan 2012). The study thus demonstrated the presence of broad-spectrum antibacterial

Table 2 Some phytochemical compounds identified in *L. nepetifolia* and their biological activities

Phytochemical compounds	Plant part	Biological activities	References
Leonotinin	Leaves	Anti-inflammatory, hepatoprotective, and antihypercholestrolemic activity	Parra-Delgado et al. (2004)
Stigmasterol	Flower	Anti-inflammatory, hepatoprotective, and antihypercholestrolemic activity	Parra-Delgado et al. (2004)
Nepetaefuran and leonotinin	Aerial part	Anti-inflammatory and antitumor activity	Ueda et al. (2015)
Methoxy-nepetaefolin hydroxy-dialactone nepetaefolinol, dehydrated nepetaefolinol, and nepetefolin	Aerial part	Antioxidant activity	Govindasamy et al. (2002), Tidke et al. (2021)
Phenylethanoid glycosides, acteoside, martynoside, lavanduflioside, 10-o-(trans-3,4-dimethoxycinnamoyl) geniposidic acid, geniposidic acid, mussaenoside, and ixoside	Stem	Antioxidant activity	Takeda et al. (1999)
Loganin and loganic acid	Stem	α-Glucosidase inhibition	Tidke et al. (2021)
Cirsiliol	Leaves and root	Antileishmanial and antimicrobial activity	de Oliveira et al. (2019), Tidke et al. (2021)
Apigenin	Leaves, stem, and root	Antiviral, antileishmanial, and antimicrobial activity	de Oliveira et al. (2019)
Luteolin	Leaves and stem	Antileishmanial and antimicrobial activity	de Oliveira et al. (2019)

compounds in the leaves, flowers, and stems of the species. Inhibition of bacterial growth by plant extracts is attributed to alkaloids, saponins, tannins, flavonoids, sterols, and terpenoids present in different plant parts (Boominathan et al. 2005; Otshudi et al. 2000). Tannic acids and tannins reportedly denature proteins, which in turn form protein tannate, a substance that makes intestinal mucosa resistant, thus reducing secretions and subsequently reducing diarrhea (Narayan 2012). Ethanolic leaf extracts of *L. nepetifolia* showed diarrhea inhibitory activity at doses of 225, 450, and 900 mg/kg in Wistar albino rats (Gakunga et al. 2013). In this study, the extract produced a significant ($p < 0.05$) reduction in the number of wet fecal pellets and a greatly reduced diarrheal tendency (Gakunga et al. 2013). Further, Gakunga et al. (2013) found that the ethanolic leaf extract of *L. nepetifolia* had an inhibitory effect on gastrointestinal transit by reducing the mean distance traveled by a charcoal meal, which has a propulsive effect; however, *L. nepetifolia* extracts inhibited this effect in the intestinal tract by significantly reducing the mean distance traveled upon administration of 225 mg/kg ($p = 0.01$). At a dose of 900 mg/kg, gastrointestinal transit was significantly ($p < 0.05$) inhibited relative to that in the positive control, atropine sulfate (Gakunga et al. 2013). It should be noted that fluid accumulation and altered motility of the gastrointestinal tract cause diarrhea; therefore, numerous antidiarrheal medicines work by inhibiting these processes. Indeed, extracts of *L. nepetifolia* caused a similar inhibition of diarrhea to that caused by the standard drug loperamide (3 mg/kg) in terms of the number of wet fecal droppings (Gakunga et al. 2013). Therefore, these findings support the traditional use of *L. nepetifolia* for treatment of diarrhea.

Ethnopharmacological Uses of *L. nepetifolia* for Treatment of Bronchial Asthma

Asthma is currently an umbrella diagnosis for a number of distinct diseases and varying phenotypes manifesting symptoms of shortness of breath, cough, wheezing, and chest tightness associated with variable airflow obstruction (Kuruvilla et al. 2019; Reddel et al. 2015). Technically, asthma is an inflammatory disorder of epithelial surfaces that typically involves allergen-driven T-helper 2 (Th2) lymphocyte polarization with coordinated production of interleukin (IL)-3, IL-13, IL-4, IL-9, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF), which are encoded in a gene cluster on chromosome 5q31−34 (Holgate and Polosa 2006). Asthma is a major chronic disease worldwide, affecting more than 334 million people (Enilari and Sinha 2019) and accounting for approximately one in every 250 deaths (Tany and Saha 2017). The use of traditional medicines in the management of asthma is increasing markedly, and *L. nepetifolia* is among the plants said to have a high potential for treatment of the disease (Akah et al. 2003). Thus, stem, leaves, and flowers of *L. nepetifolia* are used in the treatment of asthma; a decoction is swallowed, or powdered flowers are added to porridge or tea and consumed (Kingo and Maregesi 2020; Maregesi et al. 2007; Olanda et al. 2020). Utilization of *L. nepetifolia* to treat and manage asthma is supported by the fact that flavonoids present in various parts of *L. nepetifolia* have been shown to control some specific allergic reactions in asthma and other conditions (Maregesi et al. 2007). The mechanisms of action of *L. nepetifolia* against asthma include enhancing intracellular glutathione (GSH) content, reducing reactive oxygen species (ROS) levels, and preventing Ca^{2+} influx in cases of high ROS levels, and, consequently, offering protection against oxidative damage (Athwal et al. 2015; Garcia et al. 2005; Lambrechts et al. 2018). Further, Lall et al. (2019) reported that *L. nepetifolia* was among the plants that exhibited a level of antioxidant activity similar to that of the positive control, L-ascorbic acid. Generally, the antioxidant potential of plants, including *L. nepetifolia*, is attributed to the antioxidative phenolics found in the plant tissues (Lall et al. 2019). Sobolewska et al. (2012) in their study reported that methanolic and acetone extracts of *L. nepetifolia* contained moderate levels of polyphenols. Thus, the oxidative and anti-inflammatory properties of secondary metabolites in *L. nepetifolia* provide support for the use of *L. nepetifolia* for management and treatment of bronchial asthma.

Ethnopharmacological Uses of *L. nepetifolia* for Treatment of Skin Diseases

Skin diseases including ringworm, leprosy, itching, wounds, dermatitis, allergy, swelling, eczema, psoriasis, and scabies, are caused by various microorganisms or harsh environments (Suresh et al. 2012); further, they account for approximately 34% of all occupational diseases (Abbasi et al. 2010). Infectious dermatological diseases are highly prevalent in tropical countries where the majority of the population lives in developing areas characterized by poor sanitation and unhygienic food habits (Sharma et al. 2014). Morbidity due to skin diseases causes emotional and psychological stress to patients and their families, although mortality is very low (Basra and Shahrukh 2009). Numerous medicinal plants have been traditionally used to treat skin diseases, *L. nepetifolia* among them (Prashantkumar and Vidyasagar 2008). Ethnobotanical surveys conducted around the world revealed that *L. nepetifolia* has been used for a long time to treat skin diseases, such as eczema, head sores, urticaria, ringworm, itching, burns, scalds, and wounds (Anbarashan et al. 2011; Nadu 2019; Singh and Shahi 2017). Treatment preparations include leaf paste, seed paste (in some places mixed with "*Koronji*" oil), inflorescence paste (sometimes mixed with groundnut oil), root paste, whole plant paste, powdered dry leaves, and flower ashes. During treatment, the preparation is applied topically (Kalaichelvi et al. 2017; Nadu 2019; Singh and Shahi 2017).

The extensive use of *L. nepetifolia* by different societies in the treatment of skin diseases is likely due to its effectiveness (Maroyi 2013). Previous studies have reported antifungal and antibacterial activities of plant extracts (Al-Reza et al. 2010; Bajpai 2012; Ngoci et al. 2013). Thus, for example, in an *in vivo* study by Ochola et al. (2015), the extract of *L. nepetifolia* demonstrated antifungal effects by inhibiting the growth of *P. exigua* mycelia. Additionally, as noted earlier, an *in vitro* test of flower, leaf, and stem methanolic extracts of *L. nepetifolia* showed antibacterial properties against *Staphylococcus aureus*, a pathogen that causes eczema (Narayan 2012). In general, plants with a wide range of secondary metabolites, such as tannins, flavonoids, alkaloids, terpenoids, and polyphenols, possess superior antimicrobial properties (Maiyo et al. 2010) and, indeed *L. nepetifolia* is rich in these phytochemicals. In an *in vivo* experiment, *L. nepetifolia* ethanol-treated wounds healed significantly faster than the negative control, with an increased rate of contraction and a reduced epithelialization period (Nithya and Anand 2021). Plants with high anti-inflammatory and wound healing potential, and their products, contain terpenes and flavonoids (Nithya and Anand 2021). The strong wound-healing effects of medicinal plants are attributed to their constituent triterpenoids (Nayak et al. 2006). Flavonoids and terpenoids enhance wound healing mainly through their antimicrobial activities (Nithya and Anand 2021). Therefore, the wound-healing activities observed in the preclinical trial may be due to the flavonoids and terpenoids present in *L. nepetifolia.* Generally, these results support the widespread use of *L. nepetifolia* for treatment of skin diseases.

Ethnopharmacological Uses of *L. nepetifolia* for Treatment of Rheumatism

Musculoskeletal disorders, such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, systemic lupus erythematosus, gout, and intervertebral disc disease, among others, are generally categorized as "rheumatism." The diagnosis and treatment of these conditions make up approximately 10% of clinical practice (Pushpan et al. 2013). The use of *L. nepetifolia* for treatment of rheumatism has been extensively recorded among different communities. In this case, leaves, the whole plant, flowers or seeds are used (Mallick and Acharya 2013; Reddy et al. 2019; Tiwari et al. 2018) with multiple modes of administration including, infusion, decoction, or local application of paste for treating arthritis (Nayak et al. 2004; Pushpan et al. 2013; Tiwari et al. 2018). In a preclinical study, traditional and modified dosages of whole plant decoctions of *L. nepetifolia* showed significant effects ($p < 0.05$) on secondary edema and inhibitory effects on Freund's adjuvant-induced arthritis (Pushpan et al. 2017). The dry aqueous extract-treated group showed significantly decreased secondary paw edema on the 20th and 25th days, and the decoction showed similar results. The test drugs produced values similar to those of the standard drug on the 25th day of the secondary edema experiment. These findings demonstrate the beneficial effects of *L. nepetifolia* on chronic inflammation, periarthritis, and osteogenic activity. Leonotinin present in *L. nepetifolia* was identified as the active phytochemical with distinct anti-inflammatory activity (Parra-Delgado et al. 2004). In addition, Makambila-Koubemba et al. (2011) reported that stigmasterol and leonotinin isolated from *L. nepetifolia* showed significant anti-inflammatory properties ($p < 0.05$). Furthermore, the anti-inflammatory effect of *L. nepetifolia* was also attributed to flavonoids. In another study, Parra-Delgado et al. (2004) evaluated the anti-inflammatory properties of some extracts and isolates from *L. nepetifolia* in a TPA-induced edema model. This study evaluated the ability of *L. nepetifolia* extracts to block an inflammatory reaction to edemogen 12-O-tetradecanoylphorbol-13-acetate (TPA). In this case, all tested extracts exhibited anti-inflammatory effects in the TPA-induced edema test in mice, and the highest activity was observed in the ethyl acetate (EtOAc) extracts of leaves, flowers, and stems (65.75%, 69.06%, and 72.93% anti-inflammatory activity, respectively). Anti-inflammatory activity was attributed to stigmasterol, whose anti-inflammatory activity is well documented (Akihisa and Yasukawa 2001). Thus, these studies suggest that the popular claim for the use of the whole plant of *L. nepetifolia* for treatment of rheumatism is legitimate.

Ethnopharmacological Uses of *L. nepetifolia* treatment of Cancer

Cancer is one of the worst health problems globally (Subastri et al. 2018). Approximately 20 million people are diagnosed with cancer annually, and over 6 million mortalities are registered (Gurunagarajan and Pemaiah 2011). Natural products, including herbs, have been used to treat and prevent cancer (Oliveira et al. 2019). Studies have shown that decoctions of the whole plant or leaves of *L. nepetifolia* are administered as anticancer and antitumor agents in several communities (Kalaichelvi et al. 2017; Kingo and Maregesi 2020; Nadu 2019). Oliveira et al. (2019) reported that flavonoid 30,40,5-trihydroxy-6,7-dimethoxyflavone (cirsiliol), a constituent of *L. nepetifolia,* is one of the anticancer molecules; specifically, the molecule has selective cytotoxic activity on human tumor-cell lines SF-295, HL-60, and OVCAR8 (Bai et al. 2010; Li et al. 2012). In an *in vitro* study, Gurunagarajan and Pemaiah (2011) evaluated the anticancer potential of *L. nepetifolia* and *Hyptis suaveolens* Poit. against the Ehrlich ascites carcinoma (EAC) cell line. Ethanolic extracts from both plants proved cytotoxic to EAC cells. In fact, 500 μg/mL ethanolic extracts of *L. nepetifolia* (EELN) had a significantly higher percentage cytotoxicity (80.86%) compared to that (75.21%) of ethanolic extracts of *Hyptis suaveolens* Poit (EEHS) at the same concentration. Cell death caused by the plant extracts was attributed to the loss of mitochondria, one of the major markers of apoptosis (Potten 1992). Further, through DNA fragmentation analysis, both EELN and EEHS exhibited effective fragmentation of the DNA of EAC, implying that EELN can trigger apoptosis in cancer cells (Gurunagarajan and Pemaiah 2011). In another study, Vasuki et al. (2016) investigated the *in vitro* antioxidant properties of *L. nepetifolia* whole-plant ethanolic extracts using the hydroxyl radical DPPH, and nitric oxide radical scavenging methods. Due to the fact that free radicals are associated with such different acute and chronic diseases as cancer, atherosclerosis, and diabetes mellitus (Athar 2002), antioxidants are known to provide resistance to oxidative stress through free radical scavenging activity. Vasuki et al. (2016) found that the ethanolic extract of *L. nepetifolia* exhibited an *in vitro* antioxidant effect at a concentration of 20 μg/mL. The highest antioxidant activity was against nitric oxide radicals (77.07% ± 1.77% inhibition; IC_{50} = 2.03 μg/mL), followed by activity against DPPH radicals (64.47% ± 1.42% inhibition; IC_{50} = 3.07 μg/mL), and activity against hydroxyl radicals (62.96% ± 1.78% inhibition; IC_{50} = 7.55 μg/mL). Similarly, Prakash et al. (2014) studied methanolic leaf extracts for free radical scavenging activity against DPPH, and the antioxidant ability of *L. nepetifolia* was portrayed. Sobolewska et al. (2012) also obtained results consistent with Gurunagarajan and Pemaiah (2011) regarding anti-cancer activity in their *in vitro* analysis of the cytotoxicity of *L. nepetifolia* acetone and methanolic extracts towards human prostate-cancer cell line DU145. The median effective doses (ED_{50}) for AE after 24 h and 48 h of incubation were 60 and 40 μg/mL, respectively. Notably, 100% cell mortality was recorded after 48 h at a concentration of 200 μg/ml of the extract. On the other hand, the ED_{50} for ME after 24 and 48 h of incubation were 100 and 60 μg/mL, respectively. Labdane-type diterpenes found in the aerial parts of *L. nepetifolia* reportedly have cytotoxic activity and are known as cell-cycle inhibitors and apoptosis inducers (Mahaira et al. 2011) so *L. nepetifolia* AE and ME cytotoxicity towards human prostate-cancer cell line DU145 may be linked to this class of compounds. Further, Veerabadran et al. (2013) conducted an *in vitro* investigation of the antioxidant and anticancer potential of *L. nepetifolia* extracts and reported that the leaf methanolic extract had significant free radical scavenging activity with 60.57% inhibition, a percentage similar to that of the standard reference. Furthermore, the extract damaged cancer cell lines MCF-7 and Hep2 in a dose-dependent manner. A DNA fragmentation assay showed significant fragmentation at concentrations of 2.5 and 1.25 mg/mL, thus confirming that the mechanism whereby the extract inhibits the growth of Hep2 cells involves DNA fragmentation. Consistently, remarkable DNA fragmentation was detected in MCF 7 cells at a concentration of 125 μg/mL. These activities were associated with flavonoids because the compound has been confirmed to have a wide range of biological and chemical activities (Miliauskas et al. 2004). These findings fully justify the use of *L. nepetifolia* for cancer treatment.

Ethnopharmacological Uses of *L. nepetifolia* for treatment of Diabetes mellitus

Diabetes mellitus (DM) is a metabolic disorder characterized by high blood-glucose concentrations and glucose excretion in the urine (Maobe 2014). The forms of DM are type 1 and type 2, where type 1 DM is a result of the autoimmune destruction of the pancreatic beta cells that produce insulin, consequently, people with type 1 DM require insulin for survival (Imperatore et al. 2021). Meanwhile, type 2 DM is mainly caused by a combination of insulin resistance and relative insulin deficiency (American Diabetes Association 2017). By 2013, 10% of the world population was recorded as suffering from diabetes (Maobe 2014). Some studies have reported that *L. nepetifolia* is used to treat diabetes in traditional systems of medicine where the whole plant or the leaf decoction is administered to the patients (Kumar and Jnanesha 2017; Maobe 2014; Pingale et al. 2013). Ethanolic extracts of the whole plant *L.* showed significant ($p \leq 0.05$) antidiabetic activity in an alloxan rat model (Gungurthy et al. 2013). This antidiabetic activity exhibited might be due to one or more of the following activities: enhanced tissue glucose-uptake, improved pancreatic beta-cell function, or inhibited intestinal glucose-absorption (Gungurthy et al. 2013). Marrubiin, a diterpenoid lactone, is a constituent of *L. nepetifolia* known to have anti-diabetic properties (Mnonopi et al. 2012). Strong evidence suggests that marrubiin increases insulin secretion and low-density lipoprotein cholesterol (Popoola et al. 2013). In another study, marrubiin showed a significant increase in insulin and glucose transporter-2 gene expression *in vivo* (Stulzer et al. 2006). These results partly explain the effectiveness of *L. nepetifolia* in the treatment of diabetes mellitus.

Conclusions

L. nepetifolia is an important medicinal plant used to treat several diseases and other health problems around the world. Numerous studies have established the therapeutic potency of some of the phytochemical compounds found in *L. nepetifolia* for treatment of bronchial asthma, diarrhea, skin diseases, malaria, burns, cancer, diabetes mellitus, and rheumatism. The findings summarized herein provide solid evidence of the effectiveness of *L. nepetifolia* for treating these diseases. However, we cannot say that the whole phytochemical composition of this plant in each of its parts is fully known at present. In light of this, we recommend the isolation, and accurate and reliable identification of the therapeutic phytochemical constituents present in the different parts of the *L. nepetifolia* plant, coupled with additional preclinical and clinical studies, to confirm their safety and efficacy for use in the development of new drugs.

Acknowledgements

This research was funded by Development of Sustainable Application for Standard Herbal Resources (KSN2013320), Korea Institute of Oriental Medicine through the Ministry of Science and ICT, Republic of Korea.

Conflicts of Interest

The authors declare no conflict of interest in the publication of this review paper.

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