

# Phyto-pharmacological aspects of *Nepeta nuda* L.: A systematic review

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*Nepeta nuda* L. (syn. *N. pannonica* L.) is a herbaceous perennial plant that is the most widespread species of the genus *Nepeta*, the largest genera in Lamiaceae family. *N. nuda* is divided into four subspecies according to morphological differences which occur within large geographical range of distribution: subsp. *nuda*, subsp. *albiflora*, subsp. *lydiae*, and subsp. *glandulifera*. In this review, previous reports on *N. nuda* concerning its botanical description and systematics, phytochemistry, use in traditional medicine, pharmacology, and possibilities for other applications were summarized. All of these data indicate *N. nuda* as a highly promising species for application in food and pharmaceutical industries, as well as in agriculture for the development of natural pesticides.

**Key words:** *Nepeta pannonica*, subspecies, essential oil, phytochemistry, pharmacology

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## ABBREVIATIONS

ABTS – 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)

AChE – acetylcholinesterase

BHA – butylated hydroxyanisole

BHT – butylated hydroxytoluene

CUPRAC – Cupric Reducing Antioxidant Capacity

DPPH – 2,2-diphenyl-1-picrylhydrazyl

E – trans isomer

EC<sub>50</sub> – half minimal effective concentration

FRAP – Ferric Reducing Ability of Plasma

GAE – Gallic Acid Equivalent

IC<sub>50</sub> – 50 % inhibition concentration

LC<sub>50</sub> – 50 % lethal concentration

MIC – Minimal Inhibitory Concentration

RU – Rutin Equivalent

Z – cis isomer

endemics (Hadi et al., 2017), while in Turkey over 50 % out of 33 registered species are endemic (Sarikurku et al., 2018). Furthermore, 58 species from genus *Nepeta* are found in Pakistan flora, while approximately 30 species are recorded in flora of India (Süntar et al., 2018).

*Nepeta nuda* L. (syn. *N. pannonica* L.) is the most widespread species of the genus *Nepeta*. It has a wide range of growing, it is found in SE and CE Europe, C Russia, and SW Asia (Ghendov et al., 2015; Kokkini and Babalonas, 1982). Areas where *N. nuda* grows are forest clearings and meadows, at montane and subalpine altitudes up to 2.100 m (Kofidis and Bosabalidis, 2008). This species grows wild in Serbia, with two other species: *N. cataria* and *N. rtanjensis* Josifović (1975); Chalchat et al. (1998). The last one is an endangered endemic plant which grows spontaneously exclusively on Mt. Rtanj in SE Serbia Grbic-Ljaljevic et al. (2008).

## 2. METHODOLOGY

*N. nuda* is a significant source of biologically active compounds. Due to the wide growing area, it represents a significant source of raw material in pharmaceutical and food industries, as well as for organic agriculture. The goal of this review paper was to systemize data about morphology, chemistry and biological activities of *N. nuda* up to now. Data was gathered from available literature collected from different relevant multidisciplinary bibliographic online databases such as ScienceDirect Elsevier, SpringerLink, PubMed, Scopus, Scifinder, Web of Science, Wiley Online and Google Scholar.

## 1. INTRODUCTION

The name of the multiregional genus *Nepeta* L., called Nepete in Roman times and nowadays commonly known as catmints, originated from the city of Nepi in Italy (province of Viterbo, Lazio), (Josifović, 1975; Süntar et al., 2018). This genus belongs to Lamiaceae family, and has a large number of species distributed mainly through Europe, SW and C Asia, N Africa, and N America (Dirmenci, 2005)). The Irano-Turanian region is the main place of origin of this genus, with 79 species being identified in Iranian flora. Most of them (ca. 77 %) are

### 3. BOTANY

*N. nuda* is a herbaceous perennial plant that has many erect stems, from 50 to 100 cm tall. The upper part is organized in panicles. Lower branches are elongated, sharply rectangular, half-bare at the base, covered by sparse short hairs. Lower leaves are distinctly petiolate, oblong to oblong-lanceolate, cordate at the base. Upper leaves are ovate, 3-7 cm long and 1.5-3.5 cm wide. Lamina is regularly crenate-dentate, tomentose at the beginning, later nude. Flowers are blooming from June to August depending on altitude. They are hermaphrodite, with a short stem, organized in lax or dense spike-like verticillasters. Calyx is cylindrical to ovoid, 4-5 mm long, blue, green or blue-violet, with short trichomes. The crown is mostly lilac, seldom white or pink, 8-10 mm long, covered by short hairs and spotted with glands. Corolla is cylindrical, two-lipped. Corolla tube is slender, longer than calyx and glabrous inside. Upper lip is patent, flat, 2-fid, while the lower lip is 3-lobed, the middle lobe is the largest. There are four didynamous stamens, parallel with the upper lip, and they ascend under the upper lip of the corolla. Anther-cells are divergent, opening by a common slit. *N. nuda* has high pollen efficiency, 48.4 kg of pollen was measured from 1 ha. Honeybees account for 99.2 % of the total number of pollinators of this species. Nutlets are ellipsoid, 2 mm long, three angled, brownish, smooth or with a few flattened tubercles, top always with at least a few short hairs. The value mass of 1000 grains is 7.9 g (Bozek, 2003; De Pooter et al., 1987; Duda et al., 2015; Ghendov et al., 2015; Josifović, 1975).

There are four subspecies of *N. nuda* according to morphological differences (calyx and corolla color and other parameters related to flower morphology), found within a large geographical range of distribution:

- subsp. *nuda*
- subsp. *albiflora*
- subsp. *albiflora*
- subsp. *lydiae*
- subsp. *glandulifera*

Subsp. *nuda* grows throughout Europe and European part of Russia, the Crimea, in the Dnieper area and on Carpathians in Ukraine, as well as in Siberia (Boikova and Grishkina, 2019a). Subsp. *albiflora* grows in SW Asia, whereas in Europe it only grows on the Balkan Peninsula. However, the Balkans is a region where these two species overlap (Kokkini and Babalonas (1982). Subsp. *lydiae* is endemic for Turkey (W and SW Anatolia) and Greece (East Aegean Islands) (Vladimirov et al., 2013), while subsp. *glandulifera* is endemic for Turkey (Erdağ and Emek, n.d.). Furthermore, a hybrid between *N. nuda* subsp. *nuda* × *N. viscida* called *N. × tmolea* is found in Turkey (Özcan, 2019).

### 4. PHYTOCHEMISTRY

Most *N. nuda* samples contain between 0.2 % and 2.1 % of essential oil (Alim et al., 2009; Kökdil et al., 1998). Chemical compositions of *N. nuda* essential oils according to literature review is shown in Table 1. Chemical structures of noteworthy compounds are presented in Figure 1. Considering essential oil composition, it could be concluded that all *N. nuda* samples could be divided into: monoterpene-dominant and sesquiterpene-dominant class, as well as mixture class. Furthermore, it is possible to divide monoterpene-dominant class in two groups: nepetalactones-rich and nepetalactones-poor (Aras et al., 2016a)). The last one is 1,8-cineole chemotype. Essential oil from this chemotype

is herbaceous with a menthol scent, which could be due to its high content of 1,8-cineole (eucalyptol) (Formisano et al., 2011). Apart from these groups, in some samples of *N. nuda*, sesquiterpene fraction is dominant ( $\beta$ -caryophyllene oxide and spathulenol). This is noted in some other species from genus *Nepeta*: *N. gomaniana* (Hassan et al., 2011), *N. grandiflora*, and *N. clarkei* (Birkett et al., 2010). Furthermore, mixed group (nerolidol/1,8-cineole/spathulenol and trans-caryophyllene/isopulegone/cis-sabinol, and nepetalactone/ $\beta$ -bisabolene/pulegone) is also noted within *N. nuda* species.

Monoterpene-dominant nepetalactones-rich group includes two samples of Turkish *N. nuda* subsp. *albiflora*. In the first essential oil sample *E,Z*-nepetalactone (74.3 %) are dominant (Bozok et al., 2017), while the second one has a high content of three nepetalactones representing 77.2 % of total oil (*Z,E*-, *E,Z*- and *Z,Z*-nepetalactone isomers), and the sesquiterpene fraction representing 14.2 % of total oil (Kokdil et al., 1996). In *N. nuda* grown in Bulgaria a complex mixture of iridoid compounds is confirmed; except *E,E*-nepetalactone isomer (with 62.0 %), 4 $\alpha$ ,7 $\alpha$ -dehydronepentalactone was present in low concentration (1.3 %) (Handjieva et al., 1996). In the four populations of *N. nuda* from Iran collected from different localities, the *Z,Z*-nepetalactone was dominant (from 61.0 to 72.2 %), followed by *E,Z*-nepetalactone (8.7-12.6 %) (Narimani et al., 2017). *N. nuda* subsp. *nuda* collected in Greece during flowering stage contains *E,Z*-nepetalactone as the dominant compound, in verticillaster 75.7 %, and in leaf 24.7 %. This investigation indicated that different plant organs have different chemical compositions (Gkinis et al., 2010).

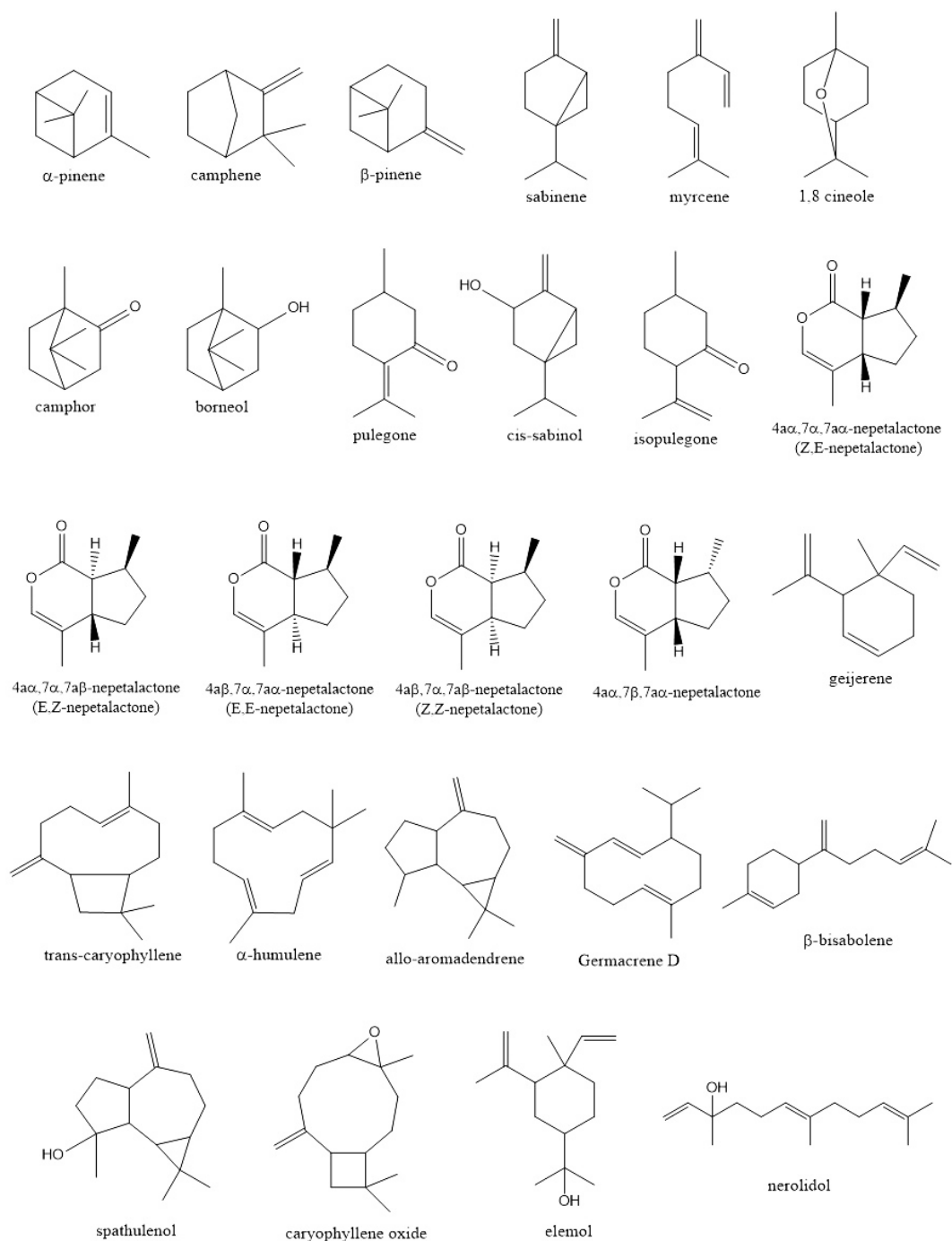
Monoterpene dominant, but nepetalactones-poor group includes four samples. According to the literature review of *N. nuda* essential oil, it could be said that these plant samples from Serbia and Montenegro is characterized by its high level of 1,8-cineole between 37.0 and 63.8 %, which differs them from all other species studied. In this samples nepetalactones are absent or present in low concentrations (up to 3.7 %), while sesquiterpenes are present in an amount between 5.3 to 12.6 % (Chalchat et al., 1998; Đorđević et al., 2019). Furthermore, in *N. nuda* subsp. *nuda* from Turkey 45 compounds (representing 94.7 % of total oil) with camphor (23.3 %), 1,8-cineole (21.0 %), borneol (18.8 %) and camphene (6.5 %) as the major components were identified. However, camphor was previously found as the dominant compound in some other species of the genus *Nepeta* (Kilic et al., 2011). Borneol is considered to be an initial product of cyclisation and the subsequent derivation of camphor and camphene. Furthermore, it is known that there are strong biosynthetic relationship between these compounds and their co-occurrence in nature (Fairlie et al., 1973).

The flowering parts of *N. nuda* subsp. *albiflora* from Turkey contain a mixture of monoterpenes and sesquiterpenes. One sample is rich in nerolidol (31.7 %), 1,8-cineole (29.1 %) and spathulenol (14.4 %) (Sarer and Konuklugil, 1996), while another sample contains trans-caryophyllene (24.0 %), isopulegone (12.6 %) and cis-sabinol (10.1 %) as major compounds (Alim et al., 2009)). Furthermore, a third sample contains nepetalactones (8.1-12.1 %),  $\beta$ -bisabolene (7.8-11.8 %) and pulegone (7.2-10.8 %) (Mancini et al., 2009). A sesquiterpene-dominant class could also be nepetalactones-rich and nepetalactones-poor species. *N. nuda* from Turkey could be placed in the first subgroup as it contains 4 $\alpha\alpha$ ,7 $\beta$ ,7 $\alpha\alpha$ -nepetalactone (18.1 %), while sesquiterpene fraction is present with 48.6 % (Bozari et al., 2013; Gormez et al., 2013). *N. nuda* subsp. *nuda* could be placed in the second subgroup, it is rich in sesquiterpene fraction (81.9 %) with  $\beta$ -caryophyllene oxide (21.8 %) and spathulenol (13.8 %) as the main compounds (Kökdil et al., 1998).

**Table 1.** Chemical composition of *Nepeta nuda* essential oil from different samples according to the literature review

Compound	ssp. <i>nuda</i> <sup>a</sup> Greece Gkinis et al. (2010)	ssp. <i>albiflora</i> Turkey Kökdil et al. (1996)	<i>N. nuda</i> Bulgaria Handjieva et al. (1996)	ssp. <i>albiflora</i> Turkey Bozok et al. (2017)	<i>N. nuda</i> Iran Narimani et al. (2017)	<i>N. nuda</i> Serbia Chalchat et al. (1998)	<i>N. nuda</i> Serbia Đorđević et al. (2019)	<i>N. nuda</i> Montenegro Chalchat et al. (1998)	ssp. <i>nuda</i> Turkey Kılıç et al. (2011)	ssp. <i>albiflora</i> Turkey Sarer and Konuklugil (1996)	ssp. <i>albiflora</i> Turkey Alim et al. (2009)	ssp. <i>albiflora</i> Turkey Mancini et al. (2009)	<i>N. nuda</i> Turkey Gormez et al. (2013)	ssp. <i>nuda</i> Turkey Kökdil et al. (1998)	ssp. <i>glanduli</i> Turkey Sarikurku et al. (2019)
	[%m/m]	[%m/m]	[%m/m]	[%m/m]	[%m/m]	[%m/m]	[%m/m]	[%m/m]	[%m/m]	[%m/m]	[%m/m]	[%m/m]	[%m/m]	[%m/m]	[%m/m]
$\alpha$ -pinene	tr	0.4	-	-	-	1.7	1	1.2	0.6	tr	-	-	-	0.5	-
camphene	-	-	-	-	-	tr	-	tr	6.5	-	1.8	-	-	-	-
$\beta$ -pinene	-	0.9	-	-	-	4.4	1.4	1.2	0.5	0.1	10	-	-	0.6	-
sabinene	1.2	-	-	-	-	1.5	1.8	0.8	3	-	-	-	-	-	-
myrcene	tr	-	-	-	-	0.7	1.8	0.3	-	tr	3	-	-	1.9	-
1,8-cineole	10	1.5	-	0.7	1.6	62.2	37	63.8	21	29.1	6.4	1.1	0.3	5.1	1.6
camphor	-	1.2	-	-	-	-	-	-	23.5	-	-	-	-	-	-
borneol	-	-	-	-	-	-	-	-	18.8	-	-	-	-	-	-
pulegone	-	-	0.4	-	2.6	-	-	-	-	-	-	9	-	-	-
Z-sabinol	-	-	-	-	-	-	-	-	-	-	10.1	-	-	-	-
isopulegone	-	-	-	-	-	-	-	-	-	-	12.6	-	-	-	-
4 $\alpha$ ,7 $\alpha$ ,7 $\alpha$ -nepetalactone (Z,E-nepetalactone)	2.9	37.5	-	-	-	-	-	-	-	-	-	2.2	-	-	-
4 $\alpha$ ,7 $\alpha$ ,7 $\beta$ -nepetalactone (E,Z-nepetalactone)	50.2	37.6	-	74.3	10.2	-	-	-	-	-	-	6.2	-	-	-
4ab,7 $\alpha$ ,7 $\beta$ -nepetalactone (Z,Z-nepetalactone)	-	2.1	-	-	68.2	-	-	-	-	-	-	1.7	-	-	-
4ab,7 $\alpha$ ,7 $\alpha$ -nepetalactone (E,E-nepetalactone)	-	-	62	-	-	-	-	-	-	-	-	-	-	-	-
4 $\alpha$ ,7 $\beta$ ,7 $\alpha$ -nepetalactone	-	-	-	-	-	-	3.7	-	-	-	-	-	18.1	-	-
Total monoterpene	64.3	81.2	62.4	74	82.6	70.5	46.7	67.3	73.9	29.2	43.9	20.2	18.4	8.1	1.6
geijerene	-	-	-	-	-	-	-	-	-	-	-	-	-	-	61
trans-caryophyllene	1.8	1.8	0.9	2	0.4	3.6	2.3	3.6	0.2	2.4	24	-	8.8	5.4	1.9
$\alpha$ -humulene	1.1	0.4	-	-	0.1	0.7	0.7	0.7	tr	0.1	0.8	0.5	3.2	0.7	0.4
allo-aromadendrene	tr	-	-	-	-	-	-	-	-	-	0.3	1	0.4	9	-
germacrene D	1.9	-	-	-	0.7	2.2	-	1.8	0.6	-	2.8	0.3	15.7	0.4	0.8
$\beta$ -bisabolene	0.7	2.7	1.7	1.3	-	0.2	-	0.3	-	-	-	9.8	-	-	-
spathulenol	-	-	-	-	0.9	0.2	-	0.2	-	14.4	7.4	2.3	6.1	13.8	1
caryophyllene oxide	9.2	4.4	5.4	1.9	0.7	2	2.3	6	-	2	-	7.1	-	21.8	1.9
elemol	0.9	-	-	-	1.2	-	-	-	-	-	-	-	14.4	1.8	1.3
nerolidol	-	-	-	-	-	-	-	-	-	31.7	0.8	-	-	-	-
Total sesquiterpene	15.6	9.3	8	5.2	4	8.9	5.3	12.6	0.8	50.6	36.1	20.8	48.6	52.9	68.3

<sup>a</sup>Reported *N. nuda* subspecies were provided. Where subspecies was unknown, species name (*N. nuda*) has been denoted.



**Fig. 1.** Chemical structures of secondary metabolites from *N. nuda*.

*N. nuda* subsp. *glandulifera* essential oil contains predominantly geigerene (Sarikurkcu et al., 2018), the elemene-type sesquiterpene, which is either synthesized in the dark or in the red light spectrum (Tabata, 1977).

The main secondary metabolites in the most *Nepeta* species are iridoid monoterpene nepetalactones (Aničić et al., 2020). Nepetalactones can appear as five diastereoisomers, due to presence of three chiral centers (Süntar et al., 2018). However, a varying nepetalactones content and variation of the individual nepetalactones present in the essential oil of different *N. nuda* species have been reported (Kökdil et al., 1996). Iridoid glucosides such as 1,5,9-deoxyloganic acid and velpetin with an unusual stereochemistry, as well as nepetanudoside A, B, C and D, are also present in *Nepeta* species (Takeda et al., 1995; 1996). Furthermore, steroids such as  $\beta$ -sitosterol, sitosterol 3-one, and sitosterol 3 $\beta$ -glucoside, and triterpenoids such as oleanolic, ursolic, and betulinic acids are also noted (Kökdil, 1999).

Tannins and coumarins are also present in *N. nuda*. The content of tannins in *N. nuda* growing in Russia was 3.86 % at the beginning of flowering and 7.58 % at the end of the vegetation period (Boikova and Grishkina, 2019a), while the content of coumarins was 4.26 % at the beginning of flowering, while at the end of the growing season it decreased to 3.10 % (Boikova and Grishkina, 2019b).

The content of total polyphenols varied from 142.40 to 282.28 mg/100 g fresh weight (Wieteska et al., 2018). However, the highest values are registered in the first year of cultivation, while a decrease is noted with aging of the crop. The total polyphenols content in *N. nuda* was 40.9 mg GAE/g of dried extract, while total flavonoids content was 20.0 mg RU/g of dried extract (Đorđević et al., 2019).

The difference in essential oil content and composition could be contributed to plant origin, altitude, climatic and other environmental conditions. It is evident that biotic and abiotic interactions in the environment influence on the secondary metabolites composition. The presence of dissimilar chemotypes in the same taxon could be explained by different growth stage and habitat, collected plant part and postharvest processing including distillation technique (Bozok et al., 2017; Chalchat et al., 1998; Handjieva et al., 1996). Thus, it could be noticed that *N. nuda* is sensitive to the environment conditions (Sarikurkcu et al., 2018). Biosynthesis of monoterpenes and sesquiterpenes in plants can be changed by enzymatic bioactivity, as well as their accumulation. However, biosynthetic enzymes are usually regulated by gene expression (Sharifi-Rad et al., 2017). Abiotic (soil and climatic conditions) and biotic factors (pests and diseases) may influence the different mechanisms and changes of enzyme activity in plants (Dehghani Bidgoli et al., 2019; Haydari et al., 2019). Therefore, significant variations in essential oil chemical composition and the amount of synthesized essential oil can be seen. Having in mind that species from Lamiaceae family hybridize with one another and that these are entomophilous plants preferred by insects, it is highly likely that spontaneous interbreeding occurred within the *Nepeta* species. This can potentially lead to changes in gene expression and enzyme activity.

## 5. TRADITIONAL USES

*N. nuda* is used as a herbal tea with slightly pungent aroma suggestive of a mix between citrus and peppermint. In Serbian traditional medicine, it is used for treating hysteria, melancholy and uterine cramps (Stamenković and Stamenković, 2015). Apart from this, it is used to relieve gastrointestinal and respiratory disorders, such as diarrhea, cough, asthma and bronchitis (Đorđević et al., 2019). However, in Bulgarian traditional medicine, this plant is used internally as a decoction against cystitis and prostate gland inflammation, and externally to

treat wounds and against mastitis in livestock (Kozuharova et al., 2014). In Russian folk medicine, *N. nuda* is used as an infusion to ameliorate asthenia and syphilis (Eisenman et al., 2013). *Nepeta* essential oil can be used in aromatherapy for nervous system disorders, mainly as a sedative, but also as an anti-anxiety, hypnotic and antispasmodic drug (Duda et al., 2015). However, there is no scientific data about the efficacy of *N. nuda* in pharmacology, apart from indirect research on antibacterial activity, which could be connected to the positive effects on gastrointestinal and respiratory tract, and on inflammations (wounds and mastitis) (Figure 2). Based on the traditional application of this plant, further investigation should be conducted towards possible application in modern phytotherapy.

## 6. PHARMACOLOGY

Different subspecies of *N. nuda* possess different biological activities due to different chemical composition and they can be used in different ways. For instance, subspecies rich in 1,8-cineole could be used in traditional medicine for inhalation (Chalchat et al., 1998), while subspecies rich in sesquiterpene alcohol nerolidol could be used either in cosmetics and household products or as food flavoring agents (Chan et al., 2016). According to review, *N. nuda* possesses antimicrobial (Alim et al., 2009; Gormez et al., 2013; Smiljković et al., 2018; Đorđević et al., 2019) and virocidal activity (Angelova et al., 2016; Todorov et al., 2015), as well as antioxidant (Alim et al., 2009; Aras et al., 2016b;a; Cvetković et al., n.d.; Sarikurkcu et al., 2018; 2019; Đorđević et al., 2019), anticancer (Kabalay et al., 2018), and allelopathic (Bozari et al., 2013; Bozok et al., 2017; Dragoeva et al., 2017) properties. It has been reported that nepetalactones have antibacterial, antifungal, insecticidal and antioxidant activities (Adiguzel et al., 2009; Grbic-Ljaljevic et al., 2008; Reichert et al., 2019; Shafaghat and Oji, 2010; Zhu et al., 2012). Apart from these activities, their enjoyable flavor and scent is an additional benefit. Therefore, it might be considered for the development of antimicrobial agents against typical causes of food-borne infections and disinfectants (Zomorodian et al., 2012). Sesquiterpene lactones are extremely important for the plant's defense; they act as antibacterials, antivirals, antifungals, insecticides and as such reduce the herbivores' appetites. They express some allelopathic potential as well. Nowadays, greater attention is paid to sesquiterpene lactones due to their cytotoxic and anticancer activity (Matejić et al., 2010).

### 6.1. Antimicrobial activity

Antimicrobial activity of the *N. nuda* subsp. *albiflora* essential oil against Gram-positive and Gram-negative bacteria and fungus, was determined by the disc diffusion assay with Gentamycin and Nystatin as positive controls (Alim et al., 2009). The oil expressed strong antibacterial activity against *Klebsiella pneumoniae* and *Salmonella typhi*, while its effectiveness against *Staphylococcus aureus*, *Escherichia coli*, *Corynebacterium diphtheriae*, *Proteus vulgaris*, *Bacillus subtilis*, and *Candida albicans* was weak. According to this study, *N. nuda* essential oil could be a natural antibacterial agent.

Ethanol extract of *N. nuda* herbs showed the best activity against Gram-positive bacteria *Micrococcus flavus*, *S. aureus* and *M. luteus*, and mild against *S. epidermidis* and *B. subtilis* (Đorđević et al., 2019). Extract also showed moderate antifungal activity against *C. albicans*.

Research was aimed to explore the potential of *N. nuda* tincture to inhibit biofilm formation and to diminish the established biofilm of oral pathogenic microorganisms (4 bacterial and 9 fungal strains). *N. nuda* tincture expresses good antimicrobial potential (MIC in range 0.8-15  $\mu$ L/well) including inhibition of biofilms. The most dominant phenolic compounds

## TRADITIONAL MEDICINE

- Against hysteria
- Against melancholy
- Against astenia (weakness)
- Against dismenorrhea
- For relive gastrointestinal disorders (diarrhea)
- For relive respiratory disorders (cough, asthma, bronchitis)
- Against cystitis and prostate gland inflammation
- Against syphilis
- For wound healing
- Against mastitis

## OTHER APPLICATIONS

- Management of plant diseases
- Allelopathic effect (natural herbicide)



## PHARMACOLOGY

- Antibacterial
  - *Bacillus subtilis*
  - *Corynebacterium diptheriae*
  - *Escherichia coli*
  - *Klebsiella pneumoniae*
  - *Micrococcus flavus*
  - *Micrococcus luteus*
  - *Proteus vulgaris*
  - *Salmonella typhi*
  - *Staphylococcus aureus*
  - *Staphylococcus epidermidis*
- Antifungal
  - *Candida albicans*
- Antiviral
  - Herpes simplex virus
- Antioxidant
- Anticancer
  - human colon cancer cell lines namely Caco-2

Fig. 2. Traditional and modern application of *N. nuda*

present in the *N. nuda* tincture were rosmarinic acid and verminoside. This study suggests that *N. nuda* tincture can be used as a mouthwash since it is safe for human use (Smiljković et al., 2018). *N. nuda* essential oil was tested against 20 plant pathogenic bacterial strains isolated from certain fruit and vegetables that showed typical symptoms of bacterial disease on their respective host plants (apricot, tomato, cherry, peach, beans and pepper) (Gormez et al., 2013). *N. nuda* essential oil showed significant antibacterial activity against most of the tested bacteria. It was found that both Gram-positive and Gram-negative bacteria were sensitive to the oil tested. There was no significant difference in susceptibility found between Gram-positive and Gram-negative bacteria. The fact that minimal inhibitory concentration of essential oil was more potent than 10 % dimethyl sulfoxide (DMSO) used as standard antibiotic was quite interesting. According to the results of this study, *N. nuda* essential oil could be used as an antimicrobial agent for treatment of plant diseases.

### 6.2. Antiviral activity

Antiviral activity on viral replication of methanol and chloroform extract of *N. nuda* subsp. *nuda* was evaluated against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) on Madin-Darby bovine kidney (MDBK) cell lines (Angelova et al., 2016; Todorov et al., 2015). The methanol extract showed the IC<sub>50</sub> of 320 and 510 µg/ml against HSV-1 and HSV-2, respectively. Viral replication was inhibited by more than 95 % in both types of herpes simplex viruses after the extract was applied in the maximal tolerated concentration.

### 6.3. Antioxidant activity

DPPH radical scavenging assay and the β-carotene–linoleic acid test were used for investigating antioxidant activity of *N. nuda* subsp. *albiflora* essential oil in comparison to synthetic antioxidant as positive control (BHT) (Alim et al., 2009). Investigated oil showed weak antioxidant activities. In addition, the FRAP value of *N. nuda* ethanol extract indicated low antioxidant activity, 0.86 mmol Fe<sup>2+</sup>/g, while the percentage of neutralizing DPPH radicals (EC<sub>50</sub>) was 86.24 µg/ml (Dorđević et al., 2019).

Methanol extract of *N. nuda* subsp. *grandulifera* contains considerable amounts of chlorogenic (63.52 mg/g extract) and ferulic acids (14.65 mg/g extract), and exhibited high antioxidant activity (Sarikurkcu et al., 2019). In β-carotene bleaching assay,

it was as active as BHT and Trolox. In the enzyme inhibitory assay, the extract showed weak inhibitory activity on AChE, α-amylase and α-glucosidase.

Several different assays were used to test antioxidant activity of *N. nuda* subsp. *glandulifera* (Sarikurkcu et al., 2018). Assays were based on different reaction mechanisms, i.e. metal chelating, reduction of ions, and reduction of stable radicals. Test results showed that the essential oil effectively scavenged and neutralized various reactive oxidant species and inhibited different enzymes connected with human diseases of modern life. Results suggest that this endemic species could be successfully used in food and pharmacological industries.

In response to oxidative stress induced by non-selective herbicide paraquat in *N. nuda* shoot cultures, the activities of oxygen scavenging enzymes catalase and peroxidase were steadily enhanced by increasing paraquat concentrations (Cvetković et al., n.d.). Furthermore, increased activities of these enzymes could be taken as circumstantial evidence for production of reactive oxygen species induced by herbicide. Polyphenol oxidase activity was progressively inhibited and, as a result, radical scavengers – phenolic compounds accumulated. This most probably occurred as a result of the plant's defense mechanism to overcome oxidative stress damage. It could be concluded that paraquat proved to be a potent elicitor, as it can stimulate accumulation of medically important rosmarinic acid in *N. nuda*.

High percentage of biologically active phenolic compounds such as chlorogenic, rosmarinic and quinic acid, has been determined in the methanol extract of leaves of *N. nuda* subsp. *lydiae* (Aras et al., 2016a). Furthermore, smaller amounts of kaempferol, *p*-coumaric and caffeic acid, apigenin, luteolin and rhamnetin were identified. Different *in vitro* methods were used to determine antioxidant activities of ethanol and water extracts of *N. nuda* subsp. *lydiae* leaves: DPPH, ABTS, FRAP and CUPRAC assays (Aras et al., 2016b). The results were compared to BHA, BHT and ascorbic acid as standard compounds. Both water and ethanol extracts exhibited high antioxidant potential in DPPH free radical scavenging assay and CUPRAC assay. However, it exhibited low potential in ABTS and FRAP assays.

### 6.4. Anticancer properties

Essential oil of *N. nuda* subsp. *lydiae* has the ability to inhibit the cell growth of human colon cancer cell lines namely Caco-

2 at moderately low concentration with LC<sub>50</sub> value of 129.6 µg/ml (Kabalay et al., 2018). Therefore, it may have promising phytochemicals that could be used in cancer treatment.

## 7. OTHER PROPERTIES/TOXICOLOGY

Corn seed was exposed to four different concentrations of *N. nuda* essential oil (0.1, 0.2, 0.4 and 0.8 µl/ml) in order to determine genotoxic effects of the essential oil (Bozari et al., 2013). The increase of essential oil concentrations resulted in the inhibition of root and stem growth. Some other changes were detected in RAPD (Randomly amplified polymorphic DNA) profiles of germinated seeds treated with this essential oil.

Different concentrations (2, 4, 6, 8, 10, 12 and 14 g/l) of *N. nuda* subsp. *nuda* water extract were tested for phytotoxic effects on wheat and cucumber (Dragoeva et al., 2017). Results of this experiment showed that even though germination was not affected, *N. nuda* extract caused deterioration in seedling growth. The shoots were not as affected as the root. The treatment with the tested extracts also resulted in the reduction of the fresh and dry weights. These harmful effects depended on the dose. These results indicate that the water soluble allelochemicals are present. *N. nuda* subsp. *albiflora* herbicidal activity was tested in a two-fold dilution manner (from 0.015 to 2.0 µl/ml) on the seeds of wheat, radish, lettuce, cress and purslane (Bozok et al., 2017). Essential oil dilution affected seed germination, radicle and plumule growth. Thus, this study shows that *N. nuda* subsp. *albiflora* essential oil should be taken into consideration as a potential candidate for weed control as a bio herbicide.

## 8. FUTURE PERSPECTIVES

All of this contributes to *N. nuda* being a highly promising plant in food and pharmaceutical industries, as well as in agriculture for the development of natural pesticides. Results indicated a high regeneration potential of *N. nuda* subsp. *nuda* during *in vitro* cultivation and *ex vivo* adaptation (Dragolova et al., 2015). Because *N. nuda* subsp. *albiflora* has potential importance as a medicinal plant, alternative propagation procedure *in vitro* germination and axillary shoot propagation is developing (Erdağ et al., 2018). Furthermore, unsustainable exploitation of plants from their natural habitat increases the pressure on endemic plants, and biotechnological methods are used to protect them. For these reasons, a simple micropropagation system for *N. nuda* subsp. *lydiae* as endemic plant is being developed (Erdağ and Emek, n.d.).

## CONCLUSION

There is a growing interest in biologically active compounds from natural sources. Because of this, many plants are in the spotlight, especially the widespread species. *N. nuda* is one of them as it possesses good antimicrobial and virocidal activities, as well as antioxidant and anticancer properties which make it suitable for application in pharmaceutical and food industries. In addition, allelopathic activity of *N. nuda* in agriculture can be used for the development of natural pesticides.

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