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Review

Nepeta cataria – Cultivation, Chemical Composition and Biological Activity

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Abstract: *Nepeta cataria*, also known as catnip or catmint, is the most widespread and intensively studied species. The name catmint is derived from the strong attraction most cats have towards this species. Because of this, it is often used in pet toy industry as a safe attractant for cats. The main compounds responsible for this reaction in cats are nepetalactones. However, *N. cataria* var. *citriodora* or lemon catnip, an aromatic herb with a lemony-mint flavor, resembles true catnip, but is not attractive to cats. This variety is a good source for industrial production of citral and an attractive raw material for food industry and cooking; it is used as a dry spicy mixture for dessert dishes, in manufacturing of cheese, sausages, alcoholic beverages (liqueurs and vermouth) and soft drinks, vegetable and fruit canned food. *N. cataria* is cultivated for ornamental purposes, and because of the long flowering duration and large production of pollen and nectar it is very suitable for beekeeping. According to scientific reports, *N. cataria* possess antioxidant, hepatoprotective and antidiabetic activities, as well as sedative, antidepressant, spasmolytic, anti-nociceptive and anti-inflammatory activities. Experiments show that this plant influences sexual activity, and expresses anticancer properties. Antimicrobial activity against a number of bacteria is also noted, as well as repellent and insecticidal properties. Nematodidal and allelopathic effects are also noted.

Keywords: *Nepeta cataria*; *Nepeta cataria var. citriodora*; nepetalactones; citral.

1. Introduction

The genus *Nepeta* is one of the largest from the Lamiaceae family, with ca. 300 species, distributed in temperate regions, mainly in central and southern Europe, the Near East, central and southern Asia, and some parts of Africa, and it is naturalized in North America. Most *Nepeta* species are endemics, especially in Southwestern Asia (Turkey and Iran). *Nepeta cataria*, also known as catnip or catmint, is the most widespread and intensively studied species [1-4]. The name catmint is derived from the strong attraction most cats have towards this species [5]. It is well known that this plant is a potent behavior-altering drug, i.e. provokes stupor or euphoria in domestic cats and large wild cats (name catnip is derived from words: nip meaning a small quantity of liquor, that intoxicates cats) [6; 7]. Because of this, it is often used in pet toy industry as a safe attractant for cats, especially for cats kept indoors in order to improve the quality of life and to attenuate stress [8; 9].

The main compounds responsible for this reaction in cats are nepetalactones. However, *N. cataria* var. *citriodora* or lemon catnip, an aromatic herb with a lemony-mint flavor, resembles true catnip, but is not attractive to cats. When prepared as tea it is a sedative and soporific, while in cooking it is used because of its fragrance [10; 11]. This variety is a good source for industrial production of citral and an attractive raw material for food industry and cooking; it is used as a dry spicy mixture for dessert dishes, in manufacturing of cheese, sausages, alcoholic beverages (liqueurs and vermouth) and soft drinks, vegetable and fruit canned food [12].

N. cataria is perennial herbaceous plant. The root is rod-shaped, long. It forms many erect quadrilateral stems, 50-100 cm high. Stems are branched, extrorsely glandular pilose with short hairs and sessile glands. Leaves are ovate, 3.5-8.0 × 2.5 cm, finely appressed pilose with many sessile glands, greyish beneath, serrate, truncate or cordate. Leaf arrangement is opposite or whorled, and petioles are up to 7 mm long. Each branch ends with a dense spike-shaped inflorescence, widely paniculate, called verticillasters condensed above, to c. 35-flowered. Flowers are small, five-membered, and double-haired. Bracteoles are linear-oblong, clearly shorter than calyx. Calyx tubular, 5-6 mm, scarcely oblique, or not amouth, densely pilose-pubescent and with sessile glands. Corolla is white with blue violet spots, 6-10 mm long. Nutlets broadly ellipsoid, c. 1.5 × 1 mm, dull, matt, obsoletely tuberculate at apex, brownish black [12-14].

In this study, the recent advances on botany, cultivation, chemical composition and bioactivity of *N. cataria* were summarized. This is based on the available literature collected from PubMed, ScienceDirect, SpringerLink, Web of Science, Scopus, Wiley Online, Scifnder, and Google Scholar among others.

2. Cultivation

N. cataria is cultivated for ornamental purposes [5], and because of the long flowering duration (late May through late August – early September) and large production of pollen and nectar it is very suitable for beekeeping [15-17]. Apart from this, because of its use in pharmaceutical and food industry, as well as in pet toy industry, *N. cataria* has been grown on a large scale. It is one of the most promising aromatic plants in Egypt [18], Ukraine [12] and North America [8; 19].

'CR9' is the first cultivar of *N. cataria* in North America developed specifically for commercial agricultural production with a more upright growth habit and higher biomass, essential oil and *Z*,*E*-nepetalactone yield [8]. Apart from that, in germplasm collection and breeding program different genotypes of *N. cataria* are used. These are characterized by completely devoid or producing little amounts of nepetalactone and by a distinct lemony aroma [19]. In Ukraine, there are two varieties of *N. cataria* var. *citriodora*: 'Melody' (for growing in the forest-steppe zone) and 'Peremozhets' (for steppe zone) [12].

N. cataria plants prefer slightly alkaline soil even though they are not very demanding about the soil-type, however, they prefer well drained ground [5]. *N. cataria* is propagated by seed. Weight of 1000 seeds is 0.5 g. Under open field conditions seed is mainly sown in autumn, conversely, if the sowing is done during spring stratification is necessary [20]. Crops that are established by seedling in the greenhouse in April are transplanted into the field in May [16].

In experiments conducted in Egypt, the seed of *N. cataria* was sown every month from October to April in nurseries to study the effect of date of sowing on germination percentage. Pure sand soil (S1), mixture of 1 vol. sand + 1 vol clay (S2) and mixture of 2 vol sand + 1 vol clay loamy (S3) were used as germination medium. Seedlings of *N. cataria* were planted in the field on 15th April in hills 30 cm apart in rows 60 cm in-between. Two harvests were performed on 15th June and 20th September. Results show that germination percentage varied between 30 to 80%. The highest percentage of germination was obtained when seeds were sown in February and March in the S3 soil medium. The germination percentage in this respect reached up to 70% and 80% [18].

Row width density spacing combinations were established to provide information on cultural management. There were three row widths (45, 90 and 135 cm) and three intra-row spacings (30, 60 and 90 cm). It is established that plant size was greatly affected by plant spacing. Uniform plant spacing of 90×90 cm produced significantly more flowers [16]. In addition, use of several organic mulches (oat straw, a flax straw mat and nonwoven wool mat) in comparison to positive (hand-weeded) and negative (non-weeded) controls, it is established that *N. cataria* plant height was significantly greater in the oat straw than the other treatments. However, there was no significant weed management treatment effect on the concentration of the nepetalactones [21].

Substrate moisture (50, 125 and 250 hPa) had a considerable effect on herbal yield of *N. cataria* var. *citriodora*. In addition, draught stress influenced the essential oil content, i.e. 50 hPa provided high yield of essential oil [22].

In Poland recommendation for fertilization is: 100 kg/ha N, 80 kg/ha P_2O_5 and 120 kg/ha K_2O [23]. Investigation on the impact of different nitrogen concentrations in nutrient solution (50, 150 and 300 mg/l) on herbal yield and content and composition of essential oil of *N. cataria* var. *citriodora* found that concentration of 300 mg/l was effective for herbal yield and favorable for maximum yield of essential oil. Furthermore, the essential oil composition was mainly affected by tested nitrogen concentrations [24].

The growth measurements of *N. cataria* plants during the growth season in Egypt showed that the fresh yield of *N. cataria* herb recorded 138.5 and 180.0 g/plant in the first and the second cut, respectively. Dry yield per hectare in this respect recorded 1.98 and 2.77 t/ha. The total yield of dry weight from two cuts was 4.75 t/ha in both harvests. The highest percentage of oil recorded (0.25%) during the first cut, against 0.19% in second cut [18].

Devastating effects of injurious insect-pests and diseases in *N. cataria* are not only harmful for the plant but also impair the quality of the produce, thus hampering its medicinal value [25]. One bacterial disease and one insect pest that affect this plant have been recorder. Xantomonas leaf spot (*Xantomonas campestris*) is a disease recorded in California. Symptoms consist of small brown flecks that are visible from both sides of the leaf. The flecks later develop into larger, dark brown, angular spots [26]. The feeding insects of small leafhopper *Eupteryx melissae* cause characteristic yellowish-white discoloration of the leaves and injury to the plants [27].

3. Chemical composition

Chemical analysis of the air dried flowering aerial parts of *N. cataria* showed 6.2% of moisture, 7.9% of ash, 15.6% crude fiber, 9.1% crude protein, 4.9% crude lipids and 62.5% carbohydrate. Fixed oil extracted from the air dried flowering aerial parts of *N. cataria* contained palmitic (20.3%), stearic (18.6%), oleic (14.2%), palmitoleic (9.6%), linoleic (9.3%), myristic (7.2%), linolenic (5.8%), arachidic (4.1%) and lauric (3.7%) acids. Unsaponifiable matter components are: henetricontane (26.0%), β-sitosterol (18.6%), hexacosane (10.2%), stigmasterol (8.9%) nonacosane (6.8%), campesterol (6.5%), α-tocopherol (5.3%), dodcane (4.0%), dotriacontane (3.0%) and pentacosane (0.8%) [28].

The aromatic volatiles are produced in the glandular trichomes on the leaf epidermis [8]. Essential oil of *N. cataria* is a colorless, mobile liquid with a pleasant herb-citrus aroma with tones of geraniums [12]. The main essential oil constituents of catmint were nepetalactones, geraniol and α-pinene, while nerol, citronellal, neral and caryophyllene oxide were the main constituents of lemon catnip [11]. The review of essential oil composition of different samples from literature is given in Table 1.

Table 1. Volatile compounds identified in *N. cataria* according to literature

Source	Reference	α-pinene	1,8-cineole	Citronellal	Neral (citral b)	Nerol (Z-geraniol)	Geraniol	Geranial (citral a)	Citronellol	Citronellyl acetate	Geranyl acetate	4aβ,7α,7aα nepetalactone (E,E-nepetalactone)	4aα,7α,7aβ nepetalactone (E,Z-nepetalactone)	4aα,7α,7aα nepetalactone (Z,E-nepetalactone)
Argentina, Cordoba Province	[29]	0.1	0.1	-	-	-	-	-	-	-	-			
Bulgaria, Balchik	[30]	-	-	-	-	-	-	-	-	-	-	11.0	24.0	-
Bulgaria, Piridop	[30]	-	-	-	-	-	-	-	-	-	-	6.0	78.0	-
Crimea, Nikita (cv. 'Peremozhets')[1]	[31]	-	-	1.6	-	-	8.0	10.5	33.1	-	-	33.8		
Egypt, Giza[2]	[18]	0.8	-	0.8	14.2	1.1	14.3	19.9	-	-	-	23.7		
Egypt, Giza (*N. cataria* var. *citriodora*)	[11]	0.5	-	14.6	8.9	21.0	0.1	-	-	-	-	-	-	-
Egypt, Giza (*N.cataria*)	[11]	2.8	-	1.0	-	-	11.7	-	-	-	-	-	-	35.2
Germany, Heidelberg (*N. cataria* var. *citriodora*)	[32]	0.7	-	0.8	3.7	-	19.6	4.9	31.1	-	-	0.6	4.5	[illegible]
Germany, Heidelberg (*N.cataria*)	[32]	0.6	-	-	0.1	-	-	0.1	-	-	-	0.7	0.2	[illegible]
Germany, Munich (*N. cataria* var. *citriodora*)[3]	[24]	-	-	1.9	13.3	16.4	29.2	17.3	12.7	tr	0.2	-	-	-
Germany, Munich (*N. cataria* var. *citriodora*)[4]	[22]	-	-	1.9	12.0	19.1	28.3	15.6	14.4	tr	tr	-	-	-
Iran, Borujerd	[33]	3.3	1.9	-	-	-	-	-	-	-	-	-	53.9	-
Iran, Reen	[34]	tr	-	tr	0.1	-	tr	0.1	-	-	-	97.7		

Iran, Shiraz	[35]	4.6	-	-	-	-	-	-	-	-	-	-	55.0	31.2
Iran, Shiraz[5]	[36]	3.4	-	-	-	-	-	-	-	-	-	-	56.8	-
Iran, Teheran[6]	[37]	-	-	-	-	32.2	4.3	52.0	9.0	-	-	-	-	-
Italy, Binasco	[38]	-	-	-	-	55.3	8.3	-	6.0	0.4	-	4.4		
Korea, Muhak	[39]	-	1.5	-	-	-	-	0.1	-	-	-	90.9		
Lithuania, Kaunas	[40]	tr	0.4	0.3	0.7		5.5	1.0	6.9	13.4	54.8			
Pakistan, Karachi	[41]	10.4	21.0				6.8				8.2			
Poland, Lodz (*N. cataria* var. *citriodora*)	[1]	-	-	1.6	6.6	24.4	23.5	8.2	14.0	-	-	-	-	-
Poland, Western Pomerania (hydro-distillation)[7]	[42]	-	-	1.0	15.0		31.8	21.6	25.3	-	-	-	-	-
Poland, Western Pomerania (steam-distillation)[7]	[42]	-	-	1.4	7.8		28.8	9.3	38.2	-	-	-	-	-
Serbia, Miljević[8]	[10]	2.5	-	-	-	-	-	-	-	-	-	-	-	28.7
Turkey, Erzurum	[43]		0.7	-	-	-	-	-	-	-	-		70.4	6.0
Ukraine, Kiew (cv. 'Melody')	[12]	-	-	-	7.4	22.4	23.3	9.4	11.4	-	-	6.1		
Ukraine, Kiew (cv. 'Peremozhets')	[12]	-	-	-	7.7	22.0	24.4	9.6	12.3	-	-	10.6		
USA, New Jersey (*N. cataria* cv. 'CL1')	[19]	-	-	-	1.9	-	10.3	2.5	19.8	-	-	-	-	-
USA, New Jersey (*N. cataria* cv. 'CL2')	[19]	-	-	-	-	-	-	-	0.2	-	-	-	0.3	0.2
USA, New Jersey (*N. cataria* cv. 'CN3')	[19]	-	-	-	-	-	-	-	0.3	-	-	-	-	0.6
USA, New Jersey (*N. cataria* cv. 'CN5')	[19]	-	-	-	1.3	-	4.4	1.5	7.7	-	-	-	-	-
USA, New Jersey (*N. cataria* cv. 'CN6')	[19]	-	-	-	2.4	-	12.7	3.4	21.8	-	-	-	-	-
USA, New Jersey (*N. cataria* cv. 'CR9')	[44]	0.5	-	-	-	-	-	-	-	-	-	-	62.6	-
USA, New Jersey (*N. cataria* var. *citriodora*)[9]	[19]	-	-	-	4.5	-	25.7	5.1	34.8	-	-	-	6.6	5.9
USA, Oklahoma (*N. cataria* var. *citriodora*)	[45]	-	-	-	4.9	-	13.7	5.6	48.3	-	-			
USA, Oklahoma (*N. cataria*)	[45]	-	-	-	-	-	-	-	-	-	-			

[1]Water-ethanol extract; [2]Average value for two harvests; [3]Average value of different nitrogen fertilization levels; [4]Average value of different water supply l stages; [6]diethyl ether extract; [7]Average value for two different GC temperature programs; [8]Average value of different plant tissue (flowers, leaves, s flowering); [9]Average value from samples harvested at different times

Nepetalactones are a specific type of monoterpene known as iridoids. The stereochemical variation of the nepetalactones is contributed to the biosynthetic pathway. Four nepetalactone stereoisomers with differing stereochemistry at the 4α and 7α positions are observed at different rations in various *Nepeta* species (referred to as *Z*,*Z*-, *Z*,*E*-, *E*,*Z*- and *E*,*E*-) [46]. However, metabolism of nepetalactone by *N. cataria* plants yielded a significant amount of dihydronepetalactone that were bound to plant components [47]. Also, nepetalactone was labeled from either nerol or citronellol [48].

In the wild *N. cataria* essential oil from 45 compounds were isolated, and the chemical composition varies little during its life cycle. Essential oil is mostly composed of citronellal, neral, geranial, citronellol, nerol and geraniol. Small amounts of other oxygenated monoterpenes were isolated, while sesquiterpenes were β-caryophyllene and α-humulene. No nepetalactone were found in the oil. This may be explained by the variation of chemical composition during the hydrodistillation. In addition, drying the plant material before distillation did not affect the composition [49].

The composition of *N. cataria* essential oil at different growth stages (vegetative, floral budding, full flowering and fruit settings) shows that nepetalactones were the major constituents of all growth stages [36; 50]. There are noted seasonal variations of volatile compounds from different *N. cataria* plant tissues (stems, leaves and flowers). In the flower oil 65 components were recorded with sesquiterpenes as the dominant component (54.8%), while the leaf oil before and during flowering contains mainly monoterpenes (54.6% and 94.0%, respectively), with *Z*,*E*-nepetalactone as the most abundant components. As for the stem oil the dominant were acids [10]. For instance, the aroma of fresh herb changes after drying due to losses of the most volatile constituents and consequently green aroma notes. In addition, differences in the quantitative composition of volatile compounds isolated by the different techniques were considerable [40]. The changes in the essential oil composition were observed across harvests suggesting that ecological factors during growth stages may play a major role [19]. Various drying methods had a significant effect on the essential oil content and composition [51].

Research conducted in Poland confirmed that the essential oil of *N. cataria* var. *citriodora* is rich in monoterpene alcohols citronellol and geraniol, and the monoterpene aldehydes neral and geranial. The yield from steam distillation was better than that from hydrodistillation, but lower concentrations of neral and geranial were obtained. Total monoterpene aldehydes was higher alter hydrodistillation whereas steam distillation gave an oil richer in monoterpene alcohols [42].

Apart of essential oil, *N. cataria* contain non-volatile compounds. The review of the main compounds usually quantified in this plant is presented in **Table 2**, while the list of individual non-volatile compounds is presented in **Table 3**.

Table 2. Quantification of phenolic and flavonoid content in *N. cataria*

Extraction	Phenolic Content	Flavonoid Content	Ref.
Methanol extract	0.75-1.4 % of dry mass	0.30-0.46% of dry mass	[52]
Ethanol extract	14.66 and 26.30 mgGAE/g dry plant	21.40-25.07 mg/100 g dry plant	[53]
70% MeOH in H_2O with 0.1% AcOH	11.3 mg/g, 12.3 mg/g		[54]

Table 3. Polyphenols identified in *N. cataria* according to literature

α-Amyrin [28]	Squalene [28]	Campesterol [28]
Stigmasterol [28]	β-Sitoserol [28]	Caffeic acid [54]
Chlorogenic acid [31]	Cichoric acid [53]	Coumaric acid [31]
Rosmarinic acid [53; 54]	Caffeoylquinic acid [31]	Acacitine-7-glycoside [31]
Quercitrin [53]	Quercetin 3-O-galactoside (Hyperoside) [53]	Coumaroyl glycoside [31]
Apigenin [31; 53; 54]		Luteolin [54]
<u>and its derivatives:</u>		<u>and its derivatives:</u>
Apigenin 7-O-glucuronide [52]		Luteolin 7-O-glucuronide [52]
Apigenin diglucuronide [54]		Luteolin 7-O-glucurono-(1→6)-glucoside [52]
Apigenin glucoside [54]		Luteolin diglucuronide [54]
Apigenin glucuronide [54]		Luteolin glucoside [54]
Apigenin-7-diglicoside [31]		Luteolin glucuronide [54]
Apigenin-7-glycoside [31]		Luteolin-7-diglicoside [31]
		Luteolin-7-glycoside [31]

4. Biological activity

The medicinal uses of plants have proved to be a good source of natural products for treating various diseases. In developing countries, the majority of the population still uses traditional folk remedies obtained from medicinal plants [55]. *N. cataria* has a long history of being used in traditional medicine as well as being used daily as seasoning, tea as soporific and sedative (headaches, pain relief, convulsions) and against gastrointestinal (stomach upsets, diarrhea, vomiting) and respiratory diseases (colds, coughs, asthma, bronchitis, sore throats, pneumonia). It has been used to induce sweating (fever) and to treat female disorders (emenagogue) and rheumatism [56]. There are references that *N. cataria* has a mild hallucinogenic effect, "cannabis like", in humans when smoked [6; 7].

Some of these applications in traditional medicine have been scientifically proven According to scientific reports, *N. cataria* possess antioxidant, hepatoprotective and antidiabetic activities, as well as sedative, antidepressant, spasmolytic, anti-nociceptive and anti-inflammatory activities. Experiments show that this plant influences sexual activity, and expresses anticancer properties. Antimicrobial activity against a number of bacteria is also noted, as well as repellent and insecticidal properties. Nematodidal and allelopathic effects are also noted.

4.1. Antioxidant activity

Reactive oxygen species (ROS) are highly reactive molecules and can damage cell structures and alter their functions. The shift in the balance between oxidants and antioxidants in favor of oxidants is termed oxidative stress, which contributes to many pathological conditions and diseases [57]. However, recently, herbs and spices have been identified as sources of various phytochemicals, many of which possess powerful antioxidant activity. Thus, herbs and spices may have a role in antioxidant defense and redox signaling [58].

The antioxidant capacities of the *N. cataria* extracts were determined using ABTS+ radical scavenging assay and averaged between 29.7 and 30.6 μM equivalent/ gDW [54]. In DPPH assay, the *N. cataria* extract showed slight antioxidant activity whereas the essential oil remained inactive. In the latter case both the extract and the essential oil exerted weak activity having inhibition ratios of linoleic acid oxidation at 16.4% and 27%, respectively [43]. Antioxidant activity of *N. cataria* essential oil was employed by DPPH free-radical scavenging, and with IC_{50} value of 80.62 μg/mL *N. cataria* essential oil could be regarded as its strong antioxidant potential [33].

4.2. Antidiabetic and hepatoprotective activity

A large number of medicinal preparations based on plants are recommended for the treatment of hyperglycemia and for their hepatoprotective effect [59]. The results obtained from *in vitro* analysis revealed that different successive extracts (petroleum ether, chloroform, ethyl acetate and ethanol) of *N. cataria* exhibited inhibitory effects against oxidative stress indices (NO and DPPH) and carbohydrate hydrolyzing enzymes (α-amylase, α-glucosidase and βgalactosidase) in linear relationships to some extent with concentration of inhibitors (dose dependant). Total ethanol, petroleum ether and chloroform extracts showed respectively the most potent reducing power, while ethyl acetate and ethanol Soxhlet exhibited moderate or low reducing activity. In addition the *in vivo* anti-glycemic, antioxidant, antilipidemic effects of chloroform, petroleum ether as well as crude ethanol extracts in comparison with gliclazide, as a reference antidiabetic drug, showed that these extracts have significant beneficial glycemic control, scavenging free radicals, normalize liver function, inhibit lipid synthesis associated with diabetic complication, as well as they play a principle role in treating and normalizing liver and pancreas structure. Hence, it could be concluded that *N. cataria* extracts may be applied clinically for reducing complications of diabetes mellitus together with the ideal anti-diabetic drug, glicalized [60].

The results of animal experiments showed that essential oil from *N. cataria* by supercritical fluid extraction significantly attenuated acetaminophen-induced liver damage. Further studies confirmed that *N. cataria* essential oil was able to increase mRNA expression of UGTs (uridine diphosphate glucuronosyltransferases) and SULTs (sulfotransferases), as well as to inhibit cytochrome CYP2E1 oxidase activities, and thereby suppressed toxic intermediate formation. Nrf-2 (nuclear factor erythroid 2–related factor 2) activation might be involved in essential oil induced up-regulation of phase II enzymes. Collectively, gathered data provided evidence that *N. cataria* essential oil protected the liver against acetaminophen induced liver injury mainly by accelerating acetaminophen harmless metabolism, implying that essential oil can be considered as a potential natural resource for developing hepatoprotective agent [61]. A significant increase of DNA damage in the liver occurred after CCl_4 administration. The damage was significantly decreased by methanol extract of *N. cataria* treatment (up to 50%). This study demonstrated that *N. cataria* methanol extract possesses anti-gentoxic effect [62].

4.3. Spasmolytic activity

Antispasmodic compounds are currently used to reduce anxiety, emotional and musculoskeletal tension, and irritability [63]. However, medicinal plants which possess antispasmotic compounds are often used in the treatment of gastrointestinal and respiratory disorders [64]. In isolated rabbit jejunum, *N. cataria* essential oil, papaverine and verapamil inhibited spontaneous and high K^+(80mM) precontractions, as well as shifted the Ca^{++} concentration–response curves (CRCs) to right, indicating calcium channel blocking activity. In isolated guinea-pig trachea, *N. cataria* essential oil and papaverine inhibited carbachol (1μM) and K^+ precontractions with similar potency, while verapamil was more potent against K^+. *N. cataria* essential oil also potentiated isoprenaline inhibitory CRCs, similar to papaverine, indicating papaverine-like PDE inhibitor activity. In isolated guinea-pig atria, *N. cataria* essential oil caused cardiodepression at around 25–80 times higher concentrations, similar to papaverine. These data indicate that *N. cataria* possesses spasmolytic and myorelaxant activities mediated possibly through dual inhibition of calcium channels and PDE, which may explain its traditional use in colic, diarrhea, cough and asthma [41].

4.4. Antidepressant and sedative activity

Mental disorders like anxiety and depression are very common today worldwide. A number of medicinal plants and medicines derived from these plants have shown antidepressant properties by virtue of combined effect of their medicinal constituents [65]. To control stress and anxiety, sedative drugs that have anxiolytic and sedative effects are used to temporarily calm the person and lead to pleasant sleep [66].

Experiments with chicks and supplementation with a hot water extract of *N. cataria* show that this plant caused a dose-dependent increase in the number, average episode duration, and average total duration of light sleep periods. This indicates that *N. cataria* possesses significant biological and potentially psychotropic activity [6]. Experiments with animals show that n-hexane extract of *N. cataria* leaves reduced immobility in the behavioral despair test but did not alter elevated plus maze and open-field parameters. Acute feeding and the acute and repeated administration of the ethanol extract of *N. cataria* leaves did not alter the behavior of mice. The data suggested that *N. cataria* has antidepressant properties [67].

4.5. Anti-nociceptive and anti-inflammatory activity

Medicinal plants are traditionally used worldwide as analgesic and for treating inflammatory disorders [68]. Anti-inflammatory activity of *N. cataria* extract was assayed by measuring nitric oxide concentrations after treating RAW 264.7 murine macrophages stimulated by *E. coli* lipopolysaccharide; the IC_{50} values averaged from 82-96 μg/mL depending on plant tissue (flowers, upper and lower leaves). All extract demonstrated radical scavenging capabilities and dose dependent activity in the nitric oxide [54].

The results of the study with *N. cataria* var. *citriodora* essential oil showed that in doses of 0.0005 and 0.001 mL/kg i.p. the general activity of female mice increased, and the 0.0005 mL/kg dose reduced their immobility. Moreover, *N. cataria* var. *citriodora* essential oil (0.0005 mL/kg) has anti-nociceptive properties, as the treated animals exhibited increased latency of tail withdrawal and reduced acetic acid-induced abdominal constrictions. Furthermore, *N. cataria* var. *citriodora* essential oil (0.0005 mL/kg) presented peripheric anti-inflammatory properties by reducing the induced edema after carrageenan injection. These effects may be due to the nepetalactone *E,E-* and *E,Z-* nepetalactone isomers, which were detected as the predominant active components in the phytochemical analysis. It was suggested that *N. cataria* var. *citriodora* essential oil mainly affected the central nervous system mechanism of pain [69].

4.6. Sexual activity

N. cataria induces pleasure in cats and humans. Because sexual behavior is involved in pleasure, the effect of *N. cataria* on sexual behavior and penile erection was evaluated in male rats that were acutely fed chow enriched with 10% *N. cataria* leaves. Furthermore, yawning was monitored as it was previously demonstrated that *N. cataria* modifies dopaminergic related behaviors and that sexual behavior is closely linked with the dopaminergic system. The general activity and the motor coordination were examined to investigate the possible motor and emotional interferences of the sexual performance. *N. cataria* treatment increased male rat's penile erection. A slightly facilitation on male rat sexual behavior and a decrease in general activity of *N. cataria* treated rats were observed. No effects on motor coordination and yawning episodes were detected by the *N. cataria* treatment. It was suggested that *N. cataria* increases penile erection and slightly improves male rat sexual behavior by affecting dopaminergic systems [70].

In addition, investigations on cats show that all cats respond to *N. cataria* but they express it actively, passively or with a combination of both types of responses, which mainly depends on age and sex, and early gonadectomy to a much lesser extent [71]. The influence of *N. cataria* var. *citriodora* dry extract on penetration of progesterone from hydrogel preparations containing 40% of ethanol into artificial lipophilic membranes which imitate *stratum corneum*, in comparison with activities of oleanolic and ursolic acids was studied. Results of this experiment have shown that *N. cataria* var. *citriodora* dry extract enhanced properties of progesterone into artificial lipophilic membranes. The extract also increased solubility of progesterone and decreased partition coefficient of progesterone [72].

4.7. Anticancer properties

Many studies have focused on the chemoprotective properties of plants. The anticancer characteristics of numerous plants are still being actively researched and some have shown promising results [73]. In the standard MTT test, the HaCaT (aneuploid immortal keratinocyte) and BEAS-2B (human bronchial epithelial *cells*) cells were exposed to different oil concentrations for 48 h. The CC_{50} of *N. cataria* oil was approximately 0.015% (v/v) for both cell lines, *N. cataria* var. *citriodora* oil exerted an equally toxic effect however at the concentration of 0.003-0.004% [32].

N. cataria plays an important role in anticancer treatment. The effect of total flavonoid extracted from *N. cataria* on human lung cancer cell line A549 based on the microfluidic device and Flow Cytometry was investigated. The results showed that *N. cataria* extract can disturb the expression of MicroRNA-126 and regulate the PI3K-AKT signaling pathway to meet the effect of anticancer. Taking all these results into consideration we can draw a conclusion that *N. cataria* extract may be used as a novel therapeutic agent for non-small cell lung cancer in the near future [74].

The cytotoxic and apoptogenic activity of methanol extracts, n-hexane, dichloromethane, ethyl acetate, n-butanol, and aqueous extracts and the essential oil obtained from the aerial parts of the *N. cataria* were evaluated with PC3, DU-145 (human prostate cancer) and MCF-7 (breast cancer) cell lines. The results suggest that further analytical elucidation of N. cataria in respect to finding new cytotoxic chemicals with anti-tumor activity is warranted [34].

4.8. Antimicrobial activity

The resistance of bacteria to antibiotics is raising serious concern globally. Medicinal plants could improve the current treatment strategies for bacterial infections [75]. The essential oil of *N. cataria* had strong inhibitory effects on the growth of three fungal species (*Bacillus cereus*, *B. subtilis* and *B. amyloliquefaciens*). The essential oil from *N. cataria* was found to have a low antimicrobial activity against *Staphylococcus aureus* while no activity was found against *Escherichia coli* and *Pseudomonas aeruginosa*. Results indicate that the significant antimicrobial effect may depend on the yield of nepetalactone [39]. Disk diffusion and broth microdilution assays were used for *in vitro* antimicrobial screening of antibacterial activities of the *N. cataria* essential oil. The essential oil showed good antibacterial activity, especially on *Salmonella typhi* [33]. The *N. cataria* essential oil exhibited activity against 11 bacteria and 12 fungi and a yeast, Candida albicans, with MIC values ranging from 12.5 to 250 μL/mL, while the methanol extract showed weaker activity [43].

The *N. cataria* essential oil exhibited antimicrobial activities against oral pathogens accumulated on the mucosal and dental surfaces of the oral cavity such as Streptococcus sp., *Enterococcus faecalis*, *Staphylococcus aureus*, *Candida* sp., at concentrations of 0.125-4.0 μL/mL. Moreover, the oil entirely inhibited growth of *Candida* species at a concentration less than 1 μL/mL. Based on these results, *N. cataria* essential oil can possibly be used as an antimicrobial agent in the treatment and the control of oral pathogens [50]. In addition, *N. cataria* can be used against common causes of food-borne infections such as bacteria (*S. aureus*, *S. flexneri*, *S. dysentery*, *S. sonnei* and *S. enterica*) and fungi (*A. flavus*, *A. fumigatus*, *A. clavatus* and *A. orizae*) [76]. *N. cataria* can be used in the complementary topical treatment of respiratory tract infections, as the oil showed high antibacterial activity against respiratory tract pathogens, including clinical isolates with reduced susceptibility to standard antibiotics [32].

4.9. Insecticidal and repellent activities

N,N-diethyl-m-toluamide (DEET), which is the most widely used insect repellent, only exhibited spatial repellency at higher concentrations of nepetalactone isomers (*Z,E*-nepetalactone and *E,Z*-nepetalactone) while *N. cataria* essential oil had excellent spatial repellency [77]. Another research showed that *N. cataria* essential oil had greater short term repellency than DEET and citronellal against the house fly (*Musca domestica*), American cockroaches (*Periplaneta americana*) and German cockroaches (*Blatella germanica*) [78].

N. cataria essential oil at a dose of 20 mg resulted in average repellency rates of 96% against stable flies (*Stomoxys calcitrans*) and 79% against houseflies (*Musca domestica*). These findings suggested that the application of a repellent could be used as part of filth fly management. Further evaluation of *N. cataria* essential oil toxicity were conducted to provide a broad spectrum safety profile of *N. cataria* essential oil use as a potential repellent for biting and nuisance insects in urban settings. The acute oral toxicity (LD_{50}) was found to be between 2710 and 3160 mg/kg BW in rats. The acute dermal toxicity (LD_{50}) was >5000 mg/kg BW, while the acute inhalation LD_{50} was observed to be >10000 mg/m3. Primary skin inhalation tested on New Zealand white rabbits showed that *N. cataria* essential oil is a moderate irritant, but non-irritant to the eye [79].

The repellent activity of two *N. cataria* essential oils (chemotype A with 91.95% Z,E-nepetalactone and chemotype B with 16.98% Z,E- and 69.83% E,Z-nepetalactone isomers) were tested by using the topical application bioassay. The oils showed high repellent activity against *Anopheles gambiae* comparable with the synthetic repellent DEET, whilst for *Culex quinquefasciatus*, lower repellent activity was recorded. Further repellency testing against *A. gambiae* by using the purified nepetalactone isomers revealed an overall lower repellent activity.Conversely, the mixtures of nepetalactones revealed not only a synergistic effect between the two, but also a surprising ratio-dependent effect. In a tick climbing repellency assay using *Rhipicephalus appendiculatus*, the oils showed high repellent activity comparable with data for other repellent essential oils. In a field trapping assay with *Dermanyssus gallinae*, addition of the oils and a combination of the two, to traps pre-conditioned with *D. gallinae*, all results show a significant reduction in trap capture. In summary, these data suggest that although the nepetalactone isomers have the potential to be used in human and livestock protection against major pathogen vectors, intact, i.e. unfractionated, *Nepeta* sp. essential oil offer potentially greater protection, due to the presence of both nepetalactone isomers [80].

An investigation of the biological effect of *N. cataria* essential oil on behavioral response of *Aedes aegypti* showed significantly higher escape rate from the contact chamber at 5% essential oil. With *Anopheles harrisoni* a higher escape response was seen at 2.5% essential oil from the contact chamber, while in noncontact chamber a higher escape response was observed at a concentration of 5%. Results showed that this compound exhibits both irritant and repellent actions [81]. The vaporization enthalpy and vapor pressure of two nepetalactone found in *N. cataria* proved to be quite effective in repelling mosquitos, comparable to DEET. The vapor pressures evaluated in this work suggested that the two stereoisomers have similar volatility to DEET at ambient temperatures [82].

4.10. Antiparasitic activity

Anisakidosis is one of the most important fish-borne zoonotic diseases related to the ingestion of nematode larvae. In vitro tests revealed a complete inactivation of parasites after 6 and 12h of treatment, at 10 and 5% of essential oil in saline solution. The data obtained showed activity against *Anisakis* L3 larvae [38].

4.11. Allelopathic activity

In order to explore the possibility of production of natural herbicides, different concentrations of *N. cataria* essential oil were applied on seeds *Hordeum spontaneum*, *Taraxacum officinale*, *Avena fatua*, *Lepidium sativum*, *N. cataria* and *Ocimum basilicum*. Based on the results, it could be concluded that essential oil of *N. cataria*, especially in higher concentrations (600 and 1200 μL/L) showed strong phytotoxic effects in the seed germination and seedling growth of examined crops and weeds [35].

5. Conclusions

Nepeta cataria L. (Lamiaceae), catnip or catmint, is a perennial herbaceous plant which is cultivated for ornamental purposes, for honey bee pastures and for being used in pharmaceutical and food industry, as well as in pet toy industry. The main bioactive compounds are nepetalactones, but there are varieties characterized by being completely devoid of or producing little amounts of nepetalactone. *N. cataria* var. *citriodora* is characterized by a distinct lemony aroma and thus called lemon catnip. *N. cataria* has a long history of application in traditional medicine, and recent investigations proved that this plant possess antioxidant, hepatoprotective, antidiabetic, sedative, antidepressant, spasmolytic, anti-nociceptive, anti-inflammatory, sexual behavioral activities, anticancer, antimicrobial, repellent and insecticidal properties, as well as nematodidal and allelopatic effects.

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