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THE PHARMACOLOGICAL IMPORTANCE OF *BALLOTA NIGRA* –A REVIEW

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ABSTRACT

Ballota nigra is a plant belonging to the Lamiaceae family. It is used traditionally for many purposes especially as neuro-sedative remedy. The chemical analysis of *Ballota nigra* showed that the plant contained phenylpropanoid glycosides, diterpenes, flavonoids, oils and betaines. Previous pharmacological investigations of *Ballota nigra* revealed that the plant possessed neurosedative, antidepressant, antioxidant, antibacterial, insecticidal, anticholinesterase and antifeedant effects. This review highlight the chemical constituents and pharmacological effects of *Ballota nigra*.

Keywords: Phenylpropanoid glycosides, *Ballota nigra*, Pharmacological investigations.

INTRODUCTION

For the past decades, there has been an increasing interest in the investigation of the pharmacological effects of different extract obtained from plants as a source of new drugs[1-61]. *Ballota nigra* is a plant belonging to the Lamiaceae family. It is used traditionally for many purposes especially as neuro-sedative remedy. The chemical analysis of *Ballota nigra* showed that the plant contained phenylpropanoid glycosides, diterpenes, flavonoids, oils and betaines. Previous pharmacological investigations of *Ballota nigra* revealed that the plant possessed neurosedative, antidepressant, antioxidant, antibacterial, insecticidal, anticholinesterase and antifeedant effects. This review was designed to highlight the chemical constituents and pharmacological effects of *Ballota nigra*.

Synonyms

Ballota nigra subsp. meridionalis (Bég.), *Ballota nigra subsp.* foetida (Vis.) Hayek, *Ballota nigra subsp.* meridionalis (Bég.) Bég., *Ballota nigra* L. subsp. nigra, *Ballota nigra subsp.* ruderalis (Sw.) Briq., *Ballota nigra* subsp. uncinata (Bég.) Patzak, *Ballota nigra*s ubsp. velutina (Posp.) Patzak [62].

Taxonomic classification

Kingdom: Plantae, Subkingdom: Tracheobionta, Superdivision: Spermatophyta, Division: Magnoliophyta, Class: Magnoliopsida, Subclass: Asteridae, Order: Lamiales, Family: Lamiaceae (alt: Labiatae),Genus: Ballota, Species: *Ballota nigra* L [63].

Common names:

Arabic: Farasyoonaswad, Sendian el ardh; English: Black horehound, Horehound; French: Ballotevulgaire; German: Stinkandorn; Italian: Cimiciottacomune; Spanish: marrubionegro [63].

Family: Labiatae

Distribution

The plant is considered to be a weed in western, central and northern Europe, but was intentionally introduced to the United States [64].

Traditional uses

Leaves of *Ballota nigra* were used as an antidote for the bite of a mad dog. It was used in European countries as sedative and tranquilizer. It is also used externally for wound-healing properties and internally for gastrointestinal disorders [65-69]. However, internally, it is used as a sedative in cases of hysteria and

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hypochondria, as a spasmolytic for stomach cramps and complaints, for whooping cough and to increase bile flow. it is also used to treat nervous, upset stomach, nausea and vomiting. In France, it is traditionally used in the symptomatic treatment of nervous disorders in adults and children, especially for sleep disorders and for the symptomatic treatment of coughs. Furthermore, its enemas and suppositories are used against worm infestation. Externally, it is used for gout [64].

Description

*Ballota nigra*is 46-153 cm tall perennial herbs. The stem is erect, ascendant 4-angled, simple or usually branched below, glandular and pubescent. Cauline leaves are ovate-orbicular to ovate, 25-78 x 30-60 mm. Middle and upper cauline leaves are 1-1.5 x long as broad; lower cauline leaves are almost as long as broad, acute(-mucronate), crenate-dentate, rotundate, truncate or sometimes reniform at base, distinctly petiolate, pubescent on both sides. Inflorescence is long, lax below. Floral leaves are ovate to elliptic-ovate, 3-38 x 2-31 mm. Each flower has 2 bracteoles, which are sessile, linear-subulate, shorter than calyx tube, 2.5-4 mm, acute, entire, pubescent on both sides. Verticillasters are 2-40 (-48) flowered. Calyx is persistent, 6-10 mm, obconical to obconicalcampanulate, dilated above into 5 teeth. Calyx teeth are 2-3(-5) mm, longer than broad, triangularacuminate, porrect, and mucronate. Margins and outside of calyx are densely glandular and nonglandular hairy, inside is not dense, 10-veined. Corolla is purple, 9-13 mm, longer than the calyx, tube with a ring of hairs inside, bilabiate, upper lip is concave, emarginate, long non-glandular hairy. The four stamens are didynamous, not included in the corolla tube[64, 70].

Part used : The aerial parts of the plant are used medicinally [64].

Chemical constituents

In root and stem flavonoids, terpenes and phenols were present in ethanol, chloroform, and ethyl acetate soluble fraction, while in leaves: flavonoids, terpenes, and phenols were present in ethanol, chloroform, and n-butanol fractions [71].

The total phenolic contents (TPC%), total flavonoid contents (TFC%) and ratio of total flavonoid content (TFC%) to total phenol content (TPC%) for *Ballota nigra subsp. nigra* were 1.701, 0.680 and 0.400, and for *Ballota nigra subsp. foetida* were1.057, 0.312 and 0.295 respectively [72].

The aerial part contained flavonoids: apigenin-7-glucoside, vicenin-2, tangeretin, luteolin-7-lactate and luteolin-7-glucosyl-lactate. It is also contained elabdane diterpenoids: ballotinone, ballonigrine, 7α-acetoxymarrubiin, ballotenol, preleosibirin and 13-hydroxyballonigrinolide. Many phenylpropanoid glycosides were isolated from an alcoholic extract including verbascoside, forsythoside B, arenarioside, ballotetroside, alyssonoside, lavandulifolioside and angoroside A and a non-glycosidic derivative, (+)-(E)-caffeoyl-L-malic acid. It contained trace volatile oil with unpleasant smell [64,73-82].

The fatty acid composition of the petroleum ether extract of *B nigra subsp. anatolica*was determined by GC/MS analysis. Thirteen components were identified, constituting 99.8% of the petroleum ether extract. These components included (%): 10-undecenoic acid 1.5%, myristic acid 1.8%, palmitoleic acid 0.4%, palmitic acid 36.0%,11,13-dimethyl-12-tetradecen-1-ol acetate 2.1%, phytol 4.6%, linoleic acid 14.3%, oleic acid 10.6%, linolenic acid 9.8%, stearic acid 9.2%, arachidic acid 4.1%, 6-hexadecenoic acid, 7-methyl 1.4% and behenic acid 4.0% [83].

Kazemizadeh *et al.*, isolated twelve compounds from the essential oil of *B. nigra subsp. anatolica*. They found that the main constituents of the essential oil of *B. nigra subsp. anatolica* were germacrene D (18.1%), nerolidolepoxyacetate (15.4%), sclareol oxide (12.1%), linalyl acetate (11.5%), and β-caryophyllene (10.5%) [84].However, Ertaş*et al.*,isolated thirteen compounds. The major components were 1-hexacosanol (26.7%), germacrene-D (9.3%) and caryophyllene oxide (9.3%) [83]. The chemical composition of essential oils obtained from the roots, stems, and leaves of *Ballota nigra*, growing in Serbia, was investigated by gas chromatography/mass spectrometry analyses. Kovats indices, mass spectra, and standard compounds were used to identify a total of 115 individual compounds. The plant produces two types of essential oils. Oils derived from stems and leaves were sesquiterpene rich (78.17% and 88.40%, respectively), containing principally beta-caryophyllene, germacrene D, and alpha-humulene, present in appreciable amounts. In contrast, oil derived from the root was dominated by p-vinylguiacol (9.24%), borneol (7.51%), myrtenol (7.13%), trans-pinocarveol (5.22%), pinocarvone (4.37%), 2-methyl-3-phenylpropanal (4.32%), and p-cymen-8-ol (4.30%) [85]. The chemical composition of the essential oil of *Ballota nigra* L. sspfoetida obtained from the flowering aerial parts was analyzed by GC/MS. From the 37 identified constituents of the oil, beta-caryophyllene (20.0%), germacrene D (18.0%) and caryophyllene oxide (15.0%) were the major components [86]. However, the major compounds identified in the flowering and fruiting aerial parts oils were beta-caryophyllene (22.6% and 21.8%), caryophyllene oxide (18.0% and 20.5%) and germacrene-D (16.5 and 13.1%) [87].

Cr was found above permissible value (above 1.5 mg/kg) in all parts of the plant. Ni was above WHO limit in *B. nigra* root and leaves (3.35 ± 1.20 mg/kg and 5.09 ± 0.47 mg/kg, respectively). Fe was above permissible value in all parts of *B. nigra* (above 20 mg/kg). Cd was above permissible value in all parts of the plant (above 0.3 mg/kg). Pbwas above WHO limit (above 2 mg/kg) in all

parts of *Ballota nigra* [71].

Pharmacological effects

Antioxidant effect

Aerial parts of *Ballota nigra* were extracted with methanol and subsequently partitioned by liquid-liquid extraction between petroleum ether, dichloromethane, ethyl acetate and n-butanol. The extracts and subfractions were assayed for DPPH and HO scavenging and phosphomolybdenum reduction. The maximum inhibition of deoxyribose degradation was demonstrated for *B. nigra* ethyl acetate and Butanol fractions (79.32 ± 1.62% and 82.04 ± 2.28%, respectively). *B. nigra* ethyl acetate had the highest reducing capacity of 318.6 ± 14.7 mg/g and 271.4 ± 2.4 mg/g ascorbic acid equivalents [88].

The antioxidant properties of ethanol extracts of 16 Ballota species belonging to the Lamiaceae family and growing in Turkey on superoxide anion formation and lipid peroxidation were investigated. The extract of *Ballota nigra* subsp. anatolica, exhibited remarkable anti-superoxide anion formation [89]. .

The antioxidant activity of five phenylpropanoid esters was investigate using cell-free experiments and cellular experiments including isolated polymorphonuclear neutrophils (PMN). Effects of phenylpropanoid esters against reactive oxygen species as superoxide anion, peroxide hydrogen, hypochlorous acid and hydroxyl radical were tested. These molecules are liberated by PMN during inflammatory disorders, so that reproduction of this process in vitro stimulating PMN by chemical stimulants was undertaken. Results concerning antioxidant investigations evidence an ability to scavenge reactive oxygen species. Inhibitory concentrations at 50% obtained are comparable to those of known antioxidant drugs (mesna or N-acetyl cysteine). Moreover, the use of different stimuli having various pathways of action on PMN oxidative metabolism permits to establish that each phenylpropanoid ester has its own particular way of action by using proteine kinase C or phospholipase C pathways [90].

Various polyphenols isolated from the European *Ballota nigra* L., including phenylpropanoid derivatives (verbascoside, forsythoside B, arenarioside, and ballotetroside and one non-glycosidic phenylpropanoid, caffeoyl-L-malic acid verbascoside, forsythoside B, arenarioside, and ballotetroside) and one non-glycosidic phenylpropanoid, caffeoyl-L-malic acid inhibited Cu^{2+}-induced LDL peroxidation. The effectiveness of these compounds was compared to the activity of quercetin, a well-known polyphenol inhibitor of Cu^{2+} induced LDL oxidation. Antioxidant efficacious doses ED_{50} of arenarioside and ballotetroside were 1.8 microM and 7.5 microM respectively, while in the same conditions, the ED_{50} of forsythoside B and verbascoside were similar (1 microM) and those of quercetin and of caffeoyl-L-malic acid were 2.3 microM and 9.5 microM respectively. Spectrophotometric studies show that quercetin is a Cu^{2+}chelator while phenylpropanoid glycosides and caffeoyl-L-malic acid are not Cu^{2+}chelators. Therefore, phenylpropanoid glycosides are strong inhibitors of Cu^{2+}-induced LDL oxidation, independent of any capacity to act as Cu^{2+}chelators [74].

The antioxidant activity of the petroleum ether (BNP), acetone (BNA), methanol (BNM) and water (BNW) extracts prepared from both the root and the aerial parts of *B. nigra subsp. anatolica* were investigated by using CUPRAC and ABTS cation radical decolourisation assays. The water extract exhibited over 80% inhibition in ABTS cation radical scavenging assay at 100 µg/mL. The water extract exhibited higher inhibition (88.00%) than the reference compounds, α-tocopherol and BHT, in ABTS cation radical scavenging assay at 100 µg/mL. The acetone and methanol extracts exhibited 70.10 and 72.60% inhibition in ABTS cation radical scavenging assay at 100 µg/ mL, respectively. The acetone, water extracts and α-tocopherol treatment exhibited 0.92, 1.10 and 1.65 inhibition in CUPRAC at 100 µg/mL, respectively [83].

Hypoglycemic effect

The hypoglycemic effect of *Ballota nigra* extract was investigated in Alloxan-induced diabetes mellitus in rats. Administration of aqueous extract of *B. nigra* extract significantly reduced glucose in both healthy and diabetic rats [91].

Neurosedative effect

Phenylpropanoid derivatives isolated from *Ballota nigra* showed neurosedative activity and exhibit potent antioxidant activities which are of therapeutic interest [73, 79]. A mixture of phenylpropanoid glycosides significantly prolonged sleep induced by pentobarbital, reduced locomotor activity in mice, and produced a slowing of the electroencephalographic trace [92]. The antidepressant activities of *B. nigra var. anatolica* was proved by behavioural tests in rats [93].

The ability of five phenylpropanoids (verbascoside, forsythoside B, arenarioside, ballotetroside, and caffeoyl malic acid) isolated from a hydroalcoholic extract, to bind to benzodiazepine, dopaminergic, and morphinic receptors was investigated. To carry out these studies, affinity tests with rat striata, entire brains and receptor rich preparations were employed. Results show that four of the five compounds are able to bind to the studied receptors. Inhibitory concentrations at 50% were determined and vary from 0.4 to 4.7 mg/ml. This may be in relation with the *Ballota nigra* known neurosedative activities [90].

Antimicrobial and insecticidal effect:

B. nigra subsp. anatolica, B. nigra subsp. uncinata and *B. nigra subsp. Foetida* showed antibacterial activity against *Listeria monocytogenes , L.*

ivanovii, *L. innocua* and *L. murrayi*. The inhibition zones diameters of the ethanolic extracts of *B. nigra subsp. foetida* were 18, 15, 10 and 15; for *B. nigra subsp. nigra* were 11, 10, 0 and 10; and for *B. nigra subsp. uncinata* were 16, 20, 0 and 10 mm, against *L. monocytogenes*, *L. ivanovii*, *L. innocua* and *L. murrayi* against *L. monocytogenes*, *L. ivanovii*, *L. innocua* and *L. murrayi* respectively [94].

The phytochemicals (flavonoids, terpenoids, saponins, tannin, alkaloids, and phenol) in different parts (root, stem, and leaves) of *Ballota nigra* was investigated and correlated to inhibition of microbes (bacteria and fungi), protozoan (Leishmania), and heavy metals toxicity. In root and stem flavonoids, terpenes and phenols were present in ethanol, chloroform, and ethyl acetate soluble fraction; these were found to be the most active inhibiting fractions against all the tested strains of bacteria, fungi, and leishmania. While in leaves flavonoids, terpenes, and phenols were present in ethanol, chloroform, and n-butanol fractions which were the most active fractions against both types of microbes and protozoan (leishmania) in in vitro study. Ethanol and chloroform fractions show maximum inhibition against Escherichia coli (17 mm). The phytochemical and biological screenings were correlated with the presence of heavy metals in selected plant *Ballota nigra* [71].

The oil was active against both Gram-negative and Gram-positive bacteria as well as against three Candida species [86].

The essential oils from the aerial parts of *Ballota nigra* L. sspfoetida (Lamiaceae) collected at flowering and fruiting times, showed antifungal activity against nine plant pathogenic fungi [87].

Phenylpropanoid glycosides isolated from generative aerial parts of *Ballota nigra* exhibited moderate antimicrobial activity against *Proteus mirabilis* and Staphylococcus aureus including one methicillin-resistant strain [95].

Ballota nigra contained diterpenes, these compounds with well-known insecticide and antifeedant activities. The whole plant of *Ballota nigra* L. is used in repellent fumigation against insects [76, 96]**.**

Anticholinesterase activity

The acetone extract of *Ballota nigra L. subsp. anatolica* showed 71.58% inhibitory activity against butyrylcholinesterase and 44.71% inhibitory activity against acetylcholinesterase enzyme at 200 µg/mL. The acetone extract indicated higher inhibitory effect against butyrylcholinesterase enzyme than the reference compound, galanthamine[83].

Contraindication and adverse effects

Black horehound is listed by the Council of Europe as a natural source of food flavouring (category N3) . This category indicates that black horehound can be added to foodstuffs in the traditionally accepted manner, although insufficient information is available for an adequate assessment of potential toxicity [97].

No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages [64].However, black horehound is reputed to affect the menstrual cycle. In view of the lack of toxicity data, the use of black horehound during pregnancy and lactation should be avoided [97] .

Dosage

Daily Dose:single dose of the drug is 2 to 4 g or by infusion three times daily, liquid extract (1:1 in 25% alcohol): 1 to 3 ml, and tincture (1:10 in 45% alcohol): 1 to 2 ml [64, 97].

CONCLUSION

This review highlights the chemical constituents and pharmacological effects of *Ballota nigra* to open the door for further pharmacological studies and clinical uses of the plant as a result of effectiveness and safety.

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