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An Update on Therapeutic Role of *Ballota Nigra* (Black Harehound)-A Review

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ABSTRACT

Ballota nigra (*B.nigra*) is a plant belonging to the Lamiaceae family. It is used traditionally for purposes of health benefits including diabetes. The chemical analysis of this plant has shown that the plant contains phenylpropanoid glycosides, diterpenes, flavonoids, oils and betaines. Previous black horehound pharmacological investigations showed that the plants its effects are neuro-sedative, antidepressant, antioxidant, antibacterial, insecticide, anticholinesterase and antifeedant. In this review, to compile the sources, chemical constituents, antioxidant, antimicrobial, and antidiabetic, anticholinesterase, and anticancer activities of *B.nigra* , classical as well as online-literature were studied which includes books on phytochemistry and the electronic search (SciFinder, Pubmed, the Web of Science, Scopus, Google Scholar and etc). The literature on the experimental and clinical trials of *B.nigra* gives clear evidence that the plant can be used as supplements to fight against life threatening diseases. This review highlights an update on the source of the plant, chemical constituents and pharmacological effects of *Ballota nigra* to open the door for further pharmacological and clinical utility of the plant.

Keywords: *Ballota nigra*, health benefits, anti diabetic, antioxidant, anti-inflammatory.

Introduction

There has been a growing interest in the investigation over the past decades of the pharmacological effects of various extracts obtained from plants as a source of new drugs. *Ballota nigra* is a plant that belongs to the family Lamiaceae. It is commonly used particularly as a neuro-sedative treatment for many purposes. *Ballota nigra's* chemical analysis showed the plant contains phenylpropanoid glycosides, diterpenes, flavonoids, oils, and betanes. Previous *Ballota nigra* pharmacological studies showed the plant has neuro sedative, antidepressant, antioxidant , antibacterial, insecticidal, anticholinesterase and antifeedant effects. This review

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has been designated in highlighting the chemical components and pharmacological effects of *Ballota nigra*. Our team has rich experience in research and we have collaborated with numerous authors over various topics in the past decade (Ariga *et al.*, 2018; Basha, Ganapathy and Venugopalan, 2018; Hannah *et al.*, 2018; Hussainy *et al.*, 2018; Jeevanandan and Govindaraju, 2018; Kannan and Venugopalan, 2018; Kumar and Antony, 2018; Manohar and Sharma, 2018; Menon *et al.*, 2018; Nandakumar and Nasim, 2018; Nandhini, Babu and Mohanraj, 2018; Ravinthar and Jayalakshmi, 2018; Seppan *et al.*, 2018; Teja, Ramesh and Priya, 2018; Duraisamy *et al.*, 2019; Gheena and Ezhilarasan, 2019; Hema Shree *et al.*, 2019; Rajakeerthi and Ms, 2019; Rajendran *et al.*, 2019; Sekar *et al.*, 2019; Sharma *et al.*, 2019; Siddique *et al.*, 2019; Janani, Palanivelu and Sandhya, 2020; Johnson *et al.*, 2020; Jose, Ajitha and Subbaiyan, 2020).

Distribution of the plant The plant is considered a weed in Western, Central and Northern Europe but was deliberately introduced to the U.S.(Marty, 1999). *Ballota nigra* Lamiaceae is a Mediterranean herb, but has a more consistent distribution of up to 800 meters above sea level in a wider range of fairly moist microhabitats; it has fewer than 15 leaves, typically erect and undulated, with white to dark pink flowers. Its distribution is positively influenced by elevation. *Ballota nigra* favors low pH soils, shares microhabitats of soil with heavy clay and silt, and organic matter. Such environments have a higher sand volume, moderatepH and fairly good soil moisture quality. The most important constituents of *Ballota nigra* are monoterpenes and sesquiterpenes(Bader *et al.*, 2003).

Synonyms

Ballota subsp nigra. *Ballota nigra* subsp: meridionalis (Bég.). Hayek, *Ballota nigra* subsp, foetida (Vis.) Meridionalis Bej., *Ballota nigra* L. SUPP. Nigra, nigra subsp Ballota. Briq., *Ballota nigra* subsp., Ruderalis (Sw.) Patzak, *Ballota nigras* subsp, uncinata (Bég.) Velutina Patzak (Posp.)

Traditional uses of *Ballota nigra*

The *Ballota nigra* leaves were used as an antidote for a mad dog's bite. In European countries it has been used as a sedative and tranquilizer. It is also used externally to treat wounds and internally to treat gastrointestinal disorders(Bézanger-Beauquesne, 1958; Yeşilada *et al.*, 1993). Within, however, it is used as a sedative in cases of hysteria and hypochondria, as a spasmolytic for stomach cramps and complaints, for whooping cough and to increase bile flow. It is also used

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to treat nervousness, stomach upset, nausea and vomiting. It is traditionally used in France in the symptomatic treatment of nervous disorders in adults and children, in particular in sleep disorders and symptomatic cough treatment. In addition, the enemas and suppositories are used against worm infestation. It is used for gout externally(Marty, 1999). Previous Ballota nigra studies demonstrated that the plant has antioxidant, antibacterial, insecticidal, anticholinesterase, and antifeedant effects(Didry *et al.*, 1999). Another study showed that a Ballota nigra extract is used to prepare pharmaceutical composition to promote skin pigmentation that helps prevent grey hair(Kolisnyk, Kovaleva and Goryacha, 2014). *Ballota nigra* aims to minimize weight and combat obesity even in the most complicated of conditions(Shukri *et al.*, 2016). Another study reports the organic content of organic acids in black horehound stems , leaves, corolla and calyces(Kolisnyk, Kovaleva and Goryacha, 2014).

Chemical constituents

B. L nigra. Black horehound, thrives along the coast, ruderal environments, neglected gardens on rich or poor soils, and is one of Europe's most common Lamiaceae species. It was used both in folk herbalism and officially, medicinally. It is mentioned, or used to be, in, for example, pharmacopoeias-French and Hungarian. Its functions include sedative, neuroprotective, spasmolytic, anti-inflammatory, antidiabetes(Qazan, 2008), and many other types of Ballota. The substances shall include: phenylethanoid / phenylpropanoid glycosides, coumarylated flavonoids, and diterpene(Bertrand, Tillequin and Bailleul, 2000; Seidel *et al.*, 2000; Tóth *et al.*, 2007; Vrchovská *et al.*, 2007); In ethanol, chloroform, and ethyl acetate soluble fraction, terpenes and phenols were present in root and stem flavonoids, while in the leaves: flavonoids, terpenes, and phenols were present in fractions of ethanol, chloroform, and n-butanol(Ullah, Ahmad and Ayaz, 2014).

Antidiabetic activity

The hypoglycemic effect of Ballota nigra extract has been reported in rats with diabetes mellitus caused by Alloxan. Giving aqueous extract of B. The nigra extract reduced glucose significantly in both healthy and diabetic rats. Administration of aqueous extract of *B. nigra* extract significantly reduced glucose in both healthy and diabetic rats(Nusier *et al.*, 2007). In addition to the verbascoside, forsythoside, arenarioside and ballotetroside phenylpropanoid glycosides, four additional compounds were isolated from Ballota nigra 's generative aerial parts: three

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phenylpropanoid glycosides, alyssonoside 5, lavandulifolioside 6, and angoroside A 7, and a non-glycosidic derivative(Janicsák, Tóth and Máthé, 2007). Beta sitosterol also exerts antioxidant activity in high fat dietary adipose tissue. A phytosterol (β-sitosterol) has been shown to improve glycemic control by activating IR and GLUT4 in high-fat adipose tissue and type 2 diabetic rats induced with sucrose(Ponnulakshmi *et al.*, 2019). Histopathological studies after eight weeks of ingestion of a high fat diet revealed all of NASH's prominent characteristics in humans(Mohan, Veeraraghavan and Jainu, 2015) .

Anti inflammatory activity

An experiment of Sever, Male Swiss albino mice and Sprague Dawley rats. The largest anti-inflammatory activity was observed in animals with an inflammatory regression of 95.7 per cent(Ullah, Ahmad and Ayaz, 2014).The purpose of this analysis was to check if the main polyphenolic compounds isolated from Ballota nigra were produced, four phenylpropanoid glycosides, verbascoside, forsythoside B, arenarioside, and ballotetroside, and one non-glycosid phenylpropanoid, caffeoyl-L-malic acid, inhibit Cu2 + -induced LDL peroxidation(Bouterfas *et al.*, 2016). Shogaol, a spicy ginger secluded compound that exhibits anti-inflammatory effects. Both Ballota nigra and Scomberomorous guttatus have the largest concentration of Pb and Zn substrates as their medicinal benefit(Rengasamy, G., Jebaraj, D.M., Veeraraghavan, V.P., Mohan, S.K., 2016; Jainu, Priya and Mohan, 2018; Chen, F.a, Tang, Y.b, Sun, Y.c, Veeraraghavan, V.P.d, Mohan, S.K.e, Cui, 2019).

Antioxidant activity

Methanolic extracts from shoots of Ballota nigra plants grown under ex vitro conditions have been assessed for the antioxidant potential. There are several mechanisms by which antioxidants can function, three different types of in vitro assays were used to determine the antioxidant ability of the plant material types tested(Antolovich *et al.*, 2002; Apak *et al.*, 2007). Finally, the LPO method was used to determine Ballota nigra extracts' ability to inhibit LA peroxidation by chain-breaking radical peroxyl scavenging(Pulido, Bravo and Saura-Calixto, 2000). LA peroxidation inhibition in Ballota nigra extracts was not very strong, at a concentration of 250 μg / mL ranging from 21-36 per cent. No significant difference between in vitro- and in vivo-derived shoot extracts was observed in the type of antioxidant activity. In methanol extracts of

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shoots from Ballota nigra plants initiated *in vitro* and *in vivo,* the antioxidant properties and total phenolic and flavonoid content were assessed. The plants were grown in a greenhouse and in the field, and analyzed during the stage of vegetation and flowering. The Ballota nigra shoot extract from wild-grown plants has also been investigated. The findings suggest that the Ballota nigra extracts' antioxidant ability appears to be due to their scavenging of free radicals and reducing metals, although they were less effective in preventing linoleic acid peroxidation. Strong antioxidant activity has been documented in aerial parts infusions. Prepared extractions of the various parts of the plant, and aqueous extraction of the aerial parts was the most effective in inhibiting both the growth and adherence of biofilms(Akinboro and Bakare, 2007).

Antibacterial activity

Antibacterial activity of *Ballota nigra* leaf hexane , chloroform, ethyl acetate , methanol, and aqueous extracts was studied using Agar well diffusion method(Vrchovská *et al.*, 2007). The antibacterial activity of Ballota nigra leaf extracts of methanol, aqueous, hexane, chloroform and ethyl acetate was evaluated using agar well diffusion method, and the inhibition zone formed by the bacterial strains shows their susceptibility to leaf extracts(Tóth *et al.*, 2007).

Anticholinesterase activity

Ballota acetone extract nigra L. SUPP. Anatolica showed 71.58% inhibitory activity against butyrylcholinesterase and 44.71% inhibitory activity against the 200 μg / mL enzyme acetylcholinesterase. The acetone extract showed a greater inhibitory effect against butyrylcholinesterase enzyme than galantamine, the reference compound.

Other medicinal properties

Ballota nigra is recommended from a medicinal point of view as an important plant and can be a potent candidate for further in vivo bioassays that would lead to the synthesis of safe herbal drugs with no or less side effects of global interest(Didry *et al.*, 1999). Phenocarbonic and hydroxy cinnamic corrosive, coumarins, flavonoids , tannins, basic oil parts are the fundamental organic substances of this plant material(Didry *et al.*, 1999). *Ballots nigra* and Fragaria vesca are known for their cytotoxic action against the cell lines of human cancer(Menon, V and Gayathri, 2016; G *et al.*, 2018). Ballota nigra has EGFR and Bcl-2 chemical components against lung cancer and it also acts orally(Rengasamy *et al.*, 2018). Breast cancer is a prevalent tumorigenesis

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in females and accounts for high global mortality and morbidity. Several studies revealed that some naturally occurring medicinal plants inhibit the growth of different cancers. Berries like strawberries can have beneficial effects on stress-mediated oxidative diseases such as cancer(Ma *et al.*, 2019). Glioma is the leading cause of cancer-related adolescent mortality and accounts for around 80% of all malignant tumors(Li, Z.a, Veeraraghavan, V.P.b, Mohan, S.K. c, Bolla, S.R.d, Lakshmanan, H.e, Kumaran, S.f, Aruni, W.g, Aladresi, A.A.M.h, Shair, O. H.M.h, Alharbi, S.A.h, Chinnathambi, A., 2020). Marsdenia tenacissima (M.t), a Chinese medicinal plant, was widely used as a clinical remedy for several cancer types(Wang *et al.*, 2019). Zingerone also has an effect on anticancer(Gan *et al.*, 2019). Biosynthesized SG-GNPs induce apoptosis and exhibit anticancer properties in melanoma cells(Wu *et al.*, 2019). Drug delivery vehicles based on nanocomplexes of CR-AuNPs can include extensive uses in diagnosing and treating human cancer(Ke *et al.*, 2019).Our institution is passionate about high quality evidence based research and has excelled in various fields ((Pc, Marimuthu and Devadoss, 2018; Ramesh *et al.*, 2018; Vijayashree Priyadharsini, Smiline Girija and Paramasivam, 2018; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Ramadurai *et al.*, 2019; Sridharan *et al.*, 2019; Vijayashree Priyadharsini, 2019; Chandrasekar *et al.*, 2020; Mathew *et al.*, 2020; R *et al.*, 2020; Samuel, 2021)

Contraindication and adverse effects

Black horehound is listed by the Council of Europe as a natural source of flavouring food (category N3). This category suggests that black horehound, although insufficient information is available to properly determine possible toxicity, can be applied to foodstuffs in the generally agreed form. No health hazards or side effects are reported, in accordance with the proper administration of prescribed therapeutic dosages(Marty, 1999). Nevertheless, Black horehound is reputed to influence the menstrual cycle. Because of the lack of toxicity evidence the use of black horehound during pregnancy and lactation should be avoided.

Conclusion

Ballota nigra (Back Horehound) contains various pharmacological properties for human health. Recent update on therapeutic role of *Ballota nigra* on experimental and clinical studies gives clear evidence that this plant can be used as supplements to fight against life threatening diseases such as diabetes mellitus. High potential of this plant classifies as the notable drug of the future.

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Therefore, immense research regarding its action at molecular level on life threatening diseases in humans are highly endorsed in order to establish clinical utility.

Conflict of interests

None declared.

References

1. Akinboro, A. and Bakare, A. A. (2007) 'Cytotoxic and genotoxic effects of aqueous extracts of five medicinal plants on Allium cepa Linn', *Journal of Ethnopharmacology*, pp. 470–475. doi: 10.1016/j.jep.2007.04.014.

2. Antolovich, M. *et al.* (2002) 'Methods for testing antioxidant activity', *The Analyst*, pp. 183–198. doi: 10.1039/b009171p.

3. Apak, R. *et al.* (2007) 'Comparative Evaluation of Various Total Antioxidant Capacity Assays Applied to Phenolic Compounds with the CUPRAC Assay', *Molecules*, pp. 1496–1547. doi: 10.3390/12071496.

4. Ariga, P. *et al.* (2018) 'Determination of correlation of width of Maxillary Anterior Teeth using Extraoral and Intraoral Factors in Indian Population: A systematic review', *World journal of dentistry*, 9(1), pp. 68–75.

5. Bader, A. *et al.* (2003) 'Composition of the essential oil ofBallota undulata, B. nigra ssp.foetida andB. saxatilis', *Flavour and Fragrance Journal*, pp. 502–504. doi: 10.1002/ffj.1257.

6. Basha, F. Y. S., Ganapathy, D. and Venugopalan, S. (2018) 'Oral hygiene status among pregnant women', *Journal of advanced pharmaceutical technology & research*, 11(7), p. 3099.

7. Bertrand, M.-C., Tillequin, F. and Bailleul, F. (2000) 'Two major flavonoids from Ballota nigra', *Biochemical Systematics and Ecology*, pp. 1031–1033. doi: 10.1016/s0305-1978(00)00015-6.

8. Bézanger-Beauquesne, L. (1958) 'Les alcaloïdes dans les plantes', *Bulletin de la Société Botanique de France*, pp. 266–291. doi: 10.1080/00378941.1958.10837879.

9. Bouterfas, K. *et al.* (2016) 'Antioxidant activity and total phenolic and flavonoids content variations of leaves extracts of white Horehound (Marrubium vulgare Linné) from three geographical origins', *Annales Pharmaceutiques Françaises*, pp. 453–462. doi: 10.1016/j.pharma.2016.07.002.

10. Chandrasekar, R. *et al.* (2020) 'Development and validation of a formula for objective assessment of cervical vertebral bone age', *Progress in orthodontics*, 21(1), p. 38.

11. Chen, F.a, Tang, Y.b, Sun, Y.c, Veeraraghavan, V.P.d, Mohan, S.K.e, Cui (2019) '6-

shogaol, a active constiuents of ginger prevents UVB radiation mediated inflammation and oxidative stress through modulating NrF2 signaling in human epidermal keratinocytes (HaCaT cells)', *Journal of photochemistry and photobiology. B, Biology*, 197, p. 111518.

12. Didry, N. *et al.* (1999) 'Isolation and antibacterial activity of phenylpropanoid derivatives from Ballota nigra', *Journal of Ethnopharmacology*, pp. 197–202. doi: 10.1016/s0378-8741(99)00019-7.

13. Duraisamy, R. *et al.* (2019) 'Compatibility of Nonoriginal Abutments With Implants: Evaluation of Microgap at the Implant-Abutment Interface, With Original and Nonoriginal Abutments', *Implant dentistry*, 28(3), pp. 289–295.

14. Ezhilarasan, D., Apoorva, V. S. and Ashok Vardhan, N. (2019) 'Syzygium cumini extract induced reactive oxygen species-mediated apoptosis in human oral squamous carcinoma cells', *Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, 48(2), pp. 115–121.

15. Gan, H. *et al.* (2019) 'Zingerone induced caspase- dependent apoptosis in MCF- 7 cells and prevents 7,12- dimethylbenz(a)anthracene- induced mammary carcinogenesis in experimental rats', *Journal of Biochemical and Molecular Toxicology*. doi: 10.1002/jbt.22387.

16. Gheena, S. and Ezhilarasan, D. (2019) 'Syringic acid triggers reactive oxygen species-mediated cytotoxicity in HepG2 cells', *Human & experimental toxicology*, 38(6), pp. 694–702.

17. G, R. *et al.* (2018) 'CYTOTOXICITY OF STRAWBERRY EXTRACT ON ORAL CANCER CELL LINE', *Asian Journal of Pharmaceutical and Clinical Research*, p. 353. doi: 10.22159/ajpcr.2018.v11i9.25955.

18. Hannah, R. *et al.* (2018) 'Awareness about the use, ethics and scope of dental photography among undergraduate dental students dentist behind the lens', *Journal of advanced pharmaceutical technology & research*, 11(3), p. 1012.

19. Hema Shree, K. *et al.* (2019) 'Saliva as a Diagnostic Tool in Oral Squamous Cell Carcinoma - a Systematic Review with Meta Analysis', *Pathology oncology research: POR*, 25(2), pp. 447–453.

20. Hussainy, S. N. *et al.* (2018) 'Clinical performance of resin-modified glass ionomer cement, flowable composite, and polyacid-modified resin composite in noncarious cervical lesions: One-year follow-up', *Journal of conservative dentistry: JCD*, 21(5), pp. 510–515.

21. Jainu, M., Priya, V. and Mohan, S. (2018) 'Biochemical evidence for the antitumor potential of Garcinia mangostana Linn. On diethylnitrosamine-induced hepatic carcinoma', *Pharmacognosy Magazine*, p. 186. doi: 10.4103/pm.pm_213_17.

22. Janani, K., Palanivelu, A. and Sandhya, R. (2020) 'Diagnostic accuracy of dental pulse oximeter with customized sensor holder, thermal test and electric pulp test for the evaluation of pulp vitality: an in vivo study', *Brazilian dental science*, 23(1). doi: 10.14295/bds.2020.v23i1.1805.

23. Janicsák, G., Tóth, E. and Máthé, I. (2007) 'TLC-densitometric investigations of phenylpropanoid glycosides in black horehound (Ballota nigraL.)', *Journal of Planar Chromatography – Modern TLC*, pp. 443–446. doi: 10.1556/jpc.20.2007.6.9.

24. Jeevanandan, G. and Govindaraju, L. (2018) 'Clinical comparison of Kedo-S paediatric rotary files vs manual instrumentation for root canal preparation in primary molars: a double blinded randomised clinical trial', *European archives of paediatric dentistry: official journal of the European Academy of Paediatric Dentistry*, 19(4), pp. 273–278.

25. Johnson, J. *et al.* (2020) 'Computational identification of MiRNA-7110 from pulmonary arterial hypertension (PAH) ESTs: a new microRNA that links diabetes and PAH', *Hypertension research: official journal of the Japanese Society of Hypertension*, 43(4), pp. 360–362.

26. Jose, J., Ajitha and Subbaiyan, H. (2020) 'Different treatment modalities followed by dental practitioners for Ellis class 2 fracture – A questionnaire-based survey', *The open dentistry journal*, 14(1), pp. 59–65.

27. Kannan, A. and Venugopalan, S. (2018) 'A systematic review on the effect of use of impregnated retraction cords on gingiva', *Journal of advanced pharmaceutical technology & research*, 11(5), p. 2121.

28. Ke, Y. *et al.* (2019) 'Photosynthesized gold nanoparticles from Catharanthus roseus induces caspase-mediated apoptosis in cervical cancer cells (HeLa)', *Artificial Cells, Nanomedicine, and Biotechnology*, pp. 1938–1946. doi: 10.1080/21691401.2019.1614017.

29. Kolisnyk, Y. S., Kovaleva, A. M. and Goryacha, O. V. (2014) 'The study of the volatile oils composition obtained from vegetative and generative organs of ballota nigra l', *Vìsnik farmacìï*, pp. 59–62. doi: 10.24959/nphj.14.1967.

30. Kumar, D. and Antony, S. D. P. (2018) 'Calcified canal and negotiation-A review', *Journal of advanced pharmaceutical technology & research*, 11(8), p. 3727.

31. Li, Z.a, Veeraraghavan, V.P.b, Mohan, S.K. c, Bolla, S.R.d, Lakshmanan, H.e, Kumaran, S.f, Aruni, W.g, Aladresi, A.A.M.h, Shair, O. H.M.h, Alharbi, S.A.h, Chinnathambi, A. (2020) 'Apoptotic induction and anti-metastatic activity of eugenol encapsulated chitosan nanopolymer on rat glioma C6 cells via alleviating the MMP signaling pathway', *Journal of photochemistry and photobiology. B, Biology*, 203, p. 111773.

32. Manohar, M. P. and Sharma, S. (2018) 'A survey of the knowledge, attitude, and awareness about the principal choice of intracanal medicaments among the general dental practitioners and nonendodontic specialists', *Indian journal of dental research: official*

publication of Indian Society for Dental Research, 29(6), pp. 716–720.

33. Marty, A. T. (1999) 'PDR for Herbal Medicines', *JAMA: The Journal of the American Medical Association*, pp. 1853–1854. doi: 10.1001/jama.281.19.1853.

34. Mathew, M. G. *et al.* (2020) 'Evaluation of adhesion of Streptococcus mutans, plaque accumulation on zirconia and stainless steel crowns, and surrounding gingival inflammation in primary molars: Randomized controlled trial', *Clinical oral investigations*, pp. 1–6.

35. Ma, Y. *et al.* (2019) 'Sesame Inhibits Cell Proliferation and Induces Apoptosis through Inhibition of STAT-3 Translocation in Thyroid Cancer Cell Lines (FTC-133)', *Biotechnology and Bioprocess Engineering*, pp. 646–652. doi: 10.1007/s12257-019-0151-1.

36. Menon, A., V, V. P. and Gayathri, R. (2016) 'PRELIMINARY PHYTOCHEMICAL ANALYSIS AND CYTOTOXICITY POTENTIAL OF PINEAPPLE EXTRACT ON ORAL CANCER CELL LINES', *Asian Journal of Pharmaceutical and Clinical Research*, p. 140. doi: 10.22159/ajpcr.2016.v9s2.13313.

37. Menon, S. *et al.* (2018) 'Selenium nanoparticles: A potent chemotherapeutic agent and an elucidation of its mechanism', *Colloids and surfaces. B, Biointerfaces*, 170, pp. 280–292.

38. Mohan, S. K., Veeraraghavan, V. P. and Jainu, M. (2015) 'Effect of pioglitazone, quercetin, and hydroxy citric acid on vascular endothelial growth factor messenger RNA (VEGF mRNA) expression in experimentally induced nonalcoholic steatohepatitis (NASH)', *TURKISH JOURNAL OF MEDICAL SCIENCES*, pp. 542–546. doi: 10.3906/sag-1404-136.

39. Nandakumar, M. and Nasim, I. (2018) 'Comparative evaluation of grape seed and cranberry extracts in preventing enamel erosion: An optical emission spectrometric analysis', *Journal of conservative dentistry: JCD*, 21(5), pp. 516–520.

40. Nandhini, J. S. T., Babu, K. Y. and Mohanraj, K. G. (2018) 'Size, shape, prominence and localization of gerdy's tubercle in dry human tibial bones', *Journal of advanced pharmaceutical technology & research*, 11(8), p. 3604.

41. Nusier, M. K. *et al.* (2007) 'Effect of Frankincense (*Boswellia thurifera*) on Reproductive System in Adult Male Rat', *JOURNAL OF HEALTH SCIENCE*, pp. 365–370. doi: 10.1248/jhs.53.365.

42. Pc, J., Marimuthu, T. and Devadoss, P. (2018) 'Prevalence and measurement of anterior loop of the mandibular canal using CBCT: A cross sectional study', *Clinical implant dentistry and related research*. Available at: https://europepmc.org/article/med/29624863.

43. Ponnulakshmi, R. *et al.* (2019) 'In silicoandin vivoanalysis to identify the antidiabetic activity of beta sitosterol in adipose tissue of high fat diet and sucrose induced type-2

diabetic experimental rats', *Toxicology Mechanisms and Methods*, pp. 276–290. doi: 10.1080/15376516.2018.1545815.

44. Pulido, R., Bravo, L. and Saura-Calixto, F. (2000) 'Antioxidant Activity of Dietary Polyphenols As Determined by a Modified Ferric Reducing/Antioxidant Power Assay', *Journal of Agricultural and Food Chemistry*, pp. 3396–3402. doi: 10.1021/jf9913458.

45. Qazan, W. S. (2008) 'Effects of Short and Long Term Treatment of Ballota undulate on Female Albino Rats Fertility and Pregnancy', *Pakistan Journal of Biological Sciences*, pp. 638–642. doi: 10.3923/pjbs.2008.638.642.

46. Rajakeerthi and Ms, N. (2019) 'Natural Product as the Storage medium for an avulsed tooth – A Systematic Review', *Cumhuriyet Üniversitesi Diş Hekimliği Fakültesi dergisi*, 22(2), pp. 249–256.

47. Rajendran, R. *et al.* (2019) 'Comparative evaluation of remineralizing potential of a paste containing bioactive glass and a topical cream containing casein phosphopeptide-amorphous calcium phosphate: An in vitro study', *Pesquisa brasileira em odontopediatria e clinica integrada*, 19(1), pp. 1–10.

48. Ramadurai, N. *et al.* (2019) 'Effectiveness of 2% Articaine as an anesthetic agent in children: randomized controlled trial', *Clinical oral investigations*, 23(9), pp. 3543–3550.

49. Ramesh, A. *et al.* (2018) 'Comparative estimation of sulfiredoxin levels between chronic periodontitis and healthy patients - A case-control study', *Journal of periodontology*, 89(10), pp. 1241–1248.

50. Ravinthar, K. and Jayalakshmi (2018) 'Recent advancements in laminates and veneers in dentistry', *Journal of advanced pharmaceutical technology & research*, 11(2), p. 785.

51. Rengasamy, G. *et al.* (2018) 'Cytotoxic and apoptotic potential of Myristica fragrans Houtt. (mace) extract on human oral epidermal carcinoma KB cell lines', *Brazilian Journal of Pharmaceutical Sciences*. doi: 10.1590/s2175-97902018000318028.

52. Rengasamy, G., Jebaraj, D.M., Veeraraghavan, V.P., Mohan, S.K. (2016) 'Characterization, partial purification of alkaline protease from intestinal waste of scomberomorus guttatus and production of laundry detergent with alkaline protease additive', *Indian Journal of Pharmaceutical Education and Research*.

53. R, H. *et al.* (2020) 'CYP2 C9 polymorphism among patients with oral squamous cell carcinoma and its role in altering the metabolism of benzo[a]pyrene', *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, pp. 306–312. doi: 10.1016/j.oooo.2020.06.021.

54. Samuel, S. R. (2021) 'Can 5-year-olds sensibly self-report the impact of developmental enamel defects on their quality of life?', *International journal of paediatric dentistry / the British Paedodontic Society [and] the International Association of Dentistry for Children*, 31(2), pp. 285–286.

55. Seidel, V. *et al.* (2000) 'Phenylpropanoids fromBallota nigra L. inhibitin vitro LDL peroxidation', *Phytotherapy Research*, pp. 93–98. doi: 3.0.co;2-x">10.1002/(sici)1099-1573(200003)14:2<93::aid-ptr558>3.0.co;2-x.

56. Sekar, D. *et al.* (2019) 'Methylation-dependent circulating microRNA 510 in preeclampsia patients', *Hypertension research: official journal of the Japanese Society of Hypertension*, 42(10), pp. 1647–1648.

57. Seppan, P. *et al.* (2018) 'Therapeutic potential of Mucuna pruriens (Linn.) on ageing induced damage in dorsal nerve of the penis and its implication on erectile function: an experimental study using albino rats', *The aging male: the official journal of the International Society for the Study of the Aging Male*, pp. 1–14.

58. Sharma, P. *et al.* (2019) 'Emerging trends in the novel drug delivery approaches for the treatment of lung cancer', *Chemico-biological interactions*, 309, p. 108720.

59. Shukri, N. M. M. *et al.* (2016) 'Awareness in childhood obesity', *Research Journal of Pharmacy and Technology*, 9(10), pp. 1658–1662.

60. Siddique, R. *et al.* (2019) 'Qualitative and quantitative analysis of precipitate formation following interaction of chlorhexidine with sodium hypochlorite, neem, and tulsi', *Journal of conservative dentistry: JCD*, 22(1), pp. 40–47.

61. Sridharan, G. *et al.* (2019) 'Evaluation of salivary metabolomics in oral leukoplakia and oral squamous cell carcinoma', *Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, 48(4), pp. 299–306.

62. Teja, K. V., Ramesh, S. and Priya, V. (2018) 'Regulation of matrix metalloproteinase-3 gene expression in inflammation: A molecular study', *Journal of conservative dentistry: JCD*, 21(6), pp. 592–596.

63. Tóth, E. *et al.* (2007) 'Martynoside, forsythoside B, ladanein and 7a-acetoxyroyleanone from Ballota nigra L', *Biochemical Systematics and Ecology*, pp. 894–897. doi: 10.1016/j.bse.2007.04.009.

64. Ullah, N., Ahmad, I. and Ayaz, S. (2014) 'In VitroAntimicrobial and Antiprotozoal Activities, Phytochemical Screening and Heavy Metals Toxicity of Different Parts ofBallota nigra', *BioMed Research International*, pp. 1–9. doi: 10.1155/2014/321803.

65. Vijayashree Priyadharsini, J. (2019) 'In silico validation of the non-antibiotic drugs acetaminophen and ibuprofen as antibacterial agents against red complex pathogens', *Journal of periodontology*, 90(12), pp. 1441–1448.

66. Vijayashree Priyadharsini, J., Smiline Girija, A. S. and Paramasivam, A. (2018) 'In silico analysis of virulence genes in an emerging dental pathogen A. baumannii and related species', *Archives of oral biology*, 94, pp. 93–98.

67. Vrchovská, V. *et al.* (2007) 'Antioxidative properties and phytochemical composition of

Ballota nigra infusion', *Food Chemistry*, pp. 1396–1403. doi: 10.1016/j.foodchem.2007.05.016.

68. Wang, Y. *et al.* (2019) 'Synthesis of Zinc oxide nanoparticles from Marsdenia tenacissima inhibits the cell proliferation and induces apoptosis in laryngeal cancer cells (Hep-2)', *Journal of Photochemistry and Photobiology B: Biology*, p. 111624. doi: 10.1016/j.jphotobiol.2019.111624.

69. Wu, F. *et al.* (2019) 'Biologically synthesized green gold nanoparticles from Siberian ginseng induce growth-inhibitory effect on melanoma cells (B16)', *Artificial Cells, Nanomedicine, and Biotechnology*, pp. 3297–3305. doi: 10.1080/21691401.2019.1647224.

70. Yeşilada, E. *et al.* (1993) 'Traditional medicine in Turkey IV. Folk medicine in the Mediterranean subdivision', *Journal of Ethnopharmacology*, pp. 31–38. doi: 10.1016/0378-8741(93)90048-a.