

Special Article: Pharmacognosy

Neem: An Overview

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Email: padmaampaarakh@gmail.com**Received:** September 26, 2023**Accepted:** November 07, 2023**Published:** November 14, 2023**Abstract**

Neem (*Azadirachta indica*) belonging to the Meliaceae family is popular tree. In Traditional System of Medicine, bark, leaf, flower, seed, oil and other parts are used for number of ailments. Number of patents has been filed for neem for pharmacological uses. This review provides a detailed view on Pharmacognosy, phytochemistry and pharmacological activity reported so far.

Keywords: Neem; *Azadirachta indica*; Pharmacognosy; Phytochemistry; Pharmacological activity; Review

Introduction

Azadirachta indica is an adaptable medicinal tree belonging to Meliaceae family. Every part of neem has some beneficial effects on human ailments and hence it has gained worldwide importance. 4000 years existence plant in India is *Azadirachta indica* [1].

A.indica also known as Margosa tree, as 'arista' or 'nimba' and 'nimbaty swasthyamdadati' in Sanskrit meaning 'to give good health'. The biological benefits of neem are enlisted in 'Charak-Samhita' and 'Susruta-Samhita', which forms the basis of Ayurvedic system of treatment. 'Azad- Darakth- E- Hind' means 'Free tree of India' in Persian. Neem is considered genetic diverse plant. In India, Neem was used for chicken pox and small pox from antiquity. It has been used for environment protection such as soil erosion, soil fertility, insecticide, pesticide etc [2].

Habitat

Although the exact native region of Neem tree is not known, it is thought to be originating naturally in south Asia and it grows in natural forests with drier-climatic condition of southern India and Burma. For many millennia, neem has been cultivated in India, Pakistan, Sri Lanka, Bangladesh, Myanmar, Thailand, Southern Malaysia, and the drier Indonesian islands from Java eastward. Neem was introduced to Fiji and Mauritius during early 19th century [3].

Climate

It is a drought resistant tree and the mean annual temperature ranges from 21 to 32°C for its growth. In India, neem

grows at temperatures between 0 to 49°C and annual rainfall of less than 600 mm. The plant is also used in afforestation programmes in arid and semi-arid regions [4].

Propagation and Cultivation

It is a hard tree, grows well in saline soils and drought conditions. Growth is slow in water-logged conditions. Propagated from seeds, which should be sown immediately after ripening, as their viability is very short. Seeds germinate within three weeks time. Root suckers and stem cuttings are also used for planting. It can be grown in all types of soil, but black-loam soil is more suitable. Within one year, the seedlings grow up to a height of 120 cm. Rapid multiplication through leaf culture has been found successful. Tissue culture techniques have been reported for the production of azadirachtin from cultures of leaves and flowers. 20 weeks old callus of leaves is reported to yield maximum concentration of azadirachtin upto 2.68 % and the 12 weeks old flower callus 2.46 % of azadirachtin on dry weight basis [5,6].

Scientific Classification of Neem

Kingdom: Plantae

Division: Magnoliophyte

Class: Magnoliopsida

Order: Sapindales

Family: Meliaceae

Genus: *Azadirachta*

Species: *indica*

Scientific name: *Azadirachta indica*

Vernacular Names

- Hindi – Nim, Nimb
- English – Margosa, Neem, Indian Lilac
- Konkani – Beva-rooku
- Bengali – Nim, Nimgach
- Marathi – Kadunimb
- Gujarathi – Limba
- Tamil – Veppamaram, Vempu, Veppam
- Punjabi – Nimb
- Malayalam – Veepu, Aryaveppu, Aruveppu, Kaippan, Veppu, Vepa
- Oriya – Nimo
- Telugu – Vepa, Yapachettu
- Kannada – Bevinmar, Kahibeavu [7]

Botanical Description

Macroscopical Characteristics

A large evergreen tree, 12 to 18m high with bitter in taste.

Bark: Dark brown to grayish, thick hard woody, external rough surface, scaly, oblique furrows, bitter taste, characteristic odor, straight trunk.

Leaved: Leaves are dark green coloured, compound, ovate-lanceolate, attenuate, opposite, imparipinnate (5-15 leaflets), serrated edges, short petioles, 3-8 cm long, with typical odor.

Fruits: Glabrous, olive like drupe, oval to roundish, green, edible and thin skinned.

Flowers: Flowers are white, fragrant, arranged in axillary panicles, protandrous, bisexual flowering.

Seed: One seeded only, dirty brown in color, with gritty touch and oily.

Microscopical Characteristics

The transverse section showed outer dark reddish brown rhytidoma consisting of 10 to 15 rows of outer most dark brown colored cells of cork, and a narrow band of stone cells lying underneath this followed by outer few rows of parenchyma and inner wide 20 to 25 rows of dark orange brown colored phloem tissue; very narrow band of phelloderm with tangentially running tannin cells and very wide phloem with discontinuous groups of crystal fibers alternating with medullary rays. Prismatic crystals of calcium oxalate traversed throughout the parenchymatous cells.

Powder Characteristics

It shows abundant fragments of rhytidoma embedded with stone cells, isolated or groups of fibres; few oval to rectangular sclerides associated with idioblast containing prismatic crystals of calcium oxalate, few simple, oval to spherical starch grains and parenchymatous cell filled tannin contents [8-10].

Traditional Actions and Uses

Bark: It is urinary astringent, acrid, pectoral, tonic, hyperdipsia, leprosy, skin diseases, eczema, leucoderma, pruritis, malaria, burning sensation, tumor, dyspepsia, intestinal worms, hepatopathy, cough, bronchitis, urine incontinence, diabetes, inflammation, wound healing, ulcer, amenorrhea, lumbago, hemorrhoids, otalgia, syphilis and fatigue.

Leaves: It is anthelmintic, insecticidal, demulcent, refrigerant, skin diseases, leucoderma, in burning sensation, leprosy, pruritus, antiseptic, ophthalmic, ophthalmopathy, intestinal worms, dyspepsia, ulcer, tuberculosis, boils, eczema, malarial and intermittent fevers.

Flowers: It is used as a refrigerant, ophthalmic, stomachic, anthelmintic, tonic, burning sensation, ophthalmopathy, colic, dyspepsia, intestinal worms and general debility.

Seeds: It is used as acrid, thermogenic, purgative, emollient, anodyne, anthelmintic, depurative, vulnerary, uterine stimulant, urinary astringent, tumors, leprosy, skin diseases, odontalgia, intestinal worms, wounds, ulcers and diabetes.

Oil: It is anthelmintic, anodyne, depurative, chronic skin diseases, syphilitic sores, ulcer, ringworm, scabies, worms, fever and leprosy [1,2,4,7].

Ayurvedic Properties

Rasa: Tikta, Kashaya

Guna: Laghu

Veerya: Sheeta

Vipaka: Katu

Doshaghnata: Kaphapitashamaka

Rogaghnata: Vidradhi, Granthi, Amavata, Vamana, Kaphapittika etc.

Karma: Vranapachana, Vranashodhana, Ampachana, Juaraghna, Vishamapwara pratibandhaka, Chakshushya etc.

Doses

Bark powder: 2 to 4 gm

Leaf juice: 10 to 20 ml;

Powder: 2-4 g.

Oil- 5 to 10 drops [11].

Chemical Constituents

More than 100 compounds, mostly triterpenoids of proto-limonoids (proto-meliacin), Limonoids (or meliacins or tetranortriterpenoids), tetranortriterpenoid- γ hydroxy butenolides, pentanortriterpenoids. Hexanortriterpenoid apart from a few nontriterpenoid constituents have been reported from various parts as detailed below.

Leaves: Azadirachtin, azadirachtol, azadirachnol, deacetyl-azadirachtinol (-3- tigloylazadirachtol), azadiradione, an isomer of epoxyszadiradione, 17 epi and 17-hydroxyazadiradione, gedunin, 7-hydroxygedunin, melianone, bol nimboeinol (7-acetoxy-7-hydroxy azadiradione), nimocin, 7-deacetoxy-nimolicinol, nimolinone, nimbochalcin and nimocetin, 21,23 24,25- diepoxytirucall-7-en-21-ol salannin, azadirachtanin, aza-

dirone, azadiradione, epoxyazadiradione, isoazadirolide, nimbadiol, nimbine, desacetylnimbine, nimbin, nimbocinolide, isonimbocinolide, nimbolide, nimocinolide, isonimocinolide, nimocinone, 2',3'-dehydrosalannol kaempferol-3-O-8-glucoside, myricetin, 3-L-arabinoside (mellitrin), 3-O-L-epigallocatechin gallate and 3-O-rutinoside, quercetin, its 3-galactoside, 3-O-L-epigallocatechin gallate and 3-O-rutinoside, nimbaflavones, scopoletin, β -sitosterol and its β -D-glucoside, amino acids, β -carotene, carbohydrates, n-hexacosanol, nomacommol, protein and vitamins.

Fruits and Seeds: Kernels yield about 400-48.9% of the oil and contain high amount of tocopherol, arachidic, linoleic, margaric, myristic, oleic, palmitic and stearic acids, azadirone, azadiradione, epoxyazadiradione (nimbinin), gedunin, meldonin, meliatriol, nimbine, nimbene, 6-desacetyl nimbine, nimbidin, nimbidol, 6-O-acetylnimbadiol, nimbidic acid, salannin, 3-desacetylsalannin, salannol and its acetate, salannolide, vepinine, vilasinin, 1,3-diacetylvilasinin, 1-tigloyl-3-acetyl-vilasinin, and tiglic acid (seed oil), in addition, azadirachtin, 22,23-dihydro-23-8-methoxy-azadirachtin (vepaol) and its C-23 epimer (isovepaol), 7-desacetyl-7-benzoyl derivatives of azadirone, azadiradione, epoxyazadiradione, 2-dihydro-epoxyazadiradione, 18,28-diepoxyazadiradione, 7-desacetyl-7-benzoyl-gedunin, acetylneotrachelone, nimbidin, nimbidinin, salannic (nimbidic) acid (seeds).

Flowers: Benzyl alcohol, β -sitosterol, thioamyl alcohol, arachidic, behenic, colic, oleic, palmitic and stearic acids, kaempferol and its 3-glucoside, quercetin-3-galactoside and myricetin-3-L-arabinoside, azadirachtin and margosene, flowerine, flowerone, O-methylazadirone and diepoxyazadirol. Other known constituents present in flowers are triterpenoid (trichilene acetate), flavanones, nimbaflavone, 3'-prenylnaringenin and 4-(2-hydroxyethyl) phenol.

Heartwood: Tannin, β -sitosterol and its glucoside, 24-methylene-cycloartenol, 4,14, α -dimethyl-3- α -ergosta-8, 24(28)-d-38-ol, 4-methyl-5 α -ergosta-8, 24(28)-dien-38-ol, nimatone, nimbene, 6-desacetyl nimbene, nimbolins A and B.

Stem bark: Vanilic acid, catechol, campesterol, stigmasterol, sitosterol, β -amyrin, lupeol, nimbin, nimbidin, nimbinin, supiol, kulonone, kulactone, kulolactone, methyl kulonate, 60-hydroxy-4-stigmastene-3-one and 68-hydroxy-4-campesten-3-one.

Wood: Gedunin, 7-deacetoxy-7-axogedunin, fraxinellone, nimbolin A, gynoecalemon, melanin A and B.

Twigs: Margosinolide, isomargosinolide, desacetyl nimbolide and desacetyl isonimbolide.

Wood Oil: Cycloeucaleanol, 24-methylene cycloartenol and β -sitosterol.

Trunk bark: Nimbiol, sugiol and bosterol, nimbolins A and B (trunk wood),

Root: 24-methylene-cycloartenol, 24-methylene-cycloartanone, cycloeucaleanol, cycloeucalenone, 4-campesten-3-one, 4-stigmastene-3-one, trans-cinnamic and vanillic acids, nimbin and nimbidin.

Besides aesculetin, campesterol, 6-hydroxy-7-methoxycoumarin, 4 α , 6 α -dihydroxy-A-homoazadirone, isomeldonin, meldonindiol, 17-acetoxy-meliacin, 6-O-acetylnimbadiol, desacetylnimbin, nimocinol, isonimocinolide and nimolinolic acid have been isolated from various parts of tree [12-17].

Identification by TLC

Stationery phase: Silica Gel GF254 precoated plates

Mobile phase: Toluene: ethyl acetate: glacial acetic acid: 5:5:1

Standard preparation: 10 mg of epicatechin is dissolved in 5 ml of methanol

Sample preparation: Reflux 5 g of drug with methanol for 8 hrs [2 times]. Filter and remove the solvent. Dissolve in 10 ml of methanol.

Spray reagent: Spray with 10% ethanol potassium hydroxide solution and observe under UV 365 nm.

Detection: Rf 0.29 corresponding to epicatechin is seen in both standard and test.

Estimation by HPTLC

Method is followed as per identification method except plate after drying is scanned at 424 nm

Content present in the sample is determined from the peak area under the curve.

Quantitative Standards

Foreign matter: Not more than 0.3 % w/w

Ash: Not more than 3.0 % w/w

Acid insoluble ash: Not more than 0.25 % w/w

Alcohol soluble extractive: Not less than 4.5 % w/w

Water soluble extractive: Not less than 5.0 % w/w [11,18]

Therapeutic Properties

The pharmacological activities of phytoconstituents reported so far from this plant is given below in the Table [13-15].

Chemical constituents	Biological activity
Nimbidin	Anti-inflammatory Antiarthritic Antipyretic Hypoglycaemic Antigastric ulcer Spermicidal Antifungal Antibacterial Diuretic
Sodium nimbidate	Anti-inflammatory
Nimbin	Spermicidal
Nimbolide	Antibacterial Antimalarial
Gedunin	Antifungal Antimalarial
Azadirachtin	Antimalarial
Mahmoodin	Antibacterial
Gallic acid, (-)epicatechin and catechin	Anti-inflammatory and Immunomodulatory
Margolone, margolonone and isomargolonone	Antibacterial
Cyclic trisulphide, cyclic tetrasulphide	Antifungal
Polysaccharides	Anti-inflammatory
Polysaccharides GIa, GIb	Antitumour
Polysaccharides GIIa, GIIa	Anti-inflammatory
NB-II peptidoglycan	Immunomodulatory (13-15)
Glycoprotein	Immunomodulatory(19)
Proline	Alzheimer's and Parkinson's disease(20,21)
Epoxyazadiradione	Human cervical cancer(22)

Pharmacological Activities

To understand the pharmacological activity it is given in form of Table below

SI No	Activity	Part of plant	Extract	Observation	Reference
1	Antioxidant activity	Leaf, flower, stem bark	Different extracts	High activity in ethanol extract in all parts	23
		Flower and seed oil	Ethanol extract	High scavenging activity in both	24
		Bark and leaves	Ethanol extract	Bark had high antioxidant activity then leaves	25
		Roots	Methanol extract	High scavenging activity	26
		Leaves	Methanol and chloroform extract	Methanol extract had better antioxidant activity	27
2	Wound healing activity	Oil	-	50% wound healing activity in non healing wound in 44% patients	28
		Leaves	Aqueous extract	Significant reduction in wound size	29,30
3	Anti-inflammatory activity	Neem fruit skin	Alcohol extract	Significant anti-inflammatory activity in rats treated with 100mg/kg dose	31
		Seed	Oil	Increased inhibition of edema in dose of 0.05-2 ml/kg	32
4	Hepatoprotective activity	Leaf	Aqueous extract	Reduced elevated levels of AST and ALT; liver necrosis was reduced	33
		Leaf	Aqueous extract	Prevented and reversed the hepatotoxic effect caused by antitubercular drugs	34,35
5	Neuroprotective activity	Neem	Standardized extract	Significantly decreased allodynia, hyperalgesia, motor coordination and motor nerve conduction velocity and reduced oxidative stress and inflammatory markers	36
		Leaf	Ethanol extract	Reversed effects of cisplatin and proved neuroprotective activity	37
6	Nephroprotective activity	Leaves	Methanol extract	Significant protective effect	38
7	Immunomodulatory activity	Oil	-	Activation of cell mediated immune mechanism against mitogens.	39
		Leaves	Infusion	Improved antibody titer growth when mixed in drinking water	40
8	Antifertility activity	Flower	Alcohol extract	It caused prolongation of diesterus phase with reduction in esterus phase and also reduced numbers of ova	41
		Neem	Oil	Reduced spermatogenesis and testosterone level is not affected	42
9	Dental health	Neem	Extracts and neem sticks	Decreased the plaque formation and gingival scores reduction	43
		Leaves	Petroleum and chloroform extract	Chloroform extract had strong antimicrobial activity against <i>Streptococcus mutans</i>	44
10	Antidiabetic activity	Leaves	Ethanol extract	Glucose level is reduced at 250mg/kg dose	45
		Root bark	Ethanol extract	Glucose level is reduced at dose of 200,400 and 800mg/kg by 54%	46
		Kernel powder	-	Alone and along with glibenclamide was capable of reducing blood glucose level and serum enzymes also	47
11	Cardioprotective activity	Leaves	Alcohol extract	Restored biochemical and hemodynamic parameters and had similar effect as cardioprotective as compared to Vitamin E	48
12	Antimicrobial activity	Leaves	Ethanol extract	Controls food borne pathogens and other spoilage organism	49
		Leaves	Ethanol extract	Zone of inhibition is greater when compared to standard	50
		Leaves and seed	Ethanol extract	MIC was found to be 31ug/ml for dermatophytes	51
13	Antiviral activity	Bark	Ethanol extract	Blocked HSV-1 virus entry into cells	52
14	Anticancer activity	Leaves	Ethanol extract	Increased death of 4T1 breast cancer cells	53
		Leaves	Ethanol extract	Decreased lymphocytic leukemia cell survival and increased death	54
		Leaves	Ethanol extract	Inhibited mammary tumor including growth and occurrence	55,56
		Leaves	Ethanol extract	suppressed prostate cancer cell lines	57
		Leaves	Ethanol extract	Suppressed MCF-2, HeLa, skin, lung,liver cancers	58
		Leaves	Ethanol extract	Tumor size decreased in buccal carcinoma in hamster	59,60
		Leaves	-	Reduction in tumor size in murine solid Ehrlich carcinoma	61
15	Pesticide activity	Seeds	Oil	Natural pesticide	62-64
16	Intestinal ischemic-reperfusion injury	Leaves	Methanol extract	Reduced myeloperoxidase levels	65

17	Colitis activity	Leaves	Methanol extract	Inhibited inflammation and colon mucosal damage; increased GSH level	66
18	Antipyretic activity	Leaves	Ethanol extract	Reduced body temperature	67

List of Few Marketed Products and Their Use

Sr.	Marketed Product	Uses
1.	NATURE NEEM OIL	Making Shampoo, Tooth Paste, Soaps, Cosmetics, Mosquito repellent, Insecticidal,
2.	TOTAL CARE	Pest Control
3.	BIOCARE	Animal Skin Care, Healing Aid For Skin Irritation, Minor Cuts, Broken Skin, Pesticidal, Insecticidal
4.	NEEM GUARD	Urea Coating Agent
5.	NATURE NEEM SEED CAKE & SEED POWDER	Organic Plant Food which increase productivity & Soil Fertility, Antifungal

Formulations and Preparations

Shankhapushpi taila, Jwarasamhara rasa, Mahamarichyadi taila, Pathyadi kvatha, Mahamanjishthadyarishta, Punarnavadi kvatha, Mahasudarshana churna, Raktashodhaka vati, Nimbaharidra khanda, Nimbarishta, Mahagandhaka vati, Nimbadi churna, Panchaguna taila, Madhyam narayana taila, Guduchyadighana kvatha [11].

Safety Aspects

The drug used traditionally in prescribed doses may be considered safe.

Conclusion

We can say neem as one plant for treatment of number of ailments. Scientifically it has been proven to be antioxidant, wound healing, antipyretic, antiallergic, antiasthmatic, anti-inflammatory, hepatoprotective, neuroprotective, nephroprotective, immunomodulatory, antifertility, dental hygiene, anti-diabetic, cardioprotective, antimicrobial, anticancer, pesticide etc. This review gives the details of chemicals isolated and pharmacological activity of the isolated compounds as well as extract. An extensive research and development work should be undertaken on neem and its products for their better economic and therapeutic utilization.

Author Statements

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Conflicts of Interest

There are no conflicts of interest.

References

1. Ali A. Textbook of pharmacognosy. New Delhi, India: publication and information directorate. 1993; 213-5.
2. Kokate C, Purohit AP, Gokhale SB. Pharmacognosy. Maharashtra, India: Nirali Prakashan. 2010; 355-7.
3. Sunarwidhi AL, Sudarsono S, Nugroho AE. Hypoglycemic effect of combination of *Azadirachta indica* A. Juss. and *Gynura procumbens* (Lour.) Merr. ethanolic extracts standardized by rutin and quercetin in alloxan-induced hyperglycemic rats. Adv Pharm Bull. 2014; 4: 613-8.
4. Kumar VS, Navaratnam V. Neem. *Neem (Azadirachta indica): prehistory to contemporary medicinal uses to humankind*. Asian Pac J Trop Biomed. 2013; 3: 505-14.
5. Ogbuewu IP, Odoemenam VU, Obikaonu HO, Opara MN, Emenalom OO, Uchegbu MC, et al. The growing importance of neem (*Azadirachta indica* A. Juss) in agriculture, industry, medicine and environment: a review. Res J Med Plants. 2011; 5: 230-45.
6. Jarvis AP, Morgan EP, VanderEsch SA, Vitali F, Hey SU, Tape A. Identification of azadirachtin in tissue culture cells of neem. Nat Prod Lett. 1997; 10: 95-8.
7. Anonymous. Medicinal plants of India. New Delhi: Indian Council of Medical Research. 1: 112-7.
8. Chandra V. Botany of neem. Annals For. 1997; 5: 182-8.
9. Mitra R. Bibliography on pharmacognosy of medicinal plants. Lucknow: National Botanical Research Institute. 1985; 53.
10. Narayana AK. Nimba –Pharmacognosy of ayurvedic drugs of Kerala, Central Research Institute. Trivendrum. 1957; 1: 25-30.
11. Anonymous. The ayurvedic Pharmacopoeia of India. part 1, Nimba(leaf & Stem bark). New Delhi: Department of Ayush. 2: 124-34.
12. Ahmed E, Nidal J, Nagib E. A review of chemical constituents and traditional usage of Neem plant (*Azadirachta indica* A. Juss.). Palestinian Med Pharm J. 2017; 2: 75-81.
13. Srivasatava SK, Agarwal B, Akhilesh K, Archana P. Phytochemicals of *Azadirachta indica* source of active medicinal constituents used for cure of various diseases: a review. J Sci Res. 2020; 64: 385-90.
14. Saleem S, Muhammad G, Muhammed AH, Syed NAB. A comprehensive review of phytochemical profile, bioactive for pharmaceutical and pharmacological attributes of (*Azadirachta indica* A. Juss.). Phytother Res. 2018; 32: 1241-72.
15. Damte M. A review on chemical composition, medicinal values and other application of *Azadirachta indica* A. Juss. agri. Biol Res. 2022; 38: 268-72.
16. Jytoi D, Sharma RB. Medicinal importance of *Azadirachta indica* A. Juss.: an overview. J Drug Deliv Ther. 2023; 13: 159-65.
17. Baby AR, Freire TB, Marques GA, Rijo P, Lima FV, Carvalho JCM, et al. Juss (Neem) as a potential natural actives for dermocosmetic and topical products: a narrative review. Cosmetics. 2022; 9: 58-61.

18. Anonymous. Quality control of Indian medicinal Plants Vol 3. New Delhi: Department of Ayush. 1999; 201-7.
19. Kundu B, Subhasis K, Sarkar AB, Baral R, Laskar S. Chemical investigation of Neem leaf glycoproteins used as immunoprophylactic agent for tumor growth restriction. *Int J Pharm Pharm Sci*. 2018; 7: 195-9.
20. Gladkevich A, Bosker F, Korf J, Yenkovyan K, Vahradyan H, Aghajanov M. Proline-rich polypeptides in Alzheimer's disease and neurodegenerative disorders – therapeutic potential or a mirage? *Prog Neuropsychopharmacol Biol Psychiatry*. 2007; 31: 1347-55.
21. Yenkovyan K, Fereshetyan K, Matinyan S, Chavushyan V, Aghajanov M. The role of monoamines in the development of Alzheimer's disease and neuroprotective effect of a proline rich polypeptide. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018; 86: 76-82.
22. Shilpa G, Renjitha J, Saranga R, Sajin FK, Nair MS, Joy B et al. Epoxyazadiradione purified from the *Azadirachta indica* seed induced mitochondrial apoptosis and inhibition of NFκB nuclear translocation in human cervical cancer cells. *Phytother Res*. 2017; 31: 1892-902.
23. Sithisarn P, Supabphol R, Gritsanapan W. Antioxidant activity of Siamese neem tree (VP1209). *J Ethnopharmacol*. 2005; 99: 109-12.
24. Nahak G, Sahu RK. Evaluation of antioxidant activity of flower and seed oil of *Azadirachta indica* A. Juss. *J Appl. Nat Sci*. 2011; 3: 78-81.
25. Ghimeray AK, Jin C, Ghimine BK, Cho DH. Antioxidant activity and quantitative estimation of azadirachtin and nimbin in *Azadirachta indica* A. Juss. grown in foothills of Nepal. *Afr J Biotechnol*. 2009; 8: 3084-91.
26. Sri U, Ibrahim M, Kumar M. Antioxidant activity and total flavonoids content of different parts of *Azadirachta indica* A. Juss. *J Med Plants Res*. 2012; 6: 5737-42.
27. Dhakal S, Aryal P, Aryal S, Bashyal D, Khadka D. Phytochemical and antioxidant studies of methanol and chloroform extract from leaves of *Azadirachta indica* A. Juss. in tropical region of Nepal. *J Pharmacogn Phytochem*. 2016; 8: 203-8.
28. Singh A, Singh AK, Narayan G, Singh TB, Shukla VK. Effect of neem oil and Haridra on non-healing wounds. *Ayu*. 2014; 35: 398-403.
29. Chundran NK, Husen IR, Rubianti I. Effect of neem leaves extract (*Azadirachta indica*) on Wound Healing. *AMJ*. 2015; 2: 199-207.
30. Osunwoke EA, Olotu EJ, Allison TA, Onyekwere JC. The wound healing effects of aqueous leave extracts of *Azadirachta indica* on Wistar rats. *J Nat Sci Res*. 2013; 3: 181-6.
31. Ilango K, Maharajan G, Narasimhan S. Anti-nociceptive and anti-inflammatory activities of *Azadirachta indica* fruit skin extract and its isolated constituent azadiradione. *Nat Prod Res*. 2013; 27: 1463-7.
32. Naik M, Agrawal D, Behera R, Bhattacharya A, Dehury S, Kumar S. Study of anti-inflammatory effect of neem seed oil (*Azadirachta indica*) on infected albino rats. *J Health Res Rev*. 2014; 1: 66-9.
33. Baligar NS, Aladakatti RH, Ahmed M, Hiremath MB. Hepatoprotective activity of the neem-based constituent azadirachtin – A in carbon tetrachloride intoxicated Wistar rats. *Can J Physiol Pharmacol*. 2014; 92: 267-77.
34. Bhanwra S, Singh J, Khosla P. Effect of *Azadirachta indica* (Neem) leaf aqueous extract on paracetamol-induced liver damage in rats. *Indian J Physiol Pharmacol*. 2000; 44: 64-8.
35. Kale BP, Kothekar MA, Tayade HP, Jaju JB, Mateenuddin M. Effect of aqueous extract of *Azadirachta indica* leaves on hepatotoxicity induced by antitubercular drugs in rats. *Indian J Pharmacol*. 2003; 35: 177-80.
36. Kandhare AD, Mukherjee AA, Bodhankar SL. Neuroprotective effect of *Azadirachta indica* standardized extract in partial sciatic nerve injury in rats: evidence from anti-inflammatory, antioxidant and anti-apoptotic studies. *Excli J*. 2017; 16: 546-65.
37. Abdel Moneim AE. *Azadirachta indica* attenuates cisplatin-induced neurotoxicity in rats. *Ind J Pharmacol*. 2014; 46: 316-21.
38. Abdel Moneim AE, Othman MS, Aref AM. *Azadirachta indica* attenuates cisplatin-induced nephrotoxicity and oxidative stress. *BioMed Res Int*. 2014; 2014: 647131.
39. Upadhyay SN, Dhawan S, Garg S, Talwar GP. Immunomodulatory effects of neem (*Azadirachta indica*) oil. *Int J Immunopharmacol*. 1992; 14: 1187-93.
40. Durrani FR, Chand N, Jan M, Sultan A, Durrani Z, Akhtar S. Immunomodulatory and growth promoting effects of neem leaves infusion in broiler chicks. *Sarhad J Agric*. 2008; 24: 655-9.
41. Gbotolorun SC, Osinubi AA, Noronha CC, Okanlawon AO. Antifertility potential of neem flower extract on adult female Sprague-Dawley rats. *Afr Health Sci*. 2008; 8: 168-73.
42. Upadhyay SN, Dhawan S, Talwar GP. Antifertility effects of neem (*Azadirachta indica*) oil in male rats by single intra-vas administration: an alternate approach to vasectomy. *J Androl*. 1993; 14: 275-81.
43. Bhambal AB, Kothari SK, Saxena SS, Jain MJ. Comparative effect of neem stick and toothbrush on plaque removal and gingival health – A clinical trial. *J adv oral*. 2011; 2: 51-6.
44. Lakshmi PN, Sowmia N, Viveka S, Brindha RJ, Jeeva S. The inhibiting effect of *Azadirachta indica* against dental pathogens. *Asian J Plant Sci Res*. 2012; 2: 6-10.
45. Dholi SK, Ramakrishna R, Mankala SK, Nagappan K. In vivo anti-diabetic evaluation of neem leaf extract in alloxan induced rats. *J Appl Pharm Sci*. 2011; 7: 100-5.
46. Patil P, Patil S, Mane A, Verma S. Antidiabetic activity of alcoholic extract of neem (*Azadirachta indica*) root bark. *Natl J Physiol Pharm Pharmacol*. 2013; 3: 142-6.
47. Bopanna KN, Kannan J, Sushma G, Balaraman R, Rathod SP. Antidiabetic and antihyperlipidemic effect of neem seed, kernel powder on alloxan diabetic rabbits. *Indian J Pharmacol*. 1997; 29: 162-7.
48. Peer PA, Trivedi PC, Nigade PB, Ghaisas MM, Deshpande AD. Cardioprotective effect of *Azadirachta indica* A. Juss. on isoprenaline induced myocardial infarction in rats. *Int J Cardiol*. 2008; 126: 123-6.
49. Mahfuzul Hoque MD, Bari ML, Inatsu Y, Juneja VK, Kawamoto S. Antibacterial activity of guava (*Psidium guajava* L.) and neem (*Azadirachta indica* A. Juss.) extracts against foodborne pathogens and spoilage bacteria. *Foodborne Pathog Dis*. 2007; 4: 481-8.
50. Ghonmode WN, Balsaraf OD, Tambe VH, Saujanya KP, Patil AK, Kakde DD. Comparison of the antibacterial efficiency of neem leaf extracts, grape seed extracts and 3% sodium hypochlorite against *E. faecalis* – an in vitro study. *J Int Oral Health*. 2013; 5: 61-6.
51. Natarajan V, Venugopal PV, Menon T. Effect of *Azadirachta indica* (neem) on the growth pattern of dermatophytes. *Indian J Med Microbiol*. 2003; 21: 98-101.

52. Tiwari V, Darmani NA, Yue BY, Shukla D. In vitro antiviral activity of neem (*Azadirachta indica* L.) bark extract against herpes simplex virus type-1 infection. *Phytother Res*. 2010; 24: 1132-40.
53. Othman F, Motalleb G, Lam Tsuey Peng S, Rahmat A, Fakurazi S, Pei Pei C, et al. Extract of *Azadirachta indica* (Neem) leaf induces apoptosis in 4T1 breast cancer BALB/c mice. *Cell J* 2011; 13: 107-16.
54. Chitta KS, Khan AN, Ersing N, Swaika A, Masood A, Paulus A, et al. Neem leaf extract induces cell death by apoptosis and autophagy in B-chronic lymphocytic leukemia cells. *Leuk Lymphoma*. 2014; 55: 652-61.
55. Elumalai P, Gunadharini DN, Senthilkumar K, Banudevi S, Arunkumar R, Benson CS, et al. Induction of apoptosis in human breast cancer cells by nimbolide through extrinsic and intrinsic pathway. *Toxicol Lett*. 2012; 215: 131-42.
56. Arumugam A, Agullo P, Boopalan T, Nandy S, Lopez R, Gutierrez C, et al. Neem leaf extract inhibits mammary carcinogenesis by altering cell proliferation, apoptosis, and angiogenesis. *Cancer Biol Ther*. 2014; 15: 26-34.
57. Gunadharini DN, Elumalai P, Arunkumar R, Senthilkumar K, Arunakaran J. Induction of apoptosis and inhibition of PI3K/Akt pathway in PC-3 and LNCaP prostate cancer cells by ethanolic neem leaf extract. *J Ethnopharmacol*. 2011; 134: 644-50.
58. Sharma C, Vas AJ, Goala P, Gheewala TM, Rizvi TA, Hussain A. Ethanolic neem (*Azadirachta indica*) leaf extract prevents growth of MCF-7 and HeLa cells and potentiates the therapeutic index of cisplatin. *J Oncol*. 2014; 2014: 321754.
59. Subapriya R, Kumaraguruparan R, Nagini S. Expression of PCNA, cytokeratin, bcl-2 and p53 during chemoprevention of hamster buccal pouch carcinogenesis by ethanolic neem (*Azadirachta indica*) leaf extract. *Clin Biochem*. 2006; 39: 1080-7.
60. Subapriya R, Bhuvaneswari V, Nagini S. Ethanolic neem (*Azadirachta indica*) leaf extract induces apoptosis in the hamster buccal pouch carcinogenesis model by modulation of bcl-2, bim, caspase 8 and caspase 3. *Asian Pac J Cancer Prev*. 2005; 6: 515-20.
61. Metwally FM, El-Mezayen HA, Moneim AE, Sharaf NE. Anti-tumor effect of *Azadirachta indica* (Neem) on murine solid Ehrlich carcinoma. *Acad J Cancer Res*. 2014; 7: 38-45.
62. Bajpai NK, Sharma VK. Use of Neem leaves as insecticides. *Ind Farmer's digest*. 1992; 25: 19-20.
63. Bajpai NK, Sharma VK. Insecticidal and residual toxicity of Neem (*Azadirachta indica*) and hemp (*Cannabis sativa*) leaf extract against larvae of Chillo partilius. *Ind J Appl Entomol*. 1997; 11: 11-8.
64. Bhatnagar B, Nama HS. Wormicidal effect of Neem leaf extract. *Neem Newsl*. 1990; 7: 30-1.
65. Omóbòwálé TO, Oyagbemi AA, Adejumobi OA, Orherhe EV, Amid AS, Adedapo AA, et al. Preconditioning with *Azadirachta indica* ameliorates cardiorenal dysfunction through reduction in oxidative stress and extracellular signal regulated protein kinase signalling. *J Ayurveda Integr Med*. 2016; 7: 209-17.
66. Ghatule RR, Shalini G, Gautam MK, Singh A, Joshi VK, Goel RK. Effect of *Azadirachta indica* leaves extract on acetic acid-induced colitis in rats: role of antioxidants, free radicals and myeloperoxidase. *Asian Pac J Trop Dis*. 2012; 2: S651-7.
67. Murthy SP, Sarsi M. Pharmacological studies on Melia Azadirachta. Part II. Estrogenic, antipyretic activity of neem oil and its fraction. *Ind J Physiol Pharmacol*. 1958; 2: 456-8.