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Ethnomedicinal potential of widely used plant *Azadirachta indica* A. Juss: A comprehensive review

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ABSTRACT

Drugs of traditional system of medicine including Unani and Ayurveda are recommended and used in various diseases since long. These drugs are mainly derived from herbs and plants. *Neem* is a pre-eminent and a sacred gift of nature. This tree is still regarded as “Wonder tree”, “Nature’s drug store”, “Divine tree”, “Heal all”, “Materia medica”, “Panacea of all diseases” and “Village dispensary” also considered as “An ancient cure for modern world”. In Unani System of Medicine (USM) it is widely used as anti-infective agent in various skin diseases (*Amrād-i Jild*) such as leprosy, syphilis, tinea, itching and in ulcers. It is very effective in painful menses and dysmenorrhea, chronic joint pain, constipation, intestinal worm (*Kirm-i Shikam*) and also prefer in the killing of head lice, diabetes and rheumatic arthritis. This study is based on a comprehensive analysis of related articles published in journals using the phrases “*Neem* or *Azadirachta indica*”, “*Neem research paper*”, “*Neem and Unani Medicine*” and “*Neem used in traditional medicine*” in electronic searches of the PubMed, SCOPUS, Google Scholar advanced search and AYUSH Research Portal. The evidence based scientific and clinical studies reported in the present review confirming the therapeutic efficacy of *Azadirachta indica* (*Neem*). Biological active phytoconstituents of *Neem* also indicate that it may serve as very effective natural medicine in different disease. In this aspect, further *in vitro* and *in vivo* studies are needed in respect to explore the recommendations of USM as well as other traditional system of medicines in term of the extensive therapeutic values of *Azadirachta indica*.

Keywords: *Neem*, *Azadirachta indica*, Phytoconstituents, Blood purifier, Skin Diseases, Unani.

INTRODUCTION

The Unani system of medicine (USM) is an oldest system of medicine in the world, originating from Greece, which has a holistic approach to treat various types of ailments. In this system of medicine, treatment is done through the four basic modes i.e., regimental therapy regimental therapy (*‘Ilāj bit Tadbīr*), dietotherapy (*‘Ilāj bil Ghidhā*), pharmacotherapy (*‘Ilāj bid Dawā*) and surgery (*‘Ilāj bil Yad*)^[1]. Pharmacotherapy (*‘Ilāj bid Dawā*) is a very important aspect of USM that includes single and compound drugs. *Neem* is a pre-eminent and a sacred gift of nature. It is known as being free of insects, disease and nematodes from centuries^[2] and was firstly discovered about 4,500 years back in India^[3]. It has been widely used traditionally. *Neem* tree is well known for its medicinal properties from thousands of years. For medicinal point of view all most all parts of neem are used widely in Unani, Ayurveda and Homoeopathic system of medicine and it has become a cynosure of modern medicine. Its latinized name, *Azadirachta indica*, is derived from the Persian. *Azad* means “free”; *dirakht* means “tree” *i-Hind* means “of Indian origin”. Hence it literally means “the free tree of India”^[4]. *Neem* is called “*Arista*” in Sanskrit a word that means “perfect”, complete and imperishable. Also, the Sanskrit name of the neem plant is “*Arishta*” meaning “reliever of sickness”. This tree is still regarded as “Wonder tree”, “Nature’s drug store”, “Divine tree”, “Heal all”, “Materia medica”, “Panacea of all diseases” and “Village dispensary” also considered as “An ancient cure for modern world”. The importance of this tree has been recognized by the US National Academy of Sciences, which published a report in 1992 entitled “*Neem- a tree for solving global problems*”. The advancement of neem research has earlier been documented^[5-8].

METHODOLOGY

We conducted a comprehensive analysis of related articles published in journals using the phrases “*Neem* or *Azadirachta indica*”, “*Neem research paper*”, “*Neem and Unani Medicine*” and “*Neem used in traditional medicine*” in electronic searches of the PubMed, SCOPUS, Google Scholar advanced search and AYUSH Research Portal. We also performed hand-search such as Hippocratic Journal of Unani Medicine, Annals of Phytomedicine and Unani classical textbooks in NRIUMSD library, Hyderabad.

Botanical descriptions:

The drug botanically known as *Azadirachta indica* A. Juss., family Meliaceae [9-10]. It is a medium to large size fast growing evergreen popular tree with straight trunk and many branches achieving height of 15-20 meters or more with favourable conditions upto the 35-40 meters and 2.5 meters in girth. Leaves are pinnate up to 30 centimetres long and each leaf has 10–12 serrated leaflets that are 3.5-8 centimetres long by 2.5 centimetres wide. The tree is covered with honey-scented, white flowers come in the early summer (March to April) that are arranged in axillary and normally more or less drooping panicles which are up to 25 cm long. There are semi-sweet, olive-size fruits, green in colour which turn golden yellow on ripening in the months of June to August that generally begin bearing at three to five years of age but do not become a fully reproducible until they are ten years old, in this age, the tree produces an average of about 20.5 kilograms of fruit per year. It is one seeded drupe, seeds ellipsoid, cotyledons thick, fleshy and oily. Bark is dark brown in colour with shallow vertical furrows. It is native of India, Burma and Pakistan, commonly growing in tropical and semitropical regions upto an altitude of 1000 meters [9, 11-15]. It is also found in Bangladesh, Srilanka, Thailand, Malaysia, Mauritius, Fiji, South Africa, East Africa, America, [16-17] Nepal, China and Myanmar [18]. About *Neem* trees reported that they can live up to 200 years [19].

Table 1. Taxonomical classification of *Azadirachta indica* A. Juss. [6]

I	Order	Rutales
II	Suborder	Rutinae
III	Family	Meliaceae
IV	Subfamily	Melioideae
V	Tribe	Melieae
VI	Genus	<i>Azadirachta</i>
VII	Species	<i>indica</i>



Figure 1. *Azadirachta indica* A. Juss. (Neem) plant and its parts. (A) Plant (B) Twigs, (C) Leaves, (D) Fruits, (E) Seeds (with endocarp), (F) Seeds (without endocarp)

Synonym: *Melia azadirachta* L., *Melia indica* Brandis, Neeb [9, 16, 20] and Margosa [17].

Table 2. Vernacular names of *Neem* [9-10, 16, 21-24].

Language/Region	Vernaculars
English	Indian Lilac, Margosa tree, Neem tree
Unani	Aazaad-Darakht-e-Hindi
Arabic	Neeb
Persian	Azad darkht-i hindi, Neeb, Nib
Urdu	Neem
Hindi	Balnimb, Nimb, Nim
Ayurvedic	Nimba, Nimbaka, Arishta, Arishtaphala
French	Agem lilas, Azadirac, Margosier
Malayalam	Arytikta, Nimbam, Aryaveppu
Sanskrit	Arishta, Arkapadapa, Hingu, Chhardighna, Vembaka
Bengali	Nim, Nimgachh,
Gujarati	Danujhada, Limbra, Limbadu
Punjabi	Bakam, Mahanim, Bukhain
Siddha/Tamil	Arulundi, Kinji, Malugam, Kaduppagai, Veppu, Vembu
Telgu	Nimbamu, Taruka, Vepa
Marathi	Balantanimba, Limba
Oriya	Limbo, Kakopholo, Nimo
Burma	Bawtamaka, Kamaka,
Marathi	Kadukhajur, Limba, Nimbay

Parts used: All parts of the plant- leaves, flowers, barks, root barks, fruits or seeds, gum and toddy or sap but mostly leaves and bark are used [21, 25-26].

Table 3. Macroscopic Characteristics of *Neem* [2, 10, 13, 19, 24].

Parts	Colour	Odour	Taste	Size	Shape
Leaf	slightly yellowish-green	indistinct	bitter	7-8.5 cm long and 1.0-1.7 cm wide	lanceolate, acute, serrate
Flower	white to pale yellow	fragrant or honey-scented	bitter	5-6 mm long and 8-11 mm wide	drooping panicles
Fruit	green initially, change into yellowish brown to chocolate brown	characteristic	semi-sweet pulp	0.5-2 cm long, 0.5-1.2 cm width and 0.6-0.9 cm thickness	smooth, varies from elongated oval to nearly roundish (ellipsoidal drupe)
Seed	externally brown, internally creamish	aromatic or garlic like after crushing	bitter	10-15 mm long, 3-5 mm width and 3-4 mm thickness	irregularly conical to ovoid
Stem Bark	externally rusty-grey, Internally yellowish	characteristic	bitter	slightly curved to flat but according to age & parts of tree varies	externally rough & fissured, Internally foliaceous

Microscopic Characteristics of Neem:

LEAF

Midrib: Leaflet through midrib reveal a biconvex outline, epidermis on both side covered externally with thick cuticle, below epidermis 4 to 5 layered collenchyma present; stele consisted of one crescent-shaped vascular bundle towards lower and two to three smaller bundle towards upper surface; rest of tissues comprised of thin-walled, parenchymatous cells having secretory cells and rosette crystals of calcium oxalate; phloem surrounded by non-lignified fibre strand; crystals also present in phloem region [19].

Lamina: There are dorsiventral structures, epidermis on either surface that composed of thin walled, tangentially elongated cells, covered externally with thick cuticle; anomocytic stomata present on lower surface only, palisade single layered; spongy parenchyma composed of 5-6 layered, thin-walled cells, traversed by a number of veins; rosette crystals of calcium oxalate present in a few cells; palisade ratio 3.0-4.5; stomatal index 13.0-14.5 on lower surface and 8.0-11.5 on upper surface [19].

Stem Bark: It exhibits outer exfoliating pieces hard, woody, considerably thick in older barks, almost entirely dead elements of secondary phloem, alternating with discontinuous tangential bands of compressed cork tissue, former composed of several layers of stone cells occurring in regularly arranged groups together with collapsed phloem elements filled with brown contents, in between the successive zones of cork tissue 3-5 layers of fibre groups with intervening thin-walled and often collapsed phloem elements present. Each zone of cork tissue comprises of several layers of regular, thin-walled cells occasionally with a few compressed rows of thick-walled cells towards [19].

Fruit: The cells of the epicarp are parenchymatous, single layered and squarish to rectangular with thick cuticle on the outer tangential walls in transverse section. The mesocarp region is composed of several layers of the parenchymatous cells which are mostly polygonal, thin walled and larger in size. The endocarp of stone cells are of different shapes and sizes. The epidermis of seed coat is single layered, thick walled, squarish to rectangular and parenchymatous in nature. The outer tangential wall of the epidermis is coated with thick cuticle. Tegmen is 8-10 layered, thick walled, hexagonal with sclerotic cells.

Integument persists as a single layered parenchyma. The two cotyledons constitute the major portion of embryo. Cotyledon consists of single layered epidermis in which cells are isodiametric and parenchymatous. The ground tissue of the cotyledon is composed of thin walled hexagonal to polygonal parenchymatous cells. These cells are filled with oil globules of different sizes. Aluerone grains are also observed in this region [9-10]. **Seed:** Seed kernel of fruit shows a thin brown testa, of isodiametric stone cells overlying integument of loosely packed parenchymatous cells; cotyledon consisting of parenchymatous cells containing abundant oil droplets [9].

Analysis of fruit/ seed powder: The crude drug powder is yellowish brown in colour. The crude drug powder shows the pieces of parenchymatous cells, endosperm, embryo epicarp, mesocarp, pitted stone cells with wide lumen and distinct wall striations, groups of lignified fibres and tracheids. Fragments of testa showing distinctly striated isodiametric stone cells [9-10].

Chemical constituents:

Azadirachta indica (Neem) has very important therapeutics role in the management of health due to rich source of different variety of biologically active principles as a whole. The chemical constituent of *Azadirachta indica* is very complex as it contains remarkably various array of phytochemicals, for example terpenoids, flavonoids, coumarins, carbohydrates, proteins, fatty acids and their esters and hydrocarbons [3]. In 1942 for the first time Nimbin a bitter compound had been isolated from *A. indica* (Neem) oil. More than 140 chemically and structurally complex bioactive compounds have been identified from different parts of the neem [27-29]. These compounds have been divided into two major classes, isoprenoids and others (non-isoprenoids) [5]. The isoprenoids comprise diterpenoids, triterpenoids and steroids containing protomeliacins, limonoids, azadirone, azadiradione, gedunin, vilasinin type of compound, C-secomeliacins such as azadirachtin, nimbin, salanin and its derivatives while the non-isoprenoids include proteins, carbohydrates, polysaccharides, sulphurous compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalcone, coumarin and tannins, aliphatic compounds etc. [30-31]. Some of the important phytoconstituents isolated from neem are azadirachtin, meliantriol, salanin, triterpenes, β -sitosterol, stigmasterol, cyclic trisulphides and tetrasulphides in leaves, nimbin, nimbidin, azadirachtin, limonoids: meliantriol, nimbidinine and nimbendoil in seeds, nimbosterol, myricitin in seeds oil and neem seed oil also contains Vitamin B and other essential acids. The oil is found to have the following fatty acids, oleic acid, stearic acid, palmitic acid, linoleic acid, and various lower fatty acids [8, 19]. Kaempferol present in flowers, deacetyl azadirachtinol in fruits, diterpens (sugiol), nimboil, nimbin, nimbidin, nimbinin, polysaccharides G1a, G1b, G2a and G3a, (-) epicatechin, catechin, margolone, margolonone and isomargolonone in bark. Other chemical constituents meliacine, gedunin, valassin, quercetin-3- galactoside, rutin, isorhamnetin, nimbolide, vilasinin, quercetin-3- galactoside, rutin, isorhamnetin, nimbolide, vilasinin, nimbinene, 6-deacetyl nimbinene, nimocinol, β -sitosterol- β -D-glucoside, nimbolin A and B, 6-deacetyl nimbinene, kaempferol-3-glucoside, mahmoodin and tigenic acid are also present. Most of these phytoconstituents belong to the chemical group of triterpenoids (limonoids) which are slightly hydrophilic and highly soluble in organic solvents such as hydrocarbon, alcohols, ketones, and esters [17, 29, 32]. The bark exudate (gum) of neem also contains a bitter alkaloid named as "margosine" [21]. The oil obtained from its seeds is act as stimulant, alterative and effective in rheumatism and skin diseases and also beneficial as a liniment for rheumatic affections. It is recently, reported that nimbidin, a compound isolated from neem oil, possessed significant anti-gastric ulcer activity in experimental animals, wherein it was exhibited to prevent ulceration by reducing gastric secretion [33].

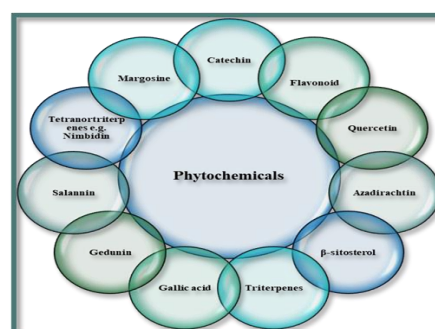


Figure 2. Some important bioactive phytochemicals of *Azadirachta indica* (Neem)

Description of the drug according to USM

Mizāj (temperament): *Hār* (Hot) 1^o *Yābis* (Dry) 1^o (all parts), Hakeem Ghulam Imam and Ali Yaar Khan quoted that its temperament is *Murakkab-ul Quwā* and *Ma'il ba Sardī* and according to Vedas the prakriti of the drug is *Bārid* (Cold) *Yābis* (Dry) but temperament of fruit or seed is *Hār* (Hot) *Raṭab* (Moist) [11, 25].

Nafa' Khāṣ (Main function): *Muṣaffī-i Dam* (blood purifier) and *Dāfi 'i Sauda*, *Dāfa 'i Ta'ffun* (antiseptic) [25, 34].

Muḍīr (Adverse effect): It has some unwanted effects for persons who has dry temperament [25].

Muṣliḥ (Correctives): Pure honey, black pepper and oils can be used to correct the unwanted effects if so any [25].

Badal (substitute): One part is substitute of other part [26].

Dose: Dried leaf - 1-3 gm powder; 10-20 gm for decoction; **stembark**- 2-4 gm powder decoction for external use, **leaves juice**- 10-20 ml, **oil**- 5-10 drops, **bark decoction**- 50-100 ml. [16] When it is used as blood purifier, the green leaf and bark juice or decoction can be taken 6-12 ml, [25] leaves and bark 7-12 gm [35].

Dosage forms: It can be used as a form of *Hubūb* (pills), *Majun*, *Marham* (ointment), *Arq* (distillates), *Suftīf* (powder), *Joshānda* (decoction), paste (*Zimād*), Juice [16, 25] and seed soil [35].

Af'āl (Actions): Neem is known as “reliever of sickness” that s why it has very effective and many functions which are as follows *Muḥallil* (resolvent), *Musakkin* (analgesic), *Mulayyin*, *Muṣaffī-i Khūn* (blood purifier), *Dāfi 'i Hummā* (antipyretic), *Dāfi 'i Ṣafrā wa Balgam*, *Muqaṭṭi'*, *Mundij* (concoctive), *Dāfi 'i Ta'ffun* (antiseptic), *Qātil-i Jarāsīm* (antimicrobial), *Qātil-i Kirm-i Shikam* (anthelmintic/vermifuge), *Munaqqā-i Qurūḥ* [10, 25]. Root bark and young fruit have tonic, antiperiodic, alterative and astringent effects. Bark is bitter, tonic, antiperiodic and astringent and also vermifuge. Bark and leaves are aphrodisiac, maturant and resolvent. Fruit shows *Muṣaffī-i Khūn* (blood purifier), purgative, emollient and anthelmintic actions. Leaves are discutient, leaf juice is anthelmintic. Oil from nuts and leaves is considered as local stimulant, antiseptic, alterative insecticide and antiseptic. Flowers have *Muṣaffī-i Khūn* (blood purifier), stimulant, tonic and stomachic effects. Gum from the bark is used as stimulant, demulcent and tonic. Toddy is having refrigerant, nutrient and alterative tonic activity. The drug also possesses anti-spirochaetal and emmenagogue properties. Fruits have purgative, emollient and anthelmintic functions. Bark, gum, leaves and seeds are also having antidote effects in snake bite and scorpion sting. [21, 23, 25, 36] Seeds have *Musakkin* (analgesic) and *Mudirr-i Hayd* (emmenagogue) actions [37]. Sap is considered as a *Muṣaffī-i Khūn* (blood purifier), refrigerant, nutrient and alterative tonic [23].

Iste'māl (Therapeutic uses):

In Unani system of medicine, all parts of neem are used as a blood purifier in all blood impurities related diseases (*Amrād-i Fasād khūn*) [35]. **Leaves:** Major therapeutic uses of leaves are anthelmintic, dermatopathies, fever and anorexia [13]. Leaves as poultice applied on boils that help in healing and prevent putrefaction. Decoction of leaves has antiseptic action so, it is used in ulcers and eczema. Fresh neem leaves juice extracted and dripped on wound that infested with

worms. Moreover, if worms present in nose then used as *Qatūr* (nasal drop) [25, 36]. Wounds are washed by decoction of leaves; dry leaves are used as dusting powder on wound and decoction of leaves are also used for bathing in itching and other skin diseases. In ear ache steam of leaves is used that is very effective [35]. Mixture of same quantity of leaf, fruit, stem bark and flowers powder, taken one spoonful with one spoonful ghee and honey (1/2 spoon) twice a day for one month in jaundice. Crushed leaves applied on head before hair wash to prevent falling of hair once a week if there is dandruff. Young leaves crushed and applied on forehead to relieve headache, once a day for 8 days [12]. Bark & leaves are also useful in otalgia (*Waja 'ul Udhun*), leucoderma, lumbago, piles, syphilis, and it cure all wounds and reduce all inflammations [23, 38]. **Stem & root bark:** It is mostly effective in helminthiasis, pyrexia, diabetes mellitus and pruritus [24]. Decoction of neem bark specially used in seasonal fever and for killing of intestinal worms [35]. Bark has blood purifier (*Muṣaffī-i Dam*) effect, used in worms infestation (*Didān-i Am'a*), and root bark used as emmenagogue (*Mudirr-i Hayd*) in amenorrhoea [38]. **Young shoots** and green twigs are crushed and used as tooth brushes (*Miswāk*) for teeth cleaning. This can cure toothache, bad breath, dental caries and gum diseases. Neem protects the mouth from various infections. **Sap** is considered effective in some chronic and long-standing cases of leprosy (*Judhām*) and other skin diseases, syphilis (*Ātishak*), atonic dyspepsia and general debility [23, 35, 38-39]. **Flowers** are usually included in the blood purifier prescriptions (*Nuskhajāt*) for blood purification used in skin diseases. Kajal of neem that is prepared by flower is also useful in eye itching [25]. It can be effectively used in some cases of atonic dyspepsia and general debility. [23] **Fruits or Seeds:** It is used in skin diseases (*Amrād-i Jild*) as blood purifier (*Muṣaffī-i Dam*) [9]. Powder of neem seed is very effective in painful menses and dysmenorrhoea due to analgesic (*Musakkin*) and emmenagogue (*Mudirr-i Hayd*) actions [37]. Seeds paste of neem applied on affected part to cure any type of skin diseases twice a day for one week [12]. Seeds oil of neem used in leprosy, syphilis, tinea, itching and nonhealing ulcers or very bad wounds, if there are worms in the wounds that are also killed by the seeds and it is also very effective in chronic joint pain. Application of the fruit alone or with other medicines on the infected wounds remove infection and heals the wounds quickly. It is also beneficial in wounds of chronic scrofula (cervical tuberculous lymphadenitis) [34-35]. Eating of ripe fruits have laxative (*Mulayyin*) and blood purifier (*Muṣaffī-i Khūn*), antihelmintic (*Qātil-i Kirm-i Shikam*) effect and used in hemorrhoids that s why it is included in the formulation of anti-hemorrhoidal tablets. Moreover, it is also very effective in the killing of head lice, if they are ground into a paste form and applied to the hair follicles [25, 35]. It is majorly used in dermatopathies, diabetes, wounds/ulcers and oedema [13]. Oil is effective in rheumatism and skin diseases due to stimulant, antiseptic and alterative effect [36]. It is very effective in swelling of skin and skin diseases (*Amrād-i Jild*) [10].

Traditional uses of neem

Skin diseases: Neem has been extensively used and significant effect on chronic skin disorders. Neem seeds oil has produced significant efficacy against ringworm, psoriasis, acne, eczema and warts [29]. It has an unfathomably cooling effect on the body, diminishing overabundance heat that can overcome the skin diseases [40]. Regular use of neem leaves and neem preparations assist in enhancing blood circulation as well as preventing hormonal imbalance which are a major cause behind some skin and hair disorders [14-42].

Table 4. Traditional uses of *Azadirachta indica* [5-6, 43-44]

S. No.	Neem Products	Medicinal Prosperities
1	Fruits/seeds	Antibacterial effect, Leprosy and intestinal worms, yield oil and cake, Relieves piles, intestinal worms, urinary disorder, epistaxis, phlegm, eye problem, diabetes, wounds and leprosy
2	Seeds oil	Analgesic, Anticholinergic, Antihelminthic, Antihistaminic, Antiprotozoal, Antipyretic, Antiviral, Bactericidal, Contraceptives, Fungicides, Insecticides, Insect & mosquito repellents, Veterinary medicines. It is also used in various cosmetics like Hair oils, Lubricants, Propellants, Shampoos, Soaps, Tooth pastes
3	Neem Cake	Animal feed, Soil fertilizer, Soil moisturizer, Soil neutralizer, Soil protectant
4	Leaves	Antidermatic, Antifungal, Anticlotting agent, Antihelminthic, Antituberculosis, Antitumour, Antiseptic, Antiviral, Contraceptive, Cosmetics, Fertilizers, Insecticides, Nematicides, Insect repellents & mosquito.
6	Twigs	Oral deodorant, Toothache reliever, Tooth cleaners,
7	Bark	Antiallergenic, Antifungal, Antiprotozoal, Antitumor, Analgesic, alternative and curative of fever Deodorant
8	Flowers	Analgesic, Stimulant, Bile suppression, elimination of intestinal worms and phlegm. It is also used in curries, nectaries as soaps
9	Gum	Effective against skin diseases like ringworms, scabies, wounds and ulcers.
10	Root, bark, leaf, flower and fruit together	Blood morbidity, biliary afflictions, itching, skin ulcer, burning sensation and leprosy.

Table 5. Various traditional categories of neem products in the market [45].

S. No.	Product Types	Brand Name
A. Herbal Drugs		
1.	Neem tablets	Neem Leaf Capsules
2.	Antifungal	Himalaya Neem
3.	Antibacterial	Organix Neem Leaf
4.	Capsules	Neemguard
5.	Neem tea	Neem Tea
6.	Rejuvenating anti stress	Amritha herbal tea
7.	Detox and weight loss	Neem Detox
8.	Blood rectifier tonic	Neem life tonic
9.	Neuro stimulant	Shiro Dhara oil
10.	Diabetics and Pancreas	Daib Neem
11.	Arthritis oil	Arthooil
B. PERSONAL HYGIENE		
1.	Soaps	Margo, Neem, Ayurcare, Clean Fair, Faith in Nature, Limda
2.	Shaving cream	Himalaya shaving cream
3.	Toothpaste	Neem activ, Himalaya dental care, Neem, Miswak, Dabur, Auromere, Herbal vedic, Organix
4.	Tooth powder	Neem
5.	Medicated soap for acne	Anti-pimple cream
6.	Body lotions	Neem Mist, Perpetua
7.	Shampoo	Auromer
8.	Hair oil	Shao neem
9.	Hair conditioners	Perpetua hair conditioners
10.	Hair rejuvenating tonics	Neem Plus
11.	Neem Plus	Dento Neem
12.	Face wash gel	Neem O Jol, Ayucare
13.	Skin toner	Neem tone
14.	Cleansing milk	Neem O Clin
15.	Washing gel	Dish wash gel
16.	Antibacterial	Neem O line
17.	Disinfectant	Secura
18.	Detergent spray	Neem cleaner

19.	Air Purifier	Neempur
20.	Face scrub	Ecosense
21.	Anti-lice	No Lice
22.	Deodorant	Ecosens
23.	Antidandruff	Ecosens
C. COSMETIC PRODUCT		
1.	Lip balm	Ecosense
2.	Eye gel	Sundari eye gel, Neem organics
3.	Night cream	Glow Neem
4.	Moisturing cream	Neemaura, Neem organics
5.	Face wash gel	Neem O Jol
6.	Body scrub	Glory Neem Scrub
7.	Body massage oil	Perpetua
8.	Face scrub	Neem orange and Neem silver
9.	Face pack	Radiance
10.	Facial massage oil	Ayucare Oil
11.	Sunscreen lotion	All natural lotion
12.	Cleansing gel	Sundari cleansing gel
13.	Pedicure	Ecosense Heel Care Stick
14.	Powder	Neem Aroma
15.	Hair Gel	Reshlon Neem Hair gel

Mashhūr Murakkabāt (Important Unani formulations)

Ḥabb-i Bawāsīr, Ḥabb-i Muṣaffī-i Khūn ^[9], *Majun Musakkin-i Dard-i Reḥam*, ^[25, 37] *Majūn Bawāsīr, Majūn Juzām, Arq Murakkab Muṣaffī-i*

Khūn ba nuskha Kalan, Arq Hāḍīm, Arq Hrābharā, Marham Jadwār, Marham Sā'ida Chūb Neem Wālā, Zimād Muhāsa, Zimad-i Bawāsīr and Rogan-i Neem ^[10, 26, 46].

Evidence based scientific studies:



Figure 3: Pharmacological activities of *Azadirachta indica* A. Juss. (Neem and its ingredients) an overview

Table 6. Biological activity of some bioactive compounds of *Azadirachta indica* (Neem) reported in scientific research. [5-6, 30, 41, 47-48]

Neem compound	Source	Biological activity
Nimbidin	Seeds	Anti-inflammatory
		Antiarthritic
		Antipyretic
		Hypoglycaemic
		Antigastric ulcer
		Spermicidal
		Antifungal
		Antibacterial
		Diuretic
Sodium nimbidate		Anti-inflammatory
Nimbin	Seed oil	Spermicidal
Nimbolide	Seed oil	Antibacterial, Antimalarial
Gedunin	Seed oil	Antifungal, Antimalarial
Azadirachtin	Seed	Antimalarial
Mahmoodin	Seed oil	Antibacterial
Gallic acid	Bark	Anti-inflammatory, immunomodulatory
(-) epicatechin, catechin	Bark	Anti-inflammatory, immunomodulatory
Margolone, margolonone, isomargolonone	Bark	Antibacterial
Cyclic trisulphide, cyclic tetrasulphide	Leaf	Antifungal
Polysaccharides	Leaf	Anti-inflammatory
Polysaccharides G1a, G1b	Bark	Antitumour
Polysaccharides G2a, G3a	Bark	Anti-inflammatory
NB-II peptidoglycan	Bark	Immunomodulatory

Anti-inflammatory Activity: The anti-inflammatory effect of Nimbidin isolated from neem tree was evaluated in carrageenin and kaolin induced paw oedema in rat model. The drug at the dose level of 40 mg/kg and 80 mg/kg was showed significant anti-inflammatory effect as compared to phenylbutazone (100 mg/kg). Nimbidin also significantly suppressed the formalin-induced arthritis of ankle joint and the fluid exudation in croton oil-induced granuloma in rats. The drug was found to be effective in both acute and chronic phases of inflammation. So, it can be considered a general anti-inflammatory agent [33] because nimbidin suppresses the functions of macrophages and neutrophils that involved in inflammation [41]. In an *in vivo* (on rat) and *in vitro* study, nimbidin showed potent anti-inflammatory and antiarthritic activities by inhibition of some of the functions of macrophages and neutrophils that are related to the inflammatory response. It also inhibits the phagocytosis and the migration of macrophages in response to inflammatory stimuli at the affected side [49].

Antimicrobial Study: All parts of neem plant play an important role in potentiality of cell wall breakdown or inhibition of growth of numerous microbes for example bacteria, viruses, parasites and pathogenic fungi. The contribution of neem in the prevention of microbial growth is explained as follows.

1-Antibacterial activity: The study of neem (*Azadirachta indica*) seed oil extract was done through agar well diffusion method, using ethanol as an organic solvent against four bacterial strains (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Salmonella typhi*) and Ampicillin used as a control. *Pseudomonas aeruginosa* (14

mm), *Salmonella typhi* (11mm) and *Staphylococcus aureus* (10 mm) showed the highest zones of inhibition while *E. coli* (9 mm) showed the least zone of inhibition in 100% concentration of extract. Ampicillin as control also exhibited high zones of inhibition on all test organism like *Pseudomonas aeruginosa* (23 mm), *Escherichia coli* (19 mm), and *Staphylococcus aureus* (18 mm) except *Salmonella typhi* that showed the least (15 mm) in 100% concentration [8].

In another study, the new tetrahydrofuran diester 1 was separated as an antibacterial component from a petroleum ether extract of neem oil (*Azadirachta indica*). This component was showed significantly effective against three standard bacterial strains, including *Staphylococcus aureus*, *E. coli* and *Salmonella enteritidis* [50]. NIM-76 (vaginal contraceptive) is a fraction of neem oil (*A. indica*), was studied for its antimicrobial effect against certain bacteria (*E. coli*, *S. typhi*, *S. dysenteroides*, *P. vulgaris*, *P. aerogenosa*, *S. faecalis* and *S. aureus*), fungi (*C. albicans*) and Polio virus. It was more effective as compared to whole neem oil especially against *E. coli* and *Pseudomonas aeruginosa* that are not inhibited by neem oil even at 15 mg/ml concentration. Ciprofloxacin (10 µg/ml) and ketoconazole (50 µg/ml) were used as positive control for bacterial strains and fungal strain (*C. albicans*), respectively in this study [51]. In a separate antibacterial study, effect of neem seed oil also evaluated against 14 strain of pathogenic bacteria. The bactericidal effect was noted due to the inhibition of cell-membrane synthesis in the bacteria [52]. In another study, the work has been done to explore the antibacterial activity of the bark, leaf, seed, and fruit extracts of neem by agar well diffusion method against bacteria- *Pseudomonas aeruginosa*, *Corynebacterium diphtheriae*, *Bacillus spp* that was isolated from adult mouth. The bark

and leaf extracts exhibited antibacterial activity against all the test bacterial strains used and zone of inhibition increased with increase in concentrations of the extracts. Moreover, seed and fruit extracts also showed antibacterial activity only at higher concentrations [53].

2-Antifungal activity: Antifungal activity of extracts of seed kernels of *Azadirachta indica* was evaluated in 10 different (hexane, methanol, chloroform, water, petroleum ether, 5% dimethylsulfoxide, dichloromethane, acetone, methanol: chloroform: water (12:5:3) and absolute alcohol) solvent system against 15 *Candida* species and fluconazole used as standard control in this study. The hexane and ethanol extracts of the seed kernels exhibited very good effect, inhibiting more than 13 out of 15 *Candida* strains while all *Candida* species were resistant to chloroform extract obtained by the successive extraction method and methanol: chloroform: water (12:5:3) extracts. Although, 9 strains out of 15 showed inhibition by a direct chloroform extract and other extracts showed satisfactory inhibition. Moreover, the result of antifungal control fluconazole was as follows- 8 were sensitive, 2 were resistant and 5 were susceptible dose dependent [54]. In another study, antifungal activity of leaf and fruit of methanol extracts of *Azadirachta indica* has been evaluated against *Alternaria solani* fungus. The Leaf extract exhibited more significant effect in retarding fungal growth than fruit extract against *Alternaria solani* [55]. In this *in vitro* study, aqueous, ethanolic and ethyl acetate extracts of leaves of neem have shown significant effect against some human pathogens - *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus terreus*, *Candida albicans* and *Microsporum gypseum* in different concentrations (5, 10, 15 and 20%). Among all these 3 extracts, the 20% concentrations of ethyl acetate extract was found to strongest inhibition of growth of these fungal strains and whereas its HPLC analysis showed the presence of nimonol [56]. A recent study has been evaluated that addition of neem powder to acrylic resin denture base materials showed antifungal activity by reducing the adhesion of *C. albicans* to denture stomatitis [57].

3- Antimalarial activity: In vivo antimalarial activity of methanolic extracts of seed kernels of ripe and unripe fruits of neem have been evaluated against early erythrocytic schizogony of *Plasmodium berghei* (rodent malaria parasite) on two (namely BALB/c and C57BL/6) infected inbred mice and parasitaemia was ruled out in C57BL/6 and BALB/c mice on day 4 after infection and after 4 days of treatment. C57BL/6 and BALB/c mice, exhibited parasitaemia of 5.4% and 7.4% respectively through treatment of extract of unripe fruits of neem with dose of 150 mg/kg and mice that treated with extracts of ripen fruits 150 mg/kg, showing a parasitaemia of 5.1% and 7.4% in C57BL/6 and BALB/c mice, respectively. Parasitaemia at day 4, reduced about 30% in C57BL/6 mice in that groups treated with the neem preparations compared to the solvent (H₂O containing 10% DMSO, 5% Tween 80) administered controls. Artesunate administered at the dose of 5 mg/kg, as effective control, reduced parasitaemia by 45% in C57BL/6 mice and by 60% in BALB/c, as compared to the respective untreated (i.e., solvent-administered) controls [58]. The effect of methanolic extracts of neem leaf and stem bark at the dose of 10 mg/kg was also evaluated against *Plasmodium berghei* infected albino mice with Artemether, Quinine and Chloroquine at the dose of 10 mg/kg were used as standard drugs. The leaf and stem bark extracts showed effective in reducing the level of parasitaemia about 51-80% and 56- 87%, respectively in infected mice and standard drugs recorded 85.49%, 73.39 and 29.85% for artemether, quinine and chloroquine respectively [59].

4- Antiviral Activity: In an experimental study, the *in vitro* antiviral effect of 4 fractions of alcoholic extract of neem seed kernel was

evaluated against Duck Plague Virus (DPV). The fraction 4 not showed any cytotoxic effects on Duck Embryo Fibroblasts (DEF) cells at concentrations lower than 31.25 µg/ml [60]. Antiviral activity was evaluated with neem bark phosphate-buffered saline (PBS) extract against Newcastle disease virus (NDV) by spot assay and micro-hemagglutination test. The result was explained that neem bark extract has significant antiviral activity at higher concentrations (1:2 dilution) during *in vitro* study but showed cytotoxic activity as well while at lower concentrations (1:8 dilution) non-significant antiviral activity was reported [61].

Wound healing effect: In a clinical study, wound healing efficacy of neem oil was evaluated in the treatment of chronic non-healing wounds. The study results showed that after 8 weeks of treatment, 50% wound healing was observed in 43.80% patients (total 60 participants) [62]. In a separate *in vivo* study, the aqueous extract of neem leaves was studied for its wound healing activity on twenty male wistar rats (control and test have 10 animals in each group) and normal saline was used on the control rats for dressing. Wound was made on the right dorso-lateral aspect of the thoracic wall of 2 cm x 2 cm diameter. Results of study were indicated that the mean % of wound contraction on day 6 for experimental group was 72.34± 2.49 while the control group was 62.39± 7.94 and the mean % of wound contraction on day 9 for experimental rats 92.20± 6.66 while that of the control group was 85.19± 7.84. The leaves extract of *Azadirachta indica* was found significantly higher (p<0.05) the day of complete wound closure in experimental group as compared to control group. [63] In another study, the ethanolic extract of neem leaves was used to test the wound healing activities, and a significant reduction in the longest diameter wounds has been observed after 15 days of treatment and there was no significant difference noted in the longest diameter of wound between neem leaves extract (test drug) and povidone iodine (control drug) [64].

Antioxidant activity: Different parts of neem plants like root, bark, leaf, flower and seed showed role in disease management by modulation of various biological activities. Antioxidant activity of different parts of Siamese neem tree (*Azadirachta indica* A. Juss var. *siamensis* Valetton, Meliaceae) in aqueous and ethanolic extracts was evaluated by 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging assay. The results indicate that extracts from leaf, flower and stem bark of the Siamese neem tree keeping strong antioxidant potential [65]. In another study, aqueous, ethanolic and methanolic extracts of flowers and seed oil of neem were explored for antioxidant activity. The study results showed that the ethanolic extract of flowers and seed oil at 200 µg/ml was found to highest free radical scavenging activity i.e., 64.17±0.02% and 66.34±0.06% respectively and this effect may occur due to the highest amount of total phenol content [66] In another study, among the methanolic and chloroform extracts of neem leaves, it has been observed that methanolic extracts possess significantly more antioxidant properties as of the chloroform extract [67]. In this comparative study, it was conformed that the bark has higher antioxidant activity (93.11%) than leaves (82.45%) even more than standard drug (vitamin C, 92%). It can be due to presence of higher phenolic contents 66.63 to 629.04 µg/mg in the bark extracts and 23.85 to 237.00 µg/mg in the leaf extracts [68].

Nephroprotective effect: In a nephroprotective study the methanolic leaves extract of neem was found significantly effective at the dose of 500 mg/kg against Cisplatin (CP) nephrotoxicity and oxidative stress in rats [69].

Antidiabetic effect: In an experimental antidiabetic study, the neem leaves extract was evaluated for antidiabetic effect in alloxan induced diabetic mice. In mice, diabetes was induced by single intraperitoneal injection of alloxan 240 mg/kg body weight then were treated with oral administration of 500 mg neem leaves extract /kg body weight for consecutive 42 days. After 42 days of treatment, result was concluded that significantly reduced the up regulated blood glucose, total plasma cholesterol such as LDL and triglyceride (TG). Besides these, showed significant increase of erythrocytes and decrease of total leukocyte count and also highest body weight gain was found. This explanation indicates that crude extract of neem leaves could be an effective alternative medicine for diabetic patients [70]. Neem (*Azadirachta indica*) seed oil studied to find out hypoglycaemic and hypolipidemic effect in alloxan (150 mg/kg in 3 doses of subcutaneous injection) induced diabetic wistar albino rats and rats were observed for plasma glucose and Lipid profile levels at the end of 48 h after alloxan induced diabetes. Test group received neem seed oil at the dose of 5 ml/kg orally for 21 days and diabetic control not given any treatment. The results were concluded that control group showed plasma glucose level 280.4 ± 14.2 , serum cholesterol 170 ± 6.1 , serum triglycerides 93.3 ± 6 and serum HDL 18.91 ± 3.18 (mg/dl) while in test group plasma glucose level 126.32 ± 6.20 , serum cholesterol 149 ± 7.0 , serum triglycerides 75.8 ± 3.6 and serum HDL 32.61 ± 0.32 (mg/dl) were showed. These results have been proved that neem seed oil was found significantly effective in the treatment of hyperglycaemia and hyperlipidaemia [71]. In another study, neem kernel powder 500 mg/kg and glibenclamide 0.5 mg/kg as single or in combination of neem kernel powder 250 mg/kg with glibenclamide 0.25mg/kg were used as an antidiabetic agent on rabbits. The results showed that these two agents, either in single or in combination form were found significantly reduce the concentration of serum glucose, lipids, and activities of serum enzymes [72]. Moreover, neem root bark extract was succeeded to reduce in blood glucose level at dose of 200 and 400 mg per kg whereas the higher dose of this extract (800 mg/kg) showed significant reduction in blood sugar level. It decreased blood glucose level by 54% as compared to control Glibenclamide (0.5 mg/kg) [73].

Cardioprotective effect: In a cardioprotective experimental study, the aqueous leaf extract of neem at a dose of 250, 500 and 1000 mg/kg was given orally in isoprenaline induced myocardial infarction in rats on the basis of haemodynamic, biochemical and histopathological parameters and vitamin E at a dose of 100 mg/kg orally used as a comparator, that is a known cardioprotective antioxidant. The study results indicated that neem leaf extract significantly normalized most of the hemodynamic, biochemical, and histopathological parameters. It is concluded that neem extract produces equipotent cardioprotective activities as compared to Vitamin E [74].

Immunomodulatory effect: Immunomodulatory properties of neem have most important benefit for the body. It amplifies both the cell mediated and lymphocytic immune systems with "Killer T" cells which have ability to destroy microbes, viruses and cancer cells through administrating toxic chemicals into the attackers [41]. In a study, the aqueous extract of neem leaf at a dose of 100 mg/kg orally was examined after three weeks and results showed potent immune stimulant activity as evidenced by both humoral and cell-mediated responses [42]. Aqueous extract of neem flowers has also been revealed that the flowers increase both specific (humoral and cell mediated immunity) and nonspecific immune responses (cytotoxic and phagocytic activity of macrophages) [75]. Also, in an *in vivo* study, the results show that neem oil has a non-specific immunostimulant effect and that it selectively activates the cell-mediated immune (CMI)

mechanisms to elicit an enhanced response to subsequent mitogenic or antigenic challenge [76].

Hepatoprotective effect: A study was done to investigate the hepatoprotective effect of azadirachtin-A in carbon tetrachloride (CCl₄) induced hepatotoxicity in rats. The results concluded that histology and ultrastructure study proved that pre-treatment with azadirachtin-A dose-dependently reduced hepatocellular necrosis. Moreover, the study results exhibit that pre-treatment with azadirachtin-A at the higher dose levels moderately restores the rat liver to normal [77]. Another study was carried out to examine the hepatoprotective effect of neem (*Azadirachta indica*) seed oil on carbon tetrachloride (CCl₄) induced hepatotoxicity in Wistar rats, in dose-dependent manner while silymarin served as a positive control. The results show that there is no significant difference ($P > 0.05$) when compared with the control in relation to about all parameters [78]. Furthermore, a study was formulated to find out hepatoprotective activity of alcoholic extract of neem leaves at a dose of 250 and 500 mg/kg per day for 30 days on Rifampin (RFI)Induced acute hepatic failure in rats. The results of this study showed that the neem leaves extract significantly normalised serum biomarkers and improved histopathological changes as compared to control group via antioxidant and ant-inflammatory pathway [79].

Role in dental health: A clinical study was done to evaluate the efficacy of neem containing mouth rinse regarding its antigingivitis effect and compared with chlorhexidine. The study results confirmed that neem containing mouth rinse is equally effective in reducing of gingival bleeding and plaque indices in both groups over a period of 21 days as compared to placebo control. Therefore, it can be used as an adjuvant therapy in the treatment of plaque induced gingivitis [80]. A comparative clinical study was performed between neem stick and a commercial toothbrush along with toothpaste to analyse the plaque removal and gingival health. The results clearly showed that there was no significant difference between these two methods of cleaning teeth and both ways significantly decrease the plaque and gingival scores as compared to baseline [81].

Anticancer activity: The anticancer activity of aqueous and ethanolic extract of neem leaves has been evaluated on various cell lines viz. breast, lung, cervical [82-84]. In an experimental study, the individual as well as combined effect of ethanolic extract of neem leaves and pH have been analysed on human breast cancer cell line MDA-MB 231 at different doses (400, 600, 800 and 1600 µg/ml each in 1% DMSO) level with pH values ranging from 6.2- 7.4. The study results were showed significance effect (about 95.7 % cytotoxicity) in combined experiment i.e., low pH (6.2) and neem extract at dose level 1600 µg/ml on MDA-MB 231 cells [84].

CONCLUSION

Traditional system of medicine particularly the Unani system of medicine are mainly depending on medicinal plants that are used in different ailments such as skin disorders, digestive disorders, sexual disorders, respiratory disorders etc. Various Unani drugs have been proved their efficacy in skin disease e.g., *Iltehab-i Jild Huzāzi* (seborrheic dermatitis) [85], *Baraş* (vitiligo) [86], skin rashes, infections, leprosy [87], psoriasis [88] and *Buthūr Labaniyya* [89]. *Neem* (*Azadirachta indica*) is one of the utmost important medicinal plants in Unani and other traditional system of medicines that are used as a blood purifier in all blood impurities related diseases, antidiabetic effect, anti-inflammatory, antiarthritic, antipyretic, hypoglycaemic, antifungal, antibacterial, diuretic, antimalarial and immunomodulatory effects. The

evidence based scientific and clinical studies reported in the present review confirming the therapeutic efficacy of *Azadirachta indica* (Neem) as mentioned in the Unani classics. Biological active phytoconstituents of *Neem* also indicate that it may serve as very effective natural medicine in different diseases. So, the data compiled in present review can be used to design the further *in vitro* and *in vivo* scientific studies to explore the ethnomedicinal potential of *Azadirachta indica*.

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Conflicts of interest

None declared.

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