



Review Article

NIMB (AZADIRACHTA INDICA): VALIDATION OF CLASSICAL PHARMACOLOGICAL PROPERTIES THROUGH REVERSE PHARMACOLOGY

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ABSTRACT

Plants have been the main source of therapeutic agents in world's most ancient system of medicine, the Ayurveda. *Nimb* (also known as Margosa tree) is one of the most commonly used plants in Ayurveda for the management of a large number of ailments. It is a member of the Meliaceae family, found commonly in India, Africa and America. *Nimb* has been used exclusively by mankind to treat various diseases since even before the availability of manuscripts that recorded the beginning of history. *Nimb* is well described in *Charak Samhita*, *Sushrut Samhita*, *Ashtang Hridayam*, *Chikitsa grantha* and *Nighantus*. It is having *Laghu guna*, *Tikta kashaya rasa*, *Sheeta virya* and *Katu vipaka*, due to which it has been considered as *Kapha-pitta shamaka*. Acharya Bhav Mishra considers it *Tridosh Shamak*. It is traditionally used in the treatment of various ailment i.e., *Krimi*, *Kushtha*, *Jwara*, *Kandu*, *Shopha* and many more. All the parts of the plant have been used in the preparation of therapeutic formulations. *Nimb* contains various bioactive compounds like Nimbinin and Nimbidin, due to which it shows antibiotic, antiulcer, anti-inflammatory, antihelmenthic, antifungal, diuretic, antihistaminic, nematocidal and spermicidal properties and other biological activities. Present paper is an effort to validate pharmacological properties of *Nimb* described in Ayurveda through reverse pharmacology.

INTRODUCTION

Azadirachta indica (Meliaceae) is a rapidly growing evergreen popular tree found commonly in India, Africa, and America^[1]. *Nimb* has been used exclusively by mankind to treat various diseases even before the availability of manuscripts that recorded the beginning of history. *Nimb* is termed as 'arista' in Sanskrit a word that means 'perfect, complete, and imperishable^[2]. The importance of the *Nimb* tree has been recognised by the US National Academy of Sciences, which published a report in 1992 entitled 'Neem-a tree for solving global problems^[3]. We Indians have long valued the *Nimb* tree; for centuries, millions have cleaned their teeth with *Nimb* twigs, smeared skin

disorders with *Nimb*-leaf juice, taken *Nimb* tea as a tonic, and placed *Nimb* leaves in their beds, books, grain bins, cupboard, and closets to keep away troublesome bugs^[4]. This tree is an incredible plant that has been declared the "Tree of the 21st century" by the United Nations^[5].

History, Origin and Distribution

The divine tree *Nimb* is mainly cultivated in the Indian subcontinent. The latinized name of *Nimb* (*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".^[6]

During excavation of Harappa and Mohan-jodaro one of the most prominent medicinal herbs they found was *A.indica*. There are an estimated 25 million trees growing all over India of which Uttar Pradesh (55.7%) occupying first place followed by Tamil Nadu (17.8%) and Karnataka (5.5%).

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Classification of *Nimb* in classical texts

In Ayurveda, *Nimb* has been classified variously as on the basis of properties, morphological characters, therapeutic values, *Doshkarma*, pharmacodynamics and many more. *Nimb* is classified in various *Gana* in *Brihatrayi* and *Nighantus* as below:

| <i>Samhita/ Nighantu</i> | <i>Gana/ Mahakashaya/Skandha</i> | References |
|----------------------------------|---|-------------------|
| <i>Charak Samhita</i> [7] | <i>Kandughna Mahakashaya</i> | CS.Su. 4.14 |
| | <i>Tikta skandhas</i> | CS.Vi. 8.143 |
| | <i>Anuvasan dravya kalpa sangrah</i> | CS.Vi. 8.150 |
| | <i>Sirovirechana dravya kalpa sangrah</i> | CS.Vi. 8.151 |
| <i>Sushrut Samhita</i> [8] | <i>Aragvadhadi gana</i> | SS.Su.38.6 |
| | <i>Guduchyadi gana</i> | SS.Su.38.50 |
| | <i>Lakshaadi gana</i> | SS.Su.38.64 |
| <i>Ashtanga hridaya</i> [9] | <i>Vaman gana</i> | AH.Su.15.1 |
| | <i>Pittashamak gana</i> | AH.Su.15.6 |
| | <i>Aragvadhadi gana</i> | AH.Su.15.17 |
| <i>Dhanvantari Nighantu</i> [10] | <i>Guduchyadi varga</i> | |
| <i>Madanpal Nighantu</i> [11] | <i>Haritakyadi varga</i> | |
| <i>Kaiyadev Nighantu</i> [12] | <i>Auoshadhi varga</i> | |
| <i>Shodhal Nighantu</i> [13] | <i>Guduchyadi varga</i> | |
| <i>Raj Nighantu</i> [14] | <i>Prabhadradi varga</i> | |
| <i>Bhavprakash Nighantu</i> [15] | <i>Guduchyadi varga</i> | |
| <i>Shaligram Nighantu</i> [16] | <i>Guduchyadi varga</i> | |
| <i>Nighantu Adarsha</i> [17] | <i>Nimbadi varga</i> | |
| <i>Priya Nighantu</i> [18] | <i>Haritakyadi varga</i> | |

Ayurvedic Pharmacodynamics[19]

| <i>Rasa</i> | <i>Guna</i> | <i>Virya</i> | <i>Vipaka</i> | <i>Doshkarma</i> |
|--------------------|--------------------|---------------------|----------------------|---------------------------|
| <i>Tikta</i> | <i>Laghu</i> | <i>Sheeta</i> | <i>Katu</i> | <i>Kaph-pitta shamaka</i> |

All scholars have considered *Rasa* as *Tikta*; *Guna* as *Laghu* and *Virya* as *Sheeta* unanimously.

Some scholars have mentioned *Grahi guna* of *Nimb* bark which is not appropriate since as per definition of *Grahi dravya* it should be *Deepan pachan ushna* and *Dravashoshak*, but *Nimb* is of *Sheeta virya* so it can be *Stambhak*. As *Nimb* is *Tikta* in *Rasa* it can be *Dravashoshak*.

There is no description of pharmacological properties of *Nimb* bark in classical texts as most commonly used plant part is stem bark. Therefore, properties in general described in texts may be that of stem bark.

Chemical Composition of *Nimb*

| | |
|-----------|---|
| Stem Bark | 1) <i>Nimbin</i> (0.04%), <i>Nimbinin</i> (0.001%), <i>Nimbidin</i> (0.4%), <i>Nimbosterol</i> (0.03%) ^[20,21] 2) DesacetylNimbin, sugiol or 7-ketoferruginol, Nimbiol ^[22,23,24,25] 3) Limonids gedunin, 7-desacteylgedunin ^[26,27] 4) Tannin (15.76%) ^[28] 5) Steroids/terpenoids, alkaloids, flavonoids, tannins, phenolics and saponins ^[29] 6) Proteins, alkaloids and minerals, amino acids like arginine, aspartic acid, cysteine, glutamic acid, isoleucine, methionine, norleucin, phenylalanine, proline, threonine, and tryptophan ^[30] |
| Leaves | 1) Vitamin C and carotene ^[31] 2) Quercetin and β -sitosterol ^[32] 3) Isoprenylated flavanone nimbaflavone ^[33] 4) Limonoid Azadirachtin A. ^[34] |

| | |
|--------------|---|
| | 5) Amino acids like glutamic acid, tyrosine, aspartic acid, alanine, proline, glutamine, cysteine ^[35] 6) Saponins, mucilage, essential oils ^[36] 7) Steroids,saponins, flavonoids ^[37] |
| FLOWERS | 1) Nimbosterol, glycoside- Nimbosterin, flavon- Nimbecitin, hydrocarbon- nonacosane, pungent essential oil ^[38] 2) Myricetin glycoside -melicitrin ^[39] 3) Tetranortriterpenoid neeflon ^[40] 4) Essential oil from flowers contained thio-amyl alcohol (7.6%), benzyl alcohol (9.67%), benzyl acetate (8.2%), sesquiterpenes viz azadirachtin, margosene. ^[41] |
| SEEDS/FRUITS | 1) HPLC yielded azadirachtins i.e., azadirachtin A, azadirachtin B, azadirachtin D ^[42] 2) Azadirachtin H and 11 β -H epimer ^[43] 3) Azadirachtin I ^[44] 4) Arabinogalactan isolated from fruit pulp contained D-galactose, L-arabinose, L-rhamnose, D-glucuronic acid ^[45] 5) Aminoacids obtained are aspartic acid, isoleucine, lysine ^[46] 6) Seed oil contained azadirone, azadiradione, epoxyazadiradione, gedunin ^[47] |
| ROOT BARK | 1) Nimbin, Nimbidin, Nimbosterol ^[48] 2) Nimbidiol ^[49] |
| Gum/Exudate | 1) Sugars present in gum are galactose, fucose, arabinose, glucuronic acid ^[50] 2) B-sitosterol, 24-methlenecycloartanol, Nimbin, azadiorne, gedunin ^[51,52] |

Validation of Classical Indications through Reverse Pharmacology

1. Vrana shodhan-ropan (Wound cleansing and healing activity)- Acharya Madhav (Md.44.16) has mentioned *Nimb* as *Vrana shodhana-ropan* (wound cleansing and healing), it is also used traditionally as wound healing drug in Washim District, Maharashtra.^[53] Wound healing property of leaves extract is also validated in animal model of rats with excisional and incisional wound by Barua C. C. et al.,2010^[54].

2. Krimighna (Anti-microbicidal activity)- In Ayurveda, *Krimighna* is used in a broad term, by *Krimighna* we consider anti-bacterial, anti-viral, anti-fungal, anti-helmenthic etc *Krimighna* property of *Nimb* is mentioned by *Madanpal Nighantu* and *Kaiyyadev Nighantu*. Acharya *Yogratnakar* has used *Nimbadi dhoopa* for *Vranjakrimi*^[55]. Acharya *sushrut* has also quoted *Krimighna* property of neem seed oil (S.Su.45.115). This property is validated by work of Khalid S A, et al. 1989^[56] in which they isolated Gedunin, an active constituent from neem seed oil that has been reported to show antimalarial activities. Also three tricyclic diterpenoids, margolone, margolonone and isomargolonone isolated from stem bark of *Nimb* were found to be active against *Serratia* species, *Klebsiella* and *Staphylococcus* which shows its antimicrobial property.^[57] In another study neem bark extract at the concentration of 50 to 100 μ g/ml have shown ability to stop the entry of HSV-1 in to cells.^[58] Neem leave extract is active against coxsackievirus

B-4, this shows its anti-viral property.^[59] Neem leaves are found to possess antifungal properties to treat hair dandruff.^[60]

3. Pramehaghna (Urinary disorder/Anti-diabetic activity)- *Pramehaghna* property has been quoted by *Kaiyadev Nighantu*, *Mahoashadha Nighantu* and *Bhavprakash nighantu*. *Nimb kwath* has been used in *Ckaradutta* in *Surameha*. This property is validated by work of G.R. Sridhar, AIIMS, New Delhi, 1987^[61] anti-hyperglycemic activity attributed to increased peripheral glucose utilization, increased insulin release, decreased glucose re-absorption.

4. Kshat-kshayahar (General tonic)- *Kshat-kshayahar* property of fruits of *Nimb* is mentioned by *Shaligram Nighantu*, *Kaiyadev Nighantu*. It is also one of the constituents of *Laghu shivagutika* and *Baladi ghrith* which are used in *Rajyakshama*. The oil obtained from seed, bark and leaves of neem shows its strong activity against gram positive, gram negative and mycobacterium tuberculosis organism thus this anti-tubercular property can be validated by the work of Chopra, Gupta & Nazir, 1952^[62]. In another study some active ingredients (phytosterol fraction) isolated from the lipid part of *Nimb* fruits, exhibit antiulcer activity in stress induced gastric lesions^[63]

5. Raktashodhaka (Blood purifier activity)- *Nimb panchang* has been said to possesses *Raktashodhaka* property which can be validated by the work of Ghimeray, Jin, Ghimire & Cho, 2009^[64]; Sithisarn, Supabphol & Gritsanapan, 2005^[65] in which all the parts of plant A. Indica like leaves,

fruit, seed, flower, and bark extracts shows strong antioxidant activity

6. Kusth (Skin disease pacifying activity)- *Nimb* has been used as in all types of *Kusth* mostly in all classical texts also it is validated by the clinical study of Ojha, 1966^[66] where *Nimbadi lepa* (contains bark as one of the contents) with buttermilk was applied once on daily basis for 6 days over body except face showed results in lepromatous cases. No toxic effects were seen.

7. Santatirodhak (Contraceptive activity)- *Nimb* bark *Dhoopan* of *Yoni* before coitus is mentioned as contraceptive by *Acharya Yogratanakar^{iv}* this property of *Nimb* has been validated in animal model where anti-fertility effects of intrauterine neem treatment (IUNT) was studied in bonnet monkeys that demonstrates that an IUNT can be used for long-term, reversible contraception, without any apparent side effects, and this prove to be an alternate to currently used intrauterine contraceptive devices (IUCD).^[67]

8. Jwaraghna (Anti-pyretic activity)- *Jwaraghna* property of *Nimb* has been mentioned by *Acharya Madhav* (Md.1.29) in which *Acharya* has quoted *Nimbadi kashaya* in *k.Jwara* this property is validated by the work of Yerima et al, 2012^[68] in this study neem bark extract has shown ability to stop entry of HSV-1in to cells. In another study by Badam, Joshi & Bedekar, 1999^[69] neem leaves extract is found active against coxsackievirus virus B-4.

9. Shothaghna (Anti-inflammatory activity)- *Nimb kwath* has been used as *Shothaghna* by many *acharyas* in their classical work such as *Chakradutta^[70]*, *Madhav chikitsa*. This is also validated by Ilango, Maharajan & Narasimhan, 2013^[71] Many plant extracts contain anti-inflammatory phytochemicals Extracts obtained from different parts of *Neem* play effective role as anti-inflammatory agent. Fruit skin of *A. indica* and phytochemical azadiradione are exceptionally good anti-inflammatory agents.

CONCLUSION

As we have seen above, *Nimb* possess number of properties to be used as a single drug and all the properties have been experimentally validated by modern researchers. The properties mentioned above in classical texts have all been validated by experiments. In classical texts still there are many properties that have not yet been evaluated by our modern scientists but were studied and experimented by our *Acharyas*. There are many traditional uses that have been validated too. Thus, *Nimb* has immense potential as a drug and it is so widely present in India so that it is cheaply available to many people.

The reverse pharmacology study of neem has opened many gates to further research that can be done by our future doctors and scientists.

Abbreviation used

AH.Su- Ashtang Hridaya sutrasthan

CS.Su- Charak Samhita sutrasthan

CS.Vi- Charak Samhita vimansthan

Md- *Madhav chikitsa*

SS.Su- Sushrut Samhita sutrasthan

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