

REVIEW ARTICLE**Neem (*Azadirachta indica*): An Elixir in Dentistry**Dr. Ravishankar T.L¹, Dr. Ramneek Kaur², Dr. Sukirat Kaur², Dr. Shyamalima Bhattacharyya²**Abstract**

Azadirachta indica (Neem) is an omnipotent tree and nature's gift to mankind for treatment of various health ailments. *Azadirachta indica* (Neem) and its ingredients have therapeutic implications and have been traditionally used worldwide especially in Indian Subcontinent. Extensive research on therapeutic benefits of *Azadirachta indica* (Neem) in oral and dental problems has proved its efficacy as an excellent and cheap antimicrobial, anti-inflammatory and anticancer agent.

Introduction

Azadirachta, a genus of *Meliaceae* family, which is indigenous to tropical and semi-tropical regions (1). From past few years, it has been widely planted in some Caribbean nations by the immigrants from Indian subcontinent. *Azadirachta* has two recognized species: *Azadirachta excelsa*, commonly known as sentang and *Azadirachta indica*, commonly known as neem, nimitree or Indian lilac (2). The review will basically focus on the versatility of neem (*Azadirachta indica*).

Azadirachta indica

The word, is derived from Persian "Azad" which means free and "dirakar" means a tree and the word, *indica* means of Indian origin hence the word *Azadirachta indica* symbolizes "a free tree of India" (3). Neem is considered as a legendary medicinal tree in Indian subcontinent (2). It is a speedy growing tree which can grow up to 30 meters tall and sometimes to 40 meters with an average girth of 2.5 meters. It is a broad green-leaved evergreen tree



The taxonomical classification (1) of neem (*Azadirachta indica*) is:

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Dipsacales
- Order: Rutales
- Suborder: Rutinae
- Family: Meliaceae
- Subfamily: Melioideae
- Tribe: Melieae
- Genus: *Azadirachta*
- Species: *indica*

Neem has been used widely in Indian ayurvedic, unani and homeopathic systems of medicines. It is considered as a miraculous tree of traditional medicine. In ancient times, neem was used for the treatments of inflammations, suppurations, septicemia, dermatological, dental problems etc. There is enough literature which provide us an evidence on several versatile properties of neem (4)

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- Antihyperglycemic (5)
- Immunomodulatory (6)
- Anti-Inflammatory (7)
- Antimalarial (8)
- Antioxidant (9)
- Antiviral (10)

Active constituents	Properties
<i>Azadirachtin</i>	Anti feedent, Insect-repellant, Anti-malarial and Anti-hormonal (1)
<i>Nimbin</i>	Anti-inflammatory, anti pyretic, anti histamine and anti fungal (24)
<i>Nimbidin</i>	Antigastric ulcer, Antiarthritic, Anti arrhythmic Anti inflammatory, Analgesic, Anti pyretic as well as Hypoglycaemic effects (22)
<i>Nimbidene</i>	Anti-inglammatory and Antipyretic (1).

- Antimutagenic (11)
- Anticarcinogenic (12)
- Antibacterial (13)
- Antifungal (14)
- Hepatoprotective (15)
- Anti-Ulcer (16)
- Anti-Fertility (17) and
- Anti-Nociceptive Activity (18)



Chemistry of neem

“Find the sweetness in the bitterness of my words. I am neem, water my qualities.”

-Xee Sheikh.

The bitter taste of neem is due to an agglomeration of complex compounds called "triterpenes" or more particularly "limonoids". In 1919, Indian pharmaceutical chemists have commenced researches on the chemical nature of neem. An acid, which was later named as “margosic acid” was discovered and hereby was considered as an acidic principle of neem (19). The most important phytoconstituent is azadirachtin, a limonoid (20). However, in the year 1942, three more active constituents of neem were isolated namely: nimbin, nimbidin and nimbinene. *Nimbin* is a constituent of triterpenoid which was isolated from Neem (21). It is assumed to be credited for majority of the biological properties of neem. *Nimbidin* is the another major bitter principle from oil of seeds of *Azadirachta indica* which potentially can sedate central nervous system (22) and *nimbinene* was the third important active constituent that was isolated from the leaves and bark of neem (Kraus and cramer in 1981)(23). For easy understanding, it has been shown in table 1.

Table 1: Active constituents and their properties

There are around 135 phytochemicals that have already been isolated from different parts of neem tree. These phytochemicals can be divided into two categories for easy understanding as shown in table 2 (1)

Isoprenoids	Non-isoprenoids
<ul style="list-style-type: none"> • Diterpenoids and triterpenoids containing protomeliacins • Limonoids (meliantrol) • Azadirone and its derivatives • Gedunin and its derivatives • Vilasinin type of compounds • C- secomeliacins such as nimbin, salanin and azadirachtin 	<ul style="list-style-type: none"> • Proteins (amino acids) • Carbohydrates (polysaccharides) • Sulphurous compounds • Polyphenolics such as flavonoids and their glycosides • Dihydrochalcone, coumarin • Tannins • Aliphatic compounds, etc.

Table 2: Types of phytochemicals in neem

Neem extracts

Neem extract contains the concentrated form of active or principle constituents derived from the parts of neem tree. These extracts should be preserved in their original concentrated form which could be used as such for the preparation of final products. These extracts can be divided into three divisions based on their source:

1. Neem Leaf Extract
2. Neem Seed Extract
3. Neem Bark Extract

Therapeutic role of Neem in oral diseases

Antibacterial activity: Neem is a natural antibacterial agent. There are many scientific studies in literature that have divulged its antibacterial properties (25). Azadirachtin and nimbinin are the active constituents of neem extract responsible for its antibacterial properties (4). There are evidence which proves the antibacterial action of neem extracts against plaque index and bacterial count of specifically *lactobacilli species* (26), *S. mutans* and *S. faecalis* (27) and Sugumari Elavarasu et al (2012) in his study displayed anti- plaque properties of neem (28). Neem chew sticks has extreme antibacterial activity against *S.mutans* (29) and *lactobacillus* (30) compared to other dental caries-causing microorganisms like: *S. salivaris*, *S.mitis* and *S.sanguis*. Hedge & Kesaria (2013) conducted a comparative study to evaluate the antimicrobial potency of neem, propolis, turmeric, liquorice and sodium hypochlorite as root canal irrigants against *E. Faecalis* and *C. Albicans*. The results declared matchless potency in impediment of the most resistant species *E. fecalis* and *candida* in root canal disinfection (30). W. N. Ghonmode et al. in 2013, compared the antibacterial efficiency of neem leaf extracts, grape seed extracts and 3% sodium hypochlorite against *E. faecalis*. They concluded that neem leaf extract has a significant antimicrobial effect against *E. faecalis* (31). Uwimbabazi Francine in 2015 concluded in his study, that the antibacterial effect of *Azadirachta indica* (Neem) can change depending on Neem parts used, the solvent used, even the state of the neem used whether it is dry or fresh, moreover the extract concentration matters a lot because each extract has its minimum inhibition concentration (MIC) which is the highest dilution of

a plant extract that still retain an inhibitory effect against the growth of a microorganism (32).

Anticariogenic activity: Chewing sticks, leaves and bark of neem has been found to be beneficial in eradicating the dental caries-causing organism. Chloroform extract of *Neem* leaf (33) and acetone extract of neem bark (34) were found to inhibit *Streptococcus mutans* and *Streptococcus salivarius* and provide an aid for treating dental caries.

Anticandidial/ Antifungal: Danya kumar NM et al. (2013) revealed that the leaves of *Azadirachta indica* (Neem) have significant anti candidial effect against *C. albicans* by preventing its colonization (33). The leaves along with its oil are therefore effective in reducing candida induced stomatitis (34). Mahmoud et al. (2012) in his study concluded that alcohol based extracts of *Azadirachta indica* (Neem) have magnificent inhibitory effect on fungus; hence can be utilized as antifungal agent (35). The fungus he predominantly targeted in his study were; *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus terreus*, *Candida albicans* and *Microsporium gypseum*.

Anti-inflammatory: Bothello et al (2008) concluded in his study that *Azadirachta indica* (Neem) based mouth rinses if used, were effective in showing significant decrease in plaque accumulation, thus preventing gingivitis and periodontitis (36). Chattopadhyay et al. (1993) experimented leaves of *Azadirachta indica* (Neem) and concluded that inflammatory effect of the leaves is by inhibiting 5-HT and PGE1 on edema induced by chemical mediators such as 5-HT, histamine, bradykinin and PGE1. Although the anti-inflammatory properties were found to be significant but were less efficient than of dexamethasone (37).

Anti plaque: Aqueous extract of *Azadirachta indica* (Neem) stick inhibited insoluble glucan synthesis thus preventing bacterial especially streptococci species aggregation on the tooth surface (38). Elavarasu S, et al. (2012) has suggested that neem oil can be used in treating dental plaque, thus reducing the possibility of dental diseases to occur (28). Pai MR et al. in 2004 (26) and Aswini Y Balappanavar et

al. in 2013 (39) found that *Azadirachta indica* (Neem) is more effective in reducing plaque and gingival inflammation in comparison to chlorhexidine gluconate mouthwash ($P < 0.05$).

Antioxidant: Free radical or reactive oxygen species are one of the main culprits in the genesis of various diseases. However, neutralization of free radical activity is one of the important steps in the diseases prevention. Antioxidants stabilize/deactivate free radicals, often before they attack targets in biological cells (40). Pandey et al. (2014) studied phytochemicals in neem for antioxidant properties. They found presence of β -sitosterol, lupeol, rutin, ellagic acid, ferulic acid and quercetin and the extract showed significant free radical scavenging activity thereby implicating its incorporation in various orofacial and skin ailments (41). A. K. Ghimeray et al. (2009) studied *Azadirachta indica* (Neem) and indicated that all the tested leaf and bark extracts/fractions of neem grown in the foothills have significant antioxidant properties (42). M. A. Hossain et al. (2013) in his study on crude extracts from leaves of *Azadirachta indica* (Neem) suggested that among all the extracts chloroform crude extracts could be used as a natural antioxidant (43).

Anticancer: Apoptosis is promoted by *Azadirachta indica* (Neem) that directly kills the cancer cell. The plant exerts anticancer effect on malignant cells by inhibition of cell proliferation, induction of cell death and enhancement of the host immune responses against tumor cells. Neem extracts not only exerts anticancer activity but also sensitizes cancer cells to immunotherapy and radiotherapy thereby, enhancing the efficacy of other chemo and radio therapeutic agents (44). L. Le Marchand, (2002) in a review on effects of flavonoids on cancer prevention found that high flavonoid intake may be correlated with a decreased risk of cancer (45). Neem contains flavonoids like: kaempferol, melicitrin, quercetin etc that plays crucial role as a barrier in cancer development (20).

In dental clinics and hospitals the use of Azadirachta indica (Neem) can be promoted in various cases as in:

Fixed orthodontic treatment: Shruti DP et al. (2014) studied microbial colonization on Orthodontic Attachments and found that the primary bacteria's which constitute dental plaque adhered on the orthodontic appliances are *Streptococcus mutans*, *Streptococcus oralis*, *Streptococcus sobrinus*, *Lactobacillus acidophilus*, *Streptococcus salivarius*, *Streptococcus mitis*, *Streptococcus sanguis*, *Streptococcus intermedius*, and *Streptococcus anginosus* (46). Ethanolic leaf extract of *Azadirachta indica* shows significant antibacterial activity against selected acidogenic oral bacteria causing dental plaque in fixed orthodontic appliance patients. They also evaluated the anti plaque activity of the extracts against *S. mutans*, *S. sanguis*, and *S. mitis* (4).

Root canal irrigant: Sodium hypochlorite has been used as root canal irrigant for decades; it causes potential weakening of the tooth structure by decreasing the hardness and structural integrity of the dentin within the root canal. To overcome this disadvantage herbal drugs are used effectively to inhibit *E. faecalis* that causes root canal failure in patients undergoing endodontic treatment. Aqueous and ethanolic extract of *Neem* leaf inhibits *S. mutans* and *E. faecalis* which cause root canal failure in endodontic procedure. Its antioxidant and antimicrobial properties makes it a potential agent for root canal irrigation as an alternative to sodium hypochlorite. Literature suggested that the *Neem* (*Azadirachta indica*) leaf extract has significant antimicrobial effect against *E. faecalis* derived from infected root canal samples. The extract was found to be efficacious compared with 2% sodium hypochlorite (47). Use of neem as an endodontic irrigant might be advantageous because it is a biocompatible antioxidant and thus not likely to cause the severe injuries to patients that occurs when NaOCl is used. A study showed significant differences in the zone of inhibition of diameters of neem extract and 2% NaOCl against *E. faecalis* and mixed culture (48).

Periodontal pathogens: Bhambal A. et al. (2011) studied the effects of *Neemstick and Toothbrush* on plaque removal and gingival health and concluded that *Neem* mouth rinses are as effective as chlorhexidine in reducing periodontal indices (49). On local drug delivery method, *Neem* showed

significant reduction in *P. gingivalis* and other pathogenic bacteria counts and enhanced periodontal health (50,51). Nayak Aarati. et al. (2011) in her study on aqueous and alcoholic extracts in neem concluded that aqueous and alcoholic extract of neem leaf showed significant antibacterial activity against *S.mutans* and *E.faecalis* (25).

Conclusion

Azadirachta indica (Neem) is an omnipotent tree and nature's gift to mankind for prevention and treatment of various health ailments. *Azadirachta indica* (Neem) and its ingredients have therapeutics implication and have been traditionally used worldwide especially in Indian Subcontinent since ancient time. Clinical based studies confirmed that *Azadirachta indica* (Neem) plays pivotal role in prevention of various diseases. In past years, extensive research on therapeutic benefits of *Azadirachta indica* (Neem) in oral and dental problems had proved its efficacy as an excellent and cheap antimicrobial, antinflammatory and anticancer agent. It's time that *Azadirachta indica* (Neem) extracts are incorporated in present day oral and dental care products as well as in treatment of various oral premalignant and malignant lesions.

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