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REVIEW PAPER OPEN ACCESS

Pharmacological and non pharmacological activity of *Azadirachta indica* (Neem) - A review

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Abstract

Azadirachta indica (Neem) which is a Mother of all therapeutical plant has been used extensively many decades ago and still been using for ritual and medicinal purposes. It's easy availability and low cost has allowed many people to gain benefit from this dynamic plant. Studies have been done widely from the leaves up to its bark to explore its therapeutical potentials. The phytochemical such as Azadirachtin, Nimbidin, Nimbin, Nimbinin, Nimbidinin, Nimbolide, Nimbidic acid, Nimbidin and Sodium Nimbidate derived from the Neem plant poses variety of pharmacological effects such as antipyretic, antiviral, analgesic, antibacterial, contraceptive and hepatoprotective effect and many more. Thus this review shows the active component and pharmacological and non pharmacological uses of Neem.

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Introduction

Azadirachta indica (*A.indica*) which commonly known as Neem belongs to the family of Meliaceae and has been used in ayurvedic treatment for more than 4000 years ago (Pankaj *et al.*, 2011) and its usage was recorded around 4500 years ago (Khatkar *et al.*, 2013). Besides that the plant is regarded as a village dispensary in India (Asif ,2013),In Sanskrit it is called as "Arishtha" which carries the meaning as the reliever of sickness. (Biswas *et al.*, 2002).

Neem is called by variety of name by different ethnicity, in Tamil it is called as Vembu (Anbarashan *et al.*, 2011), Hindi: Nim, English: Lilac, Margosa tree,Neem tree. Kannada: Bemu, Bevinamara. Sanskrit: Arista, Nimba, Nimbah, Picumarda (Hasmat *et al.*, 2012). Persian name for Neem is *Azad-Drakath-E- Hind* (Khatkar *et al.*, 2013). In Malaysia the Indian called Neem as Veepelai in tamil, Chinese called as Ying lian in Mandrin and the Malay's called it as daun Semambu (Anonymous, 2010).

Neem is native to east India and Burma and grows much in South East Asia (SEA) and West Africa and it is cultivated in Pakistan, Peninsular Malaysia, Singapore, Philippines, Australia (Hashmat *et al.*, 2012). Plantation of Neem in small scale in Europe and United States of America as shown success (Kumar *et al.*, 2013).

Neem tree is bout 12-18 metres in height with a circumference up to 1.8-2.4metres (Bempah *et al.*, 2011). Neem is a flowering plant which will produce flower on 3-5 years of age (Bempah *et al.*, 2011) in which the flowers are 4-7mm in length and 6-10mm in width (Sultana *et al.*, 2011). The flower has a jasmine like odour and white in colour (Bempah *et al.*, 2011). The leaves are dark green in colour up to 30cm in length (Bempah *et al.*, 2011) and has 3 lobed stigmata and seeded drupes (Jafari *et al.*, 2013). The fruit of Neem is about 2cm long with white kernels and when mature its able to produce 50kg of fruit yearly (Bempah *et al.*, 2011). The branch of Neem is dense with up to 10cm in length and has a dark brown bark (Sultana *et al.*, 2011). Futhermore, Neem tree is able to adapt very dry condition (Bempah *et al.*, 2011; Sultana *et al.,* 2011) which is up to 120°C with minimal rain fall of 18 inches per year (Kumar *et al.*, 2013). Besides that, these plant can grow well in calcareous soil with the pH up to 8.5 (Debashri and Tamal, 2012).

Previous study has been done widely on Neem plant from its stem up to its bark and,thus this review combines the idea from variety of the research which has been done on Neem and provides a better understanding of its medicinal and non medicinal property.

Taxonomical Classification of *Azadirachta indica* (Pankaj *et al.,* 2011).

Order- Rutales
Suborder- Rutinae
Family- Meliaceae
Subfamily- Melioideae
Tribe- Melieae
Genus- Azadirachta
Species- Indica

History

Siddha Medical system which was defined as preventive against mortality was originated to mankind 10,000 BC to 4000 BC ago and it was the oldest medical system to human being, in this medical system the first plant to be mentioned was the great sacred tree Neem by the Great Sage Agathiyar. During the ancient period the recording of data took place on palm leaf and called as palm leave manuscript (Kumar *et al.*, 2013).

During the digging of Harappa and Mohenjo- Daro by the British Archeologist in 1992, they found clay pots consisting of Neem and a skull which shows a cranial surgery has done. This event shows us the advancement of medical system involving surgery and phytopharmacology during the ancient period (Kumar *et al.*, 2013).

Hindu's believe

Planting of Neem tree in front of house is said to be passage to heaven. Neem leaves is hung in front of the door or gates to chase away the bad evil. During marriages the brides will take a bath in the water filled with eem leaves and the new born will be laid on Neem leaves to allow them to expose to an protective aura (Drabu *et al.*, 2012).

Fig. 1A. Shows *Azadirachta indica* plant (Sultana *et al.*, 2011).

Biological activities of Neem

Nimbidin is the primary crude extract which is obtained from the oil of seed kernels from the Neem. From Nimbidin some tetranortriterpenes can be separated which includes Nimbin, Nimbinin, Nimbidinin,Nimbolide and Nimbidic acid. Nimbidin and sodium Nimbidate poses an Anti-inflammatory activity in formalin induced arthritis in rats and has antiulcer effects, antihistamine by blocking H_2 receptor. Nimbidin shows spermicidal activity in human and rats. Furthermore , studies has been done on fasting rabbits by administrating oral Nimbidin which results in reduced blood glucose level. It also poses antifungal activity against *Tinea rubrum* and *Mycobacterium Tuberculosis*. In dogs, administration of Sodium Nimbidinate causes diuresis therefore it indicates that Sodium Nimbidinate as a diuretic agent. Nimbolide poses anti-malarial activity against *plasmodium falciparum* and antibacterial activity against *Staphylococcus aureus* and *Staphylococcus coagulase* and Gedunin also contain anti fungal and anti malarial activity (Kumar *et al.*, 2010).

Azadirachtin, is a tetranortriterpenoid which encompass primary and secondary antifeedant and disrupt moulting, inhibiting the growth and causes malformation of larval of certain insects. Mahmoodin which is a deoxygedunin obtained from seed oil of Neem plant has moderate anti bacterial action. Condensed tannin which obtain from the bark of *Azadirachta Indica* has the ability to restrain the generation of chemiluminescence by activated human polymorphonuclear neutrophils (PMN), in which this compound point out the inhibition of oxidative burst of PMN during inflammation. The three tricyclic diterpenoids, margolone, margolonone as well as isomargolonone which is obtained from the stem bark poses antibacterial activity against *Klebsiella*, *Staphylococcus,* and *Serratia* species (Pankaj *et al.,* 2011). Separation of compound from the fresh and matured leaf's through stem distillation such as cyclic trisulphide, tetrasulphide; has antifungal activity against *Trichophyton mentagrophytes*. A-polysaccharide from the bark of neem prevent the inflammation of the induced carrageenin into the mouse. NB II which is peptidoglycan of low molecular weight encompass anticomplement activity which is obtained from the bark of neem through aqueous extract. The phytosterol fraction, found from the lipid part of the Neem fruits reveals antiulcer activity in stress or serotonin induced gastric lesions or due to drugs such as indomethacin or acetylsalicyclic acid (Kumar *et al.*, 2010; Pankaj *et al.*, 2011).

Pharmacological Activity of Azadirachta Indica

Analgesic effect

In a Study done by Kumar *et al.*, (2012) by using albino rats, it was found that Neem seed oil (NSO) of 2ml/kg body weight is comparable to morphine with a dose of 1mg/kg body weight, NSO produces a better analgesic effect than morphine with 45 minute of interval and in another similar study done by Srinivasa *et al.*, (2014) it were stated that neem resembles indomethacine.

Antipyretic effects

Methanol extract of Neem leaves shows antipyretic effects when administrated orally in rabbits and rats (Parveen, 2013).

Fig. 1B. Shows *Azadirachta indica* twigs (Manisha *et al.*, 2014).

Antifungal effects

In a study done by Mondali *et al.*,(2009) shows that the ethanolic extract of *A.indica* leaves is more effective against *Rhizopus* and *Aspergillus* compared to aqueous leaf extract. Aqueous and ethanolic extract of neem leaves were found effective against *Candida albicans* by which these organism shows sensitivity at the concentration of 15% and 7.5% on aqueous extract and the Minimum Inhibitory Concentration (MIC) was 7.5%. In the ethanolic extraction *Candida albicans* were found to be susceptible at the concentration of 15%, 7.5% and 3.75%, besides that; the MIC were 3.75% (Aarati *et al.*, 2011).

Fig. 1C. Leaf of *Azadirachta indica* (Manisha *et al.*, 2014).

Antibacterial

The methanol extract of of *A.indica* leaves shows antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Proteus vulgaris*, *Salmonella typhi*, and showed low activity on *Pseudomonas aeruginosa* but it is inffective against *Escherichia coli*. The petroleum ether and methanol extract of *A.Indica* leaves were highly effective against *Candida albicans* (Grover *et al.*, 2011). Futhermore the hexane extract from *A.indica* bark shows antimicrobial activity against *Escherichia coli* (Abalaka *et al.*, 2012). In another study done by Vashist and Jindal, (2012) the *Azadirachta indica* seeds poses an antibacterial activity against the bacteria that causes eye infection (Ophthalmic infection) such as *Staphylococcus aureus, Staphylococcus pyogenes, Escherichia coli* and *Pseudomonas* aeruginosa. Aqueous extract and hexane extract were used and it was found that hexane extract was much more effective than aqueous extract by producing larger zone of inhibition with smaller MIC (1.59 to 25 mg/ml) and MBC (3.17 to 50 mg/ml).

Fig. 1D. Fruit of *Azadirachta indica* (Manisha *et al.*, 2014).

Antiviral

Neem leaves is found to be effective against Dengue virus type -2 in which it halts the replication of the virus itself in an invitro environment and in the laboratory animals (Rao *et al.*, 1969). The aqueous extract of Neem bark were found to be effective against Herpes simplex virus type 1 by blocking its entry into natural target cell (Tiwari *et al.*, 2010), even though Neem does not cure but it shows the abilitiy to prevent smallpox, chickenpox and fowl pox (Bhowmik *et al.*, 2010).

Fig. 1E. Seed of *Azadirachta indica* Endocarp (Manisha *et al.*, 2014).

Contraceptive

According to Bansal *et al.*, (2010) the addition of sodium nimbidinate salt in aqueous form to semen of rat and human results in death of sperm in different percentage. Neem oil claimed spermicidal activity against rhesus monkey human spermatozoa in invitro condition, and when the oil is used in intra vaginally it prevents pregnancy in rats with concentration of 20 microlitre and in rhesus monkey and women were about 10 mililitre (ml) and the oral dose as low as 25 micro litre prevents implantation in rats and does not show any side effects upon repeated application. Similarly, Neem extract (Nim-76) is found to be effective than raw neem oil which act as spermicidal with no alteration in hormonal values. According to Khillare and Shrivastav (2003), aqueous extract of old and tender leaves shows 100% of mortality of the sperms without altering its morphology (head, mid-piece and tail).

Hepatoprotective

Young stem bark extract of *Azadirachta indica* were used to analyse the hepatoprotective activity by inducing carbon tetrachloride as acute hepatotoxic agent in rats and uses Silymarin as a standard hepatoprotective agent. A dose of 200mg/kg and 500mg/kg were choosen for the studies. Upon administration of *Azadirachta indica*, it stabilize the levels of Serum glutamate oxaloacetate transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT), Alkaline Phosphatase (ALP) , Serum bilirubin and elevates total protein amount. Thus, this plant clearly notify the improvement of the functional status of liver cells (Gomase *et al.*, 2011).

Fig. 1F. Seed of *Azadirachta indica* without Endocarp (Manisha *et al.*, 2014).

Antihyperglycemic agent

In a dose of 800 mg/kg Neem root bark extract shows anti hyperglycemic effects upon tested with overnight fasted wistar albino rats of either sex and in alloxan induced diabetic rats but it is not significant as glibenclamide (Patil *et al.*, 2013). A dose of 250 mg/kg of aqueous extract of fresh leaves of Neem was administrated orally onto streptozotocin induced and its associated retinopathy in rats for 16 weeks and resulted in significant fall in blood glucose level and serum lipids and there were slight increase in HDL level. The slight increase indicates the extract as positive effect in lipid metabolism of diabetic rats. Futhermore the plant completely reversed the unusual changes in the retina of the rats (Hussain, 2002). Aqueous neem fruit extract were found to be effective as blood glucose lowering agent at the dose of 500mg/kg in normoglycemic albino rabbits upon oral administration (Rao *et al.*, 2012).

Other Uses

Larvacidal

In a research done by Maragathavalli *et al.*, (2012) third and fourth instar larvae of *Aedes aegypti* and *Culex quinquefaciatus* were exposed to various concentration (50mg ,100mg ,150mg ,200 mg) of methanol and ethanol extract of Neem leaves and it was found that methanol extract of 200 mg shows 90% of mortality against *Aedes aegypti*. Besides that,

the ethanol extract against *Aedes aegypti* shows 85% of mortality rate with the maximal concentration of 200mg. Followed by methanol extract of Neem leaves against *Culex quinquefaciatus* which demonstrate 90% of mortality with the concentration of 200mg and the result is similar to ethanol extract with same concentration against *Culex quinquefaciatus*. In another study done by Okumu *et al.*, (2007) by using Neem oil extracted from the seeds *Azadirachta indica* against *Anopheles gambie* larvae, shows high mortality rate at the concentration of 32 ppm (Parts per Million) and inhibit adult emergence by 99.3%.

Fig. 2A. Shows palm leaf of therapeutic uses of Neem tree (Kumar *et al.*, 2013).

The above palm manuscript is about 350 years old and called as Agathiyar Gunavandam, its discloses the pharmacological uses of Neem, which specifies the use of Neem such as the flower is used to treat bile disorder, the bark used to prevent or treat CNS and paralysis disorder and the leaves used to treat ulcer (Kumar *et al.*, 2013).

Poultry Uses

Neem oil is used to prevent aflatoxin which is produced by *Aspergillus flavus* due to contamination of the poultry feed and the Neem leave extract antagonises the production of Patulin caused by *Penicillium expansium*. The processed Neem cake poses a good appetizer characteristic together with wormicidal activity which is used as poultry feed. Futhermore, Neem leaves has a significant amount of protein, minerals (except Zinc) and digestable amounts of crude protein and total digestible proteins which serves a better nutrition to the poultry animals such as goat, sheep and cow (Girish and Bhat , 2008) . In a research done by Chandrawathani *et al.*, (2013) it was found that Neem leave water extract shows an potential to reduce the egg counts of *Haemonchus contortus* which is the major helminth infecting the goat farming in Malaysia. The Neem leave water extract shows the ability as an antihelminth for just two weeks and for the next upcoming weeks there is an increase in the egg count upon examing the fecal via microscope. Therefore the dosage should be revised and optimising the dosage on the tested animal should be done.

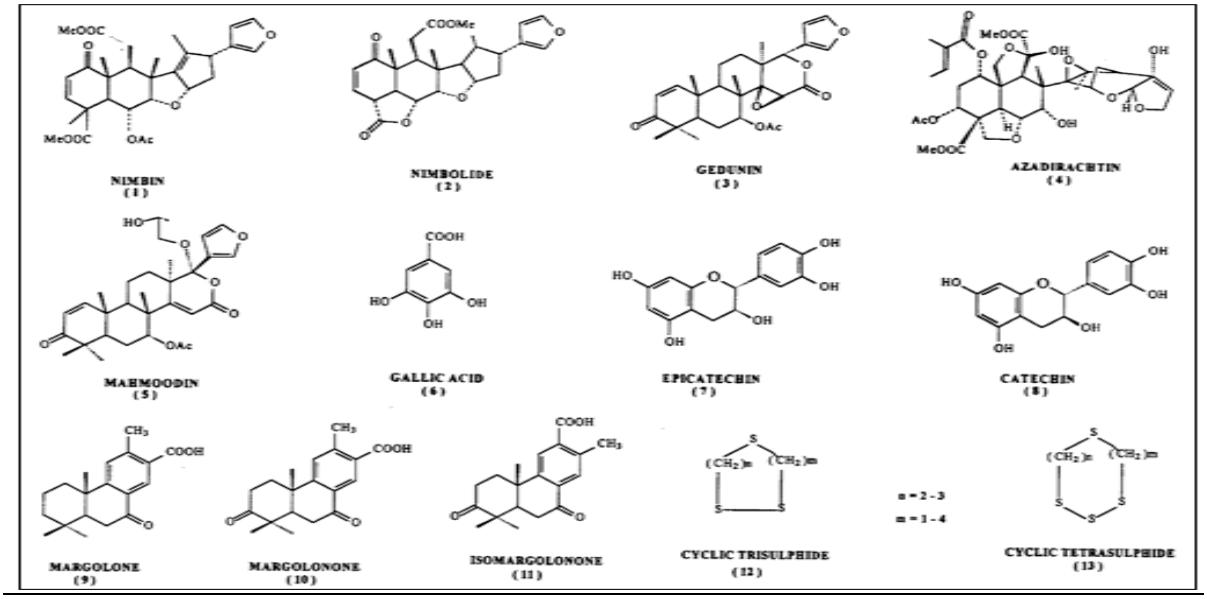

Fig. 4A. Shows Chemical Structures Found in Neem (Biswas *et al.*, 2002).

Fertilizer

Neem cake which is a residue upon extraction of Neem oil from the seed can be used as biofertilizer by which it will nourishes the plants and increase the yield of crops (Lokanadhan *et al.*, 2012). Furthermore, in a research done to elucidate the effects of Neem leaves, wood ash and modified Neem leaves (Neem leaves + wood ash) on growth of tomato and the effects of extracts on the soil after harvesting the tomato. The research shows that the modified Neem leaves shows the highest value of plant height, stem girth, leaf area and number of branches of the tomato plants compared to individual application of Neem leaves and wood ash. The poultry manure shows increased in height stem girth compared to Neem leaves extracts. The soil chemical condition were improved by the modified Neem leaves extract, by which it shows the highest value of organic matter, Nitrogen, Phosphorus, Potassium, Calcium and Magnesium in the soil compared to poultry manure and individual application of Neem leaves and wood ash (Moyin-Jesu *et al.*, 2012).

Pesticide

In a research done by Musabyimana *et al.,* (2001) it was stated that the wetting of banana corm or pseudostem with Neem cake extract, aqueous Neem seed powder, Neem kernel powder or with emulsified Neem oil will distrupt the settling response, egg laying, and larval feeding of *Cosmopolites sordidus* which is known as The Banana Corm Borer.

Conclusion

Since these sacred Neem plant has been known for its broad range of medicinal activity. Thus, research should be carried out on combining the bioactive components of *Azadirachta indica* with other therapeutically important plants in order to cure the diseases that yet to be cured by the modern medication and to the diseases that have been develop resistance to the current drugs.

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