

Active Constituent in Neeem (Azadirachta Indica) and Their Therapeutic Role

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ABSTRACT

Azadirachta indica (Neem) may be a member of the Meliaceae family and its role as health-promoting effect is attributed because it's rich source of antioxidant. The studies supported animal model established that neem and its chief constituents play pivotal role in anticancer management through the modulation of assorted molecular pathways including p53, pTEN, NF- κ B, PI3K/Akt, Bcl-2, and VEGF. it's considered as safe medicinal plants and modulates the various biological processes with none adverse effect. quite 150 compounds are isolated from different parts of neem and these are divided into two major classes isoprenoids and non-isoprenoids, which are proteins and

carbohydrates. Further, it consists of sulphurous compounds, polyphenolic compounds like flavonoids and their glycosides, dihydrochalcone, coumarin, tannins and aliphatic compounds. All parts of the Melia Azadirachta viz., leaves, flowers, seeds, fruits, roots and bark are used traditionally for the treatment of inflammation, infections, fever, skin diseases, dental disorders, etc. Every a part of the arishth viz., roots, seeds, flowers, bark, leaves, fruit pulp and its constituents are demonstrated to exhibit immune modulatory, anti-inflammatory, anti hyperglycaemic, antiulcer, antimalarial, antifungal, antibacterial, antiviral, antioxidant, antimutagenic, antidiabetic and anticarcinogenic properties.

I. INTRODUCTION

NEEM



Synonym :

Margosa

Biological Source :

It consists of all aerial parts known as Azadirachta indica

Family : Meliaceae

Geographical Source :

India, Pakistan, Sri Lanka, Thailand, Malaysia, Mauritius, Fiji, South Africa and East Africa.

Macroscopic characters :

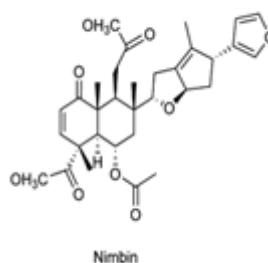
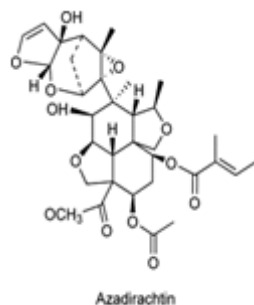
Leaves Alternate exstipulate, imparipinnate, leaflets

5.0-10cm in length lanceolate closely clustered towards the end of branches. The leaves have serrate margin green colour and bitter to test.

Bark : Moderately thick, rough, brown in colour longitudinally & obliquely furrowed internally starchy white laminated with characteristic smell of neem and bitter in use

Chemical Constituent : Chemicals are isolated from the classes belong to diterpenes (sugiol) Nimbol(bark) Triterpenes beta-sitosterol

stigmasterol(leaf) Limonoids : Maliantriol(seed oil) nimbidiol (seed oil) Nimbendiol (seed oil) and azadirachtan (seed) sulphurous compounds : There are number of cyclic tri & tetrasulphides (leaves)



Flavonol glycosides: Nimaton, quercetin, myricetin, kaempferol, Neem leaves contain not less than 1.0% w/w of rutin.

Leaves :

Azadirachtin - Insect repellent

Meliantriol - Anti-feedant

Salanin Anti-feedant

Seeds :

Nimbin Anti-viral action

Nimbidin: Anti-viral action

Azadirachtin - Insect repellent

Flowers : Nimbosterol, Myricetin, kaempferol - Insecticidal

Fruits: Deacetyl azadirachtinol - Paralyzes insect swallowing mechanisms

Bark : Nimbin, Nimbinin, Nimbidin - Anti-viral
Margolone, Margolonone - Antibacterial

Roots : Better for reforestation, Compounds with antibacterial and antifungal properties.

Neem oil contains 2% bitter (sulphur containing compound) nimbin, nimbidin, nimbinin, and nimbidol.

Azadirachtin-k new tetraterpenoid isolated from seed kernel (compound such as nimbolide, olichinolide B, nimbin, 6-deacetylnimbin, salanin, azadiradione)

Standards of quality :

Foreign organic matter	NMT 02.0 %
Ash	NMT 12.0 %
Acid insoluble ash	NMT 02.0%
Loss on drying	NMT 12.0 %
Alcohol soluble extractives	NLT 07.0 %
Water soluble extractives	NLT 19.0 %

Azadirachta indica may be a rapidly developing evergreen tree found commonly in India, Africa, and America. It's been utilized in ayurvedic remedies for quite 4,000 years because of its medicinal residences. Neem is cited as 'arista' in Sanskrit, a phrase that means 'best, complete and imperishable'. Arishtha is that the Sanskrit name of the Melia Azadirachta, which means 'reliever of sickness' and hence is taken into consideration as 'Sarabrogaribarini'. The tree is thought to be a "village dispensary" in India. The importance of the margosa has been recognised by the USA National Academy of Sciences, which put up a go into 1992 entitled "Neem-a tree for fixing international issues. It grows in many geographical region and

West Africa; some trees have currently been planted within the Caribbean and a number of other vital American international locations, which include Mexico. The people of India have long respected the neem tree; for hundreds of years, millions have cleaned their teeth with neem twigs, smiered pores and skin issues with neem-leaf juice, taken neem tea as a tonic, and placed neem leaves in their beds, books, grainbins, cupboards, and closets to stay away difficult bugs. The quantity of advantages of neem is listed in historic documents like "Charak-Samhita" and "Susruta-Samhita". It's commonly said as 'Indian Lilic' or 'Margosa', belongs to the circle of relatives Meliaceae, subfamily Meloideae and tribe Melieae. Neem is

that the most flexible, multifarious timber within the tropics, with gigantic capacity. It possesses the foremost useful non-wooden products (leaves, bark, vegetation, end result, seed, gum, oil, and neem cake) of any different tree species. it's regarded to own antiallergenic, antidermatic, antifeedent, antifungal, antipyorrhoeic, antiscabic, cardiac, diuretic, insecticidal, larvicidal, nematocidal, spermicidal, and different organic activities. because of those activities, Neem has located substantial packages, making it an inexperienced treasure . Neem has grown to be essential within the global context nowadays because it gives solutions to the important concerns surfing mankind. Neem (*Azadirachta indica*) is taken into account innocent to humans, animals, birds, beneficial bugs, and earthworms, and has been accepted by the US Environmental Protection Agency to be used on food crops. 5. Neem (*Azadirachta indica*) of the circle of relatives *Melia meliaceae* is an evergreen tree of medicinal capability located in most tropical international locations. Biologically lively standards isolated from exceptional parts of the plant encompass:

azadirachtin, meliacin, gedunin, salanin, nimbin, valassin and lots of different derivatives of those standards. Meliacin paperwork the sour ideas of seed oil, the seed additionally comprise tignic acid (5-methyl-2-butanic acid) to blame for the distinct odour of the oil. Those compounds belong to natural products referred to as triterpenoids (Limonoids). The active concepts are slightly hydrophilic but freely lipophilic and tremendously soluble in organic solvents like hydrophilic alcohols, ketones, and esters.

BOTANICAL DESCRIPTION OF NEEM

Neem tree goes to the family *Meliaceae* which is found in plenty in tropical and semitropical regions like India, Bangladesh, Pakistan, and Nepal. It's a fast-growing tree with 20–23 m tall and trunk is straight and features a diameter around 4–5 ft. The leaves are compound, imparipinnate, with each comprising 5–15 leaflets. Its fruits are green drupes which turn golden yellow on ripening within the months of June–August. Taxonomic position of *Azadirachta indica* (Neem).in Table

Order	Rutales
Suborder	Rutinae
Family	Meliaceae
Subfamily	Melioidae
Tribe	Melieae
Genus	<i>Azadirachta</i>
Species	<i>indica</i>

ACTIVE COMPOUNDS IN NEEM

more than 150 compounds had been remoted from different parts of neem. The compounds were divided into two major lessons; isoprenoid (Chatterjee and Pakrashi, 1991) like terpenoids and triterpenoids containing protomeliacins, limonoids, azadirone and its derivatives, gedunin and its derivatives, vilasinin kind of compounds and C- secomeliacinssuch as nimbin, salanin and azadirachtin) and non-isoprenoids, which are proteins, carbohydrates, sulphurous compounds, polyphenolics along with flavonoids and glycosides, dihydrochalcone, coumarin and tannins, aliphatic compounds, *Azadirachta indica* L. (neem) shows therapeutics function in health control because of wealthy supply of diverse types of components. The most essential active constituent is

azadirachtin and the others are nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinat, gedunin, salannin, and quercetin

Leaves comprise components including nimbin, nimbanene, 6-desacetylnimbinene, nimbandiol, nimbolide, ascorbic acid, n-hexacosanol and amino acid, 7-desacetyl-7-benzoylazadiradione, 7-desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione, and nimbiol . Quercetin and β -sitosterol, polyphenolic flavonoids, were purified from neem clean leaves and were recognized to have antibacterial and antifungal houses and seeds hold valuable components inclusive of gedunin and azadirachtin

MECHANISM OF ACTION OF ACTIVE COMPOUNDS

Neem (*Azadirachta indica*), a member of the Meliaceae family, has therapeutic implication within the diseases prevention and treatment. But the precise molecular mechanism within the prevention of pathogenesis isn't understood entirely. It's considered that *Margosa* shows therapeutic role because of the rich source of antioxidant and other valuable active compounds like azadirachtin, nimbolin, nimbin, nimbidin, nimbidol, salannin, and quercetin.

Possible mechanism of action of neem tree is presented as follows.

Neem (*Azadirachta indica*) plants parts shows antimicrobial role through inhibitory effect on microbial growth/potentiality of cell membrane breakdown. Azadirachtin, a fancy tetranortriterpenoid limonoid present in seeds, is that the key constituent to blame for both antifeedant and toxic effects in insects. Results suggest that the ethanol extract of neem leaves showed *in vitro* antibacterial activity against both *Staphylococcus aureus* and MRSA with greatest zones of inhibition noted at 100% concentration.

Neem plays role as radical scavenging properties because of rich source of antioxidant. Azadirachtin and nimbolide showed concentration-dependent antiradical scavenging activity and reductive potential within the following order: nimbolide > azadirachtin > ascorbate. Neem ingredient shows effective role within the management of cancer through the regulation of cell signaling pathways. Neem modulates the activity of varied tumour suppressor genes (e.g., p53, pTEN), angiogenesis (VEGF), transcription factors (e.g., NF- κ B), and apoptosis (e.g., bcl2, bax). Neem also plays role as anti-inflammatory via regulation of proinflammatory enzyme activities including cyclooxygenase (COX), and lipoxygenase (LOX) enzyme.

BIOLOGICAL ACTIVITIES OF NEEM COMPOUNDS

Nimbidin :- It is a crude drug having bitter principle extracted from oil of seed kernels of

azadirachta indica having different biological activities. Some tetranortriterpenes including nimbin, nimbidin, nimbolide, nimbidic acid have been isolated. Nimbidin and sodium nimbidate gives anti-inflammatory activity against carrageenin induced acute paw oedema in rats, formalin induced arthritis. Also observed anti-ulcer effect with nimbidin in preventing acetylsalicylic acid. Oral administration of nimbidin gives hypoglycemic effect in fasting rabbits.

Nimbolide:- It shows anti-malarial activity by inhibit the growth of *Plasmodium falciparum*. It shows anti-bacterial activity against *S. aureus* or *S. coagulans*.

Gedunin :- Isolated from neem seed oil to possess the both activity of anti-fungal and anti-malarial.

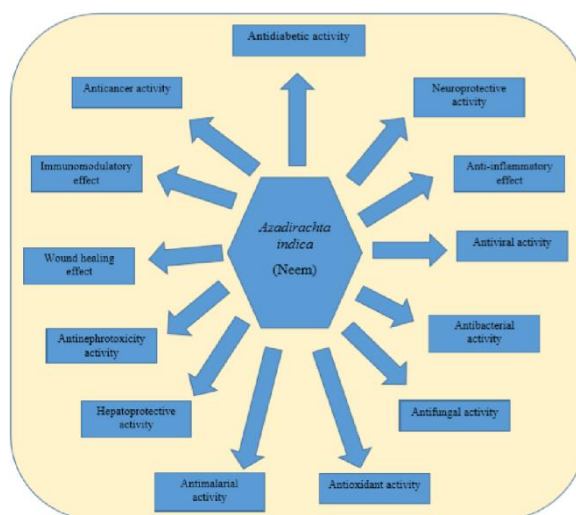
Mahmoodin:- It is a deoxygedunin isolated from seed oil to show moderate anti-bacterial action against strains of human pathogenic bacteria. Condensed tannins from bark contain gallic acid, (+)

epigallocatechin. Epicatechin and catechin are responsible for inhibit generation of chemiluminescence by activated human polymorphonuclear neutrophil (PMN); Indicating these inhibit oxidative burst of PMN during inflammation. Triterpenoids, margolone, margolonone, and isomargolonone isolate from neem stem bark active against *Klebsiella*, *Staphylococcus* and *Serratia* species.

Polysaccharide :- Extracted from bark inhibit carrageenin-induced inflammation in mouse.

Two water soluble polysaccharide G1A and G1B isolate from bark of *Meli azadirachta* shows strong anti-tumor effect regression of tumors when it is administered in mice at a daily dose of 50mg/kg for 4 days from 24 hours after subcutaneous inoculation of sarcoma 180 cells.

Two more polysaccharide G2A and G3A isolate from *M. azadirachta* bark shows anti-inflammatory effect on carrageenin induced oedema in mice.



1) Antioxidant Activity : The process through which free radicals are created, may be a normal function of the body but the resulting molecules are unstable and might damage other cells. A series of disorders, including disorder, eye health, cataracts and devolution, age-related neurodegeneration (decline of the brain cells and nervous system) and even cancer occurs due to high levels of free radicals. Neem protects against chemically induced carcinogens and liver damage by boosting antioxidant levels.

2) Anti- diabetic Activity : A study was undertaken to judge the 70% alcoholic neem root bark extract (NRE) in diabetes and results showed that neem root bark extract showed statistically significant leads to 800 mg/kg dose . Another experiment was performed to look at the pharmacological hypoglycemic action of neem tree in diabetic rats and results showed that in a very glucose tolerance test with neem extract 250 mg/kg demonstrated glucose levels were significantly less as compared to the control group and Melia Azadirachta significantly reduce glucose levels at 15th day in diabetic rats Studies using in vivo diabetic murine model, A. indica, and B. spectabilis chloroform, methanolic, and aqueous extracts were investigated and results showed that A. indica chloroform extract and B. spectabilis aqueous, methanolic extracts showed a decent oral glucose tolerance and significantly reduced the intestinal glucosidase activity . Another important study suggested that leaves extracts of tree and Andrographis paniculata have significant antidiabetic activity and will be a possible source for treatment of diabetes .

3) Anti-fungal Activity : From time immemorial it's believed that Neem is effective against certain fungi that infect the shape. Some important fungi

against which neem preparations are found to be effective are: athlete's foot fungus that infects hair, skin and nails; a ringworm that invades both skin and nails of the feet, fungus develops in intestinal tract, bronchi, lungs, and mucous membranes and a fungus that's a part of the conventional mucous flora which will get out of control resulting in lesions in mouth (thrush), vagina, etc. Extracts of neem leaf, neem oil seed kernels are effective against certain fungi including Trichophyton, Epidermophyton, Microspor, Trichosporon, Geotricum and Candida .

4) Anti-bacterial : Neem derives compounds especially Azadirachtin is well-known for its role as antibacterial agent. it's a complex tetranortriterpenoid limonoid present within the seeds moreover as leaves which is highly to blame for toxic effect on microbes.

Extracts of the leaves, seed and bark possesses a wide spectrum of antibacterial action against Gram-negative and Gram-positive microorganisms, including M. tuberculosis and streptomycin resistant strains. In vitro, it inhibits Vibrio cholerae Klebsiella pneumoniae, M. tuberculosis and M. pyogenes. Antimicrobial effects of neem extract are demonstrated against Streptococcus mutans and S. faecalis . except for azadirachtin, other components such as nimbidin, nimbin, nimbolide, gedunin, mahmoodin, margolone, and cyclic trisulfide contribute to the anti-bacterial activity of neem .Further, neem extracts are a ray of hope to cure deadly diseases viz., Chagas disease in geographical area which was uncontrolled by any other means of medicines. This disease is caused by a parasite which is carried by an insect called conenose bug. Research has shown that feeding neem to the bugs not only frees them of parasites,

but azadirachtin prevents the young insects from molting and also the adults from reproducing

5) Anti-viral Activity : Aqueous leaf extract offers antiviral activity against Vaccinia virus, Chikungunya and measles virus. Nimbin and nimbidin have been found to have antiviral activity. They affect potato virus X, vaccinia virus, and fowl pox virus.

6) Anti-cancer Activity : Neem leaf aqueous extract effectively suppresses oral somatic cell carcinoma induced by 7, 12-dimethylbenz[a] anthracene (DMBA), as revealed by reduced incidence of neoplasm. A study conducted in chemoprotective neem compounds viz., azadirachtin, nimbolide and limonoid enriched extracts on models of buccal carcinogenesis in hamsters. Overall studies were tested positive to cut back the expression and cell proliferation antigens. Further, researchers have shown prominent anti-cancerous activities from limonoid-derived compounds from neem. Amongst these, both 1-O-deacetylchinchinoline B and 15-O-deacetylnimbolindin-B are proved to be beneficial to hinder cell growth in human cervical adenocarcinoma. A recently discovered alkaloid-derived limonoid, azadiramide-A, is primarily found in Neem leaf ethanolic extracts, showed to forestall cell growth and induce apoptosis in both the estrogen independent MDAMB-231 and estrogen dependent MCF-7 cell lines of carcinoma in individuals.

7) Anti-malarial Activity : Neem seed and leaf extracts are effective against both chloroquin-resistant and sensitive strain malarial parasites. One in every of the neem's components, "gedunin" (a limonoid), is as effective as quinine against malaria. Malaria is one all told the pandemic diseases causing various deaths every year in India and variety of other countries. China has adopted neem in an exceedingly big because of reap the antimalarial effects of neem. The anti-malarial formulation "QuinaHausa" prepared in China are available in India yet. Neem oil treated mosquito nets and mosquito-repellent cheap tablets have become popular, due of growing problems of resistance to conventional treatments, it's becoming more and harder to manage malaria. Clinical trials have been conducted to check the efficacy of neem extracts to control hyperlipidemia during a gaggle of malarial patients severely infected with *P. falciparum*. The lipid level, especially cholesterol, was found to be lower during therapy when put next to non-malaria patients.

8) Anti-inflammatory, antipyretic and analgesic activity : The chloroform extract of stem bark is

effective against carrageenin-induced paw oedema in rat and mouse ear Inflammation. Inflammatory stomatitis in children is cured by the bark extract. Antipyretic activity has been reported in neem oil. A methanol extract of the leaves exerts antipyretic effect in male rabbits. The plant also possesses analgesic activity mediated through opioid receptors in laboratory animals. Anti-inflammatory and antipyretic activities in various extracts have been reviewed.

9) Dentistry Activity : study was made to assess the efficacy of neem supported mouth rinse regarding its

antigingivitis effect and study confirmed that *A. indica* mouth rinse is equally effective in reducing periodontal indices as chlorhexidine. Another study was disbursed to evaluate the antimicrobial properties of organic extracts of neem against three bacterial strains. Neem seed and leaf extracts are effective against both chloroquin-resistant and sensitive strain malarial parasites. One in every of the neem's components, "gedunin" (a limonoid), is as effective as quinine against malaria. Malaria is one altogether the pandemic diseases causing various deaths every year in India and kind of other countries. China has adopted neem in an exceedingly big thanks to reap the antimalarial effects of neem. The anti-malarial formulation "QuinaHausa" prepared in China are available in India yet. Neem oil treated mosquito nets and mosquito-repellent cheap tablets became popular, due of growing problems of resistance to plain treatments, it's becoming more and harder to manage malaria. Clinical trials are conducted to check the efficacy of neem extracts to manage hyperlipidemia during a gaggle of malarial patients severely infected with *P. falciparum*. The lipid level, especially cholesterol, was found to be lower during therapy when put next to non-malaria patients causing decay and results showed that petroleum ether and chloroform extract showed strong antimicrobial activity against *S. mutans*. Chloroform extract showed strong activity against *Streptococcus salivarius* and third strain *Fusobacterium nucleatum* was sensitive to both ethanol and water extract. Earlier finding confirmed that dried chewing sticks of neem showed maximum antibacterial activity against *S. mutans* as compared to *S. salivarius*, *S. mitis*, and *S. sanguis*.

10) Wound Healing Effect : Numerous plants/their constituents play a really important role within the wound healing effect. A study was made to gauge the wound healing activity of the extracts of leaves of *A. indica* and *T. cordifolia* using excision and

incision wound models in Sprague Dawley rats and results revealed that extract of both plants significantly promoted the wound healing activity in both excision and incision wound models. Furthermore, in incision wound, durability of the healing tissue of both plants treated groups was found to be significantly higher as compared to the control group. Other results showed that leave extracts of margosa promote wound healing activity through increased inflammatory response and neovascularization.

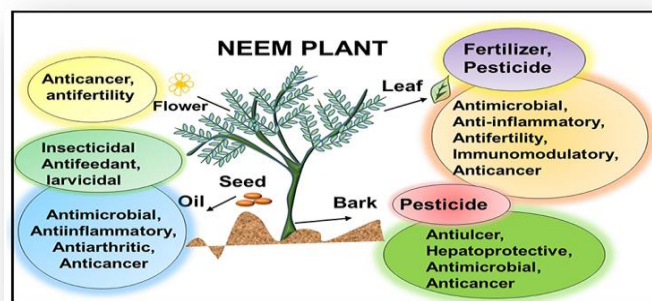
11) Hepatoprotective Activity : The aqueous extract of neem leaf was found to offer protection against paracetamol induced liver necrosis in rats. The elevated levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transpeptidase (GGT) indicative of liver damage were found to be

significantly reduced on administration of the neem leaf aqueous extract.

12) Antifertility effect :Neem oil proved spermicidal against rhesus monkey and human spermatozoa in vitro .In vivo studies showed that intravaginal application of neem oil prior to coitus can prevent pregnancy. The effect is possibly due to activation of cell mediated immune reaction

13) Anti-ulcer Effect : It produces effect in rats exposed to restraint cold stress by preventing mucus depletion and mast cell degranulation. An aqueous extract of neem bark has been shown to posses highly potent antacid secretory and antiulcer effect.

14) Hypoglycaemic Activity : It significantly decreases blood sugar level and prevents adrenaline as well as glucose-induced hyperglycaemia. A significant effect was also observed by feeding neem oil to fasting rabbits.



MEDICINAL USES OF NEEM

PART	MEDICINAL USES
Leaf	Leprosy,eye problem,epistaxis,intestinal worms,anorexia,skin ulcer
Bark	Analgesic,alternative and curative of fever
Fruit	Relieves piles urinary bladder disorder, wounds and leprosy etc
Flower	Bile suppression elimination of intestinal worms and phlegm.
Twig	Relieves cough and asthma piles phantom tumor diabetes
Gum	Ringworm, scabies wounds and ulcer
Seed pulp & oil	Leprosy and intestinal worms

Leaves :

Neem leaves have great restorative residences. however it is convenience in Pest the executives and ailment control they can likewise be sustained to animals whilst blended with other grain. Neem leaves are utilized in sure portions of

Indian as manure in rice fields, specifically in the south Indian states. In certain countries, Neem leaves are utilized as mulch in tobacco and tomato fields. They can be all around viably used to execute weeds with the aid of spreading them over plant roots to keep dampness. Neem leaves can

likewise be applied to shield stored woolen and silk garments from creepy crawlies

Twigs & Bark :

If you were born in India, you would have seen individuals bite away at a neem twig. For a long time now, a neem twig is the thing that individuals utilized as a make-do toothbrush. It kills germs, keeps up the soluble dimensions in your salivation, keeps microscopic organisms under control, treats swollen gums and furthermore gives you more white teeth. The twig additionally shreds into strings, practically like fibers that likewise wreck and forestall plague.

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Fruits :

They are unpleasant laxative antihemorrhoidal and antihelmintic (vermifuge) in nature

Flowers :

Maximum pieces of the neem tree are terribly unsightly, except for its flowers. The white and delicate neem flowers with their gray buds are too cute to even remember eating and unimaginably restorative. The flowers have a sweet, almost ethereal jasmine scent during the night and bloom once in the night direction and again later in the night. In the middle of a storm, you'll see a group of them scattered under a tree. otherwise known as Vepampoo in Tamil, these neem flowers can be applied fresh, dried or in powdered form. generally in the south they are used to cook many dishes: flower rice, pachadi, rasam, lentils and that's just the beginning. they are often cooked dry and sprinkled over the dish for additional decoration. Neem flowers can be used to treat anorexia, nausea, belching and intestinal worms.

Neem oil :

Neem oil, which is separated from the neem seeds, has rich therapeutic properties that make it an incredible compound in beauty products and other excellent substances: cleaning products, hair oil, hand wash, cleanser and so on. It can treat a large number of skin diseases and is known as an incredible mosquito repellent. Neem can be mixed with coconut oil and applied on the body as well. In India, young children are believed to be supported with neem oil as a sort of cure-all. In addition to being an incredible Ayurvedic healer, neem oil can be used to secure a variety of plants. It can also be used in creams, cleansers and more



II. CONCLUSION

Neem is the one of the best nontoxic biological sources for development of modern drugs. Neem having the most of these effects on the different activity and their therapeutic role in the body. Therefore wide variety of the extract extend their benefit for the traditionally medical folklore. Clinical based studies confirmed that neem plays pivotal role in prevention of diseases. The role of active ingredient as the popularity of natural merchandise or their derivatives in the remedy and prevention of diseases is increasing international because of fewer side consequences. Neem and its fixatives have healing propositions and are commonly used for the duration of the world, specially in the Indian subcontinent, due to the fact that historic instances. Scientific examinations have confirmed that neem performs an essential position in aversion to various sicknesses. The position of dynamic fixations as a chemopreventive effect has

been located in numerous tumors through the stability of various cellular signaling pathways. A small and hard exam need to depend upon the creatures to recognize the exact mechanism of movement within the treatment of sicknesses.

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