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Review Article

Traditional, Pharmacological and Patenting Potential of Neem (*Azadirachta indica*): A Review

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ABSTRACT

Since ancient time, herbal drugs were highly used in the prevention and cure of various human illnesses. In India, *Azadirachta indica* being commonly known as Neem or Margosa is one of the multi-functional trees; belonging to Meliaceae family. In 1992, the US National Academy of Sciences was published a report entitled 'Neem- a tree for solving global problems'. It is still considered as 'village dispensary' throughout the India. There are two species of *Azadirachta* which have been investigated; *Azadirachta indica* that is found in the Indian subcontinent and *Azadirachta excelsa* Kack that is homegrown to Indonesia and Philippines. A large number of pharmacologically active substances have been identified and isolated from the different parts of neem including azadirachtin, meliacin, gedunin, salanin, nimbin, valassin and various other components which are derived from these main compounds. Many different studies have been evaluated and authenticated for its various traditional and pharmacological activities like itching, leprosy, wound healing, spermicidal, anti-inflammatory, insecticidal, antidiabetic and analgesic etc. In the beginning of 1979, patenting on neem was started by CSIR to separate the active compounds from neem oil. Its great implantation fights with soil erosion, global warming, deforestations and desertification world-wide. In 2002, World Neem Conference raised the neem tree as an industrial or commercial plant. This review is going to explore comprehensively; traditional, pharmacological potential along with patenting, environmental & industrial significant of various parts of neem tree with safety concerns.

Keywords: *Azadirachta indica*, NSO, Patent, neem, India.

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INTRODUCTION

Herbal drugs possess a great medicinal and broad growth potential world-wide. They are highly useful in the prevention and cure of various human illnesses. In India, *Azadirachta indica* being commonly known as Neem or Margosa is one of the multi-functional trees; belonging to Meliaceae family. It consist a number of significant non-wood products such as leaves, oil, bark, flowers, fruits, seed, gum, and neem cake and wood products like root and stem than other species. It is one of the most promising trees of 21st century being highly investigated plant. [1] It is an evergreen and believed holy tree among the Hindu community and used in various rituals, ceremonies and in New Year celebrations. [2] Since ancient time, neem being one of the most versatile medicinal trees; each and every part of the neem has been extensively used in the treatment of various domestic human illnesses. It is well versed medicinal tree of tropical region having intense activity. In 1992, the US National Academy of Sciences was published a report entitled 'Neem- a tree for solving global problems'. It is still regarded as 'village dispensary' throughout the India.

Earlier researches had been demonstrated that it has been highly utilized in Homoeopathic, Unani and Ayurveda medicine system and have become the guidance for modern medicine exposure. [3]

Neem is a big tree of about 25 m height with semi-straight to straight trunk. It forms 3 m girth; crown like structure with broad spreading branches. For its better growth; temperature range is between 0°C- 49°C. Generally it starts producing fruits after 3-5 years. The neem tree remains alive up to 2 centuries. It has a good tolerability to a large extent of topographic, edaphic and climatic alterations. It shows a good growth in dry, stony soils and even on hard calcareous soils. It requires minimum rainfall between 150-250 mm to grow up whereas 450-1200 mm is optimum for natural growth. It grows highly at pH ranging from 4-10. [4] The leaves are compound, impair-pinnate and each comprising 5-15 leaflets. It contains many flowered panicles often in the leaf axils. It produces ellipsoid, glabrous and yellow fruits with 12-20 mm in length. Initially fruits are green but turn in yellow on ripening and produce aromatic smell like

garlic. After autumn season, new leaves and flowers come between March-April. Generally fruits get matured during April-August; could vary depending on the locality of tree. [5]

There are two species of *Azadirachta* which have been investigated; *Azadirachta indica* that is found in the Indian subcontinent and *Azadirachta excelsa* Kack that is homegrown to Indonesia and Philippines. [6] The former develops as a woods tree in many countries including India, Bangladesh, Burma, Pakistan, Sri Lanka, Malaysia, Thailand and Indonesia. Now, neem trees are largely growing in about 72 countries of Asia, Africa, Australia, North, Central and South America. [1]

In the middle of 20th century, the neem tree products were extensively investigated. Earliest, the first bitter compound nimbin was isolated from neem oil. A large number of pharmacologically active compounds have been identified and isolated from the different parts of neem including azadirachtin, meliacin, gedunin, salanin, nimbin, valassin and various other components which are derived from these main compounds. [2] The seed contains tignic acid which is responsible for the aromatic odor of neem oil. [6]

Synonyms: [1, 5] *English:* Indian Lilac, Margosa tree, Neem tree; *Persian:* Azad- Darakth E Hind; *Hindi/Urdu:* Neem or Nim; *Arabic:* Neeb; *Bengali:* Nim, Nimgachh; *Gujarati:* Danujhada, Limbado, Limra, Limdo; *Sanskrit:* Arista, Nimba, Nimbah, Picumarda; *Kannada:* Bemu, Bevinamara, Bimu, Kaybevu; *Punjabi:* Kakam, Drekh.

Traditional Uses of Neem

In India, different parts of the neem tree have been highly used as traditional and Ayurvedic medicine. The fruit, leaf and bark are the main medicinal attribute of neem tree. They were used in the treatment of various ailments such as leprosy, skin ulcers, intestinal worms, analgesic, cough, asthma and ring worm etc. [3]

It was also used in the treatment of dengue fever and genital herpes virus. Neem leaves extract has been found very effective in the inhibition of sexually transmitted diseases (STDs). A neem based cream had been used as vaginal lubricants to treat vaginal infections caused by organisms like *Candida*, *Trichomonas* and *Giardinella vaginalis* [7].

Table 1: Different extracts of neem with various pharmacological potential

S. N.	Different extracts of neem	Pharmacological Potential	Reference
1.	Methanolic extract of Neem leaf, stem, bark and seed	Antimalarial	8
2.	Hexane extract of Neem seed	Anti-fertility	13
3.	Aqueous, ethanolic, methanolic & ethyl acetate leaf extracts	Antifungal	14, 15
4.	Aqueous & ethanolic leaf extracts	Anti-gastric ulcer	16
5.	Ethanolic & methanolic leaf extracts	Antibacterial	18
6.	Hydro alcoholic macerate, absolute alcohol & hydro alcoholic leaf extracts	Skin renewal effect	24
7.	Ethanolic root extract	Antioxidant	27
8.	Methanolic leaves extract	Anti-snake venom	28
9.	Ethanolic & methanolic leaf extracts	Wound healing	29, 30
10.	Acetone, chloroform & ethanolic extracts of leaf, root, seed and bark	Larvicidal	31
11.	Acetone extract of neem seed	Insecticidal	36
12.	Aqueous leaves extract	Anxiolytic	38

Table 2: Different Chemical Constituents and their Pharmacological potential

S. N.	Source	Active constituents	Pharmacological Potential	Reference
1.	Seed Oil	Azadirachtin	Antimalarial	8
2.	-	Sodium Nimbidate	Anti-inflammatory	9, 10
3.	Seed Oil	Nimbidin	Anti-inflammatory Antipyretic Antidiabetic Anti-fertility Antifungal Anti-gastric ulcer Antibacterial.	9, 10 10 11, 12 13 14, 15 16 17, 18
4.	Seed Oil	Nimbin	Anti-fertility	13
5.	Seed Oil	Gedunin	Antimalarial, Antifungal.	8

				14, 15
6.	Seed Oil	Nimbolide	Antibacterial	17, 18
7.	Seed Oil	Mahmoodin	Antibacterial Mosquito repellent Analgesic	17, 18 21 22
8.	Bark	Gallic Acid, (-) Epicatechin & Catechin	Anti-inflammatory Immunomodulatory	9, 10 19
9.	Bark	Margolone, Margolonone & Isomorgolonone	Antibacterial	17, 18
10.	Leaf	Cyclic Trisulphide, nimolol & Cyclic Tetrasulphide	Antifungal	14, 15
11.	Leaf	Polysaccharides	Anti-inflammatory Hepatoprotective Analgesic Skin renewal effect Hypolipidemic	9, 10 20 23 24 25, 26
12.	Bark	Polysaccharides G2a & G3a	Anti-inflammatory	9, 10
13.	Bark	NB-2 Peptidoglycan	Immunomodulatory	19
14.	Leaf	-	Alzheimer's disease	32
15.	Leaf	AIPLAI	Anti-snake venom	28
16.	Whole neem extract	-	Anticonvulsant Anti-allergic	34 37
17.	Bark	Silvose T Silvose TRS	Toothpaste Mouth wash	41 41

Pharmacological potential of neem

Antimalarial activity

BC Akin Osanaiye et al have evaluated the antimalarial activity of neem extracts against *Plasmodium berghei* infected albino mice. Various extracts of neem including leaf, stem-bark and seed were extracted with methanol and their efficacy tested using 4th day suppression test and secondary biological detection methods. It concluded, neem leaf and stem-bark extracts were decreased the parasitemia level in *Plasmodium berghei* infected mice with 51 - 80% and 56 - 87% respectively. [8]

Anti-inflammatory and antipyretic activity

The rats were divided into six groups, each consisting 6 animals. Group I: Control (distilled water 0.5 ml *p. o.*); Group II: Standard (aspirin 200 mg/kg *p. o.*); Group III: NSO (0.25 ml/kg); Group IV: NSO (0.5 ml/kg); Group V: NSO (1 ml/kg); and Group VI: NSO (2 ml/kg) *i. p.*). The hind paw edema was induced by the administration of 0.1ml (1% carrageenan suspension) in normal saline beneath the plantar region of right hind paw while left hind paw was taken as control. It was found that NSO (2 ml/kg) exhibited maximum (53.14%) inhibition of right hind paw edema volume after 4th hour of carrageenan administration. It concluded, NSO exhibits significant anti-inflammatory effect. [9] The neem extracts were proved for its acute oral toxicity, anti-inflammatory and antipyretic potentials. It exhibited significant anti-inflammatory (hind paw edema) and antipyretic response. [10]

Anti-diabetic activity

The hypoglycemic evaluation of neem root-bark extract was done by giving glucose *p. o.* 60 minutes after administering standard drug Glibenclamide. It was administered in doses of 200, 400 & 800 mg/kg in rats then blood glucose levels were checked after each 30 minutes up to 4 hours. The hypoglycemic activity was observed in alloxan induced diabetic rats with continuous dosing for 15 days. It exhibited statistically significant effect solely at dose 800 mg/kg. In conclusion, neem root-bark has been exhibited anti-hyperglycemic and hypoglycemic activity but not effective as Glibenclamide. [11] After 24 hours treatment, neem 250 mg/kg single dose study reduced glucose (18%), cholesterol (15%), triglycerides (32%), urea (13%), creatinine (23%), and lipids (15%). [12]

Anti-fertility activity

Neem seed oil showed spermicidal action against rhesus monkey and human spermatozoa *in vitro*. Some *In vivo* studies have been demonstrated, intravaginal application of neem oil anterior to sexual intercourse can inhibit pregnancy. The hexane extract of neem seed is responsible for completely diminishing pregnancy in rodents when given 10% *p. o.*, without any side effect. [13]

Antifungal activity

Antifungal activity of *Azadirachta indica* (neem) leaf extract was studied against 3 fungal species including *Aspergillus flavus*, *Alternaria solani* and *Cladosporium*. Four different concentrations (25%, 50%, 75% and

100%) of ethanolic and methanolic leaves extract were prepared and estimated on fungal species by disc diffusion method. Antifungal activity of neem leaf extract was compared with standard antifungal drug Ketoconazole. In conclusion, both methanolic and ethanolic extracts of *Azadirachta indica* exhibited growth inhibitory effect against *Aspergillus flavus*, *Alternaria solani* and *Cladosporium*. [14] The antifungal activity of aqueous, ethanolic and ethyl acetate neem leaves extract was evaluated on growth of few human pathogens such as *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus terreus*, *Candida albicans* and *Microsporium gypseum* *in vitro*. [15]

Anti-ulcer activity

Mohapatra B. Bhusan et al have studied the anti-ulcer potential of aqueous and ethanolic leaf extract of *Azadirachta indica* (NLEa & NLEe) in Wistar albino rats. They used pylorus ligation, cold restraints stress and forced swimming test as screening models. The neem leaves extract (400 mg/kg) significant ($P < 0.05$) decreased gastric volume, free acidity, total acidity, combined acidity and ulcer index as compared to control. It concluded that aqueous & ethanolic leaf extracts have antiulcer potency which would be because of cytoprotective effect of neem. [16]

Antibacterial activity

The antimicrobial activity of neem was studied against pathogenic gram positive bacteria *Bacillus subtilis* and gram negative bacteria *Escherichia coli*, *Salmonella typhi* and *Vibrio cholera* using agar well diffusion method. Both extracts were exhibited higher inhibition zone against *Vibrio cholerae* and *Bacillus subtilis* than *E. coli* and *S. typhi*. [17] Antimicrobial activity of alcoholic neem leaves extract was evaluated against human pathogenic bacteria including *E. coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella typhimurium* and *Bacillus pumilus*. The methanolic and ethanolic extracts have shown the maximum inhibition on *Bacillus pumillus*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* in an ascending order and compared with gentamycin 200mg and gentamycin 10mg. [18]

Immuno-modulatory activity

The immune stimulatory effect of neem seed oil was evaluated in mice. Peritoneal macrophages exhibited increased phagocytic action and expression of MHC class II antigens on treatment with neem oil *i. p.* It also increased the production of gamma interferons; lymphocyte proliferative action *in vitro* as compared to control. It concluded that neem seed oil is a non-specific immuno-modulator. [19]

Hepatoprotective activity

Effect of neem leaf extract was evaluated on serum enzymes such as glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, acid phosphatase and alkaline phosphatase level increased by paracetamol in rats. The serum enzyme levels were much increased in paracetamol induced rats as compared to those receiving paracetamol and neem leaf extract simultaneously. The neem leaves extract treated group was significantly protected from hepatic damage induced by paracetamol. It was also confirmed by histopathological examination of liver. [20]

Mosquito repellent action

Aremu O. et al have demonstrated the mosquito repellent action of Neem Seed Oil (NSO) against *Anopheles gambiae* mosquito. The different concentrations of NSO cream and Deet showed duration of repellent action in descending order 10.0% > Deet > 7.5% > 5.0% > 2.5%. This study confirmed that NSO cream is an effective mosquito repellent at concentrations 7.5 and 10.0% w/w. [21]

Analgesic activity

Kumar Sanjay et al have reported the analgesic potential of Neem Seed Oil on albino rats by tail flick method. Different doses 0.25, 0.5, 1 and 2 ml/kg were given to rats intraperitoneally. Neem seed oil exhibited a significant analgesic effect at the doses 1 and 2 ml/kg when compared to morphine; revealing a dose-dependent effect. [22] The analgesic effect of Neem Leaf Extract (NLE) was also studied using experimental tail flick model to thermal stimulation. The results were statistically analyzed using chi-square test. It concluded that both doses of NLE increased the tail flick latency time in the dose dependent manner. [23]

Skin renewal effect

Among the various neem leaf extracts, hydro-alcoholic extracts, absolute alcohol extracts and hydro-alcoholic macerates exhibited a significant skin renewal effect. It was estimated using dansyl chloride fluorescence method. It concluded that hydro-alcoholic macerate extract showed maximum % increase in renewal effect by 27.5 % as compared to hydro-alcoholic and alcoholic extracts as 23.75 % and 23.12 % respectively. [24]

Hypolipidemic activity

Various parameters such as cholesterol, phospholipids, total lipids and triglycerides were used for evaluation of hypolipidemic activity on overnight fasting inbred Swiss albino rats. They were sacrificed by cervical dislocation at the last day of 4th week. It significantly decreased total lipids, free & esterified cholesterol & total cholesterol and triglycerides levels in both serum and liver. It concluded that neem leaf extract might be helpful in controlling the atherosclerosis proliferation and hypercholesterolemia. [25]. In another study, neem leaf extract significantly decreased the cholesterol, total cholesterol, triglycerides,

LDL and VLDL, and total lipids level in streptozotocin induced diabetic rats while HDL and cholesterol levels were remained unaltered. [26]

Antioxidant activity

The antioxidant effect of ethanolic extract of neem root was evaluated using reducing power assay, ferrous ion chelation ferrous ion chelation and DPPH free radical scavenging assay. In reducing power assay, maximum absorbance was found to be 1.523 ± 0.026 at $100 \mu\text{g/ml}$ and compared with standard ascorbic acid ($2.811 \pm 0.013 \mu\text{g/ml}$) and BHA ($2.031 \pm 0.019 \mu\text{g/ml}$). The chelating ability was estimated to $19.01 \pm 0.024 \mu\text{g/ml}$ and compared with standard EDTA $8.87 \pm 0.035 \mu\text{g/ml}$. It also contains highly phenolic constituents ($238.81 \pm 0.98 \text{ mg/g}$ of gallic acid equivalent). This study concluded that neem root extract possess a significant antioxidant potential. [27]

Anti- snake venom effect

Azadirachta indica PLA2 inhibitor (AIPLAI) was isolated and purified from methanolic leaf extract of neem. It successfully prevented the Russell and Cobra's snake venoms- phospholipase A2 enzymes in a dose dependent manner. It (AIPLAI) highly significantly ($P < 0.05$) prevented the catalytic response of Cobra venom PLA2 enzymes (*Naja naja* and *Naja kaouthia*) as compared to the prevention of crude RVV PLA2 enzymes (*Daboia russelli*) following the same laboratory conditions. This study concluded that AIPLAI is one of the good hopeful constituents for the novel preparation of anti- snake venom drug in future. [28]

Wound healing activity

The wound healing effect was studied on the ethanolic leaves extract of neem by topical application using Excision wound model. This study concluded that ethanolic leaves extract of neem demonstrated better and faster wound healing action and compared with standard Povidone Iodine ointment in Excision wound model. [29] In another study, wound healing effect of the neem leaf extract was studied through wound contraction, rate of skin breaking intensity and histopathological test of healing tissues. The methanolic leaves extract of neem was significantly increased the wound healing potential in both the Excision and Incision wound models. In conclusion, the tensile strength in the wound healing tissue of neem (*A. indica*) treated animals was highly significant ($P < 0.05$) as compared to the control group, in Incision wound model. [30]

Larvicidal Activity

Different parts of neem including bark, leaf, root, and seed extracts were evaluated for its larvicidal effect with different solvents such as acetone, chloroform, and ethanol against *A. aegypti* larvae. In this bioassay, leaf acetone and root chloroform extracts showed 100% mortality at the concentration of 1000 ppm among these

in 24 h against *A. aegypti* larvae. In conclusion, this study demonstrated the toxic effect of neem (*A. indica*) crude extracts against *A. aegypti* larvae. [31] In the Islamic Republic of Iran, neem extract was studied against mosquito larvae under laboratory and field conditions. In field trials, mortality extent of *Anopheles* spp. larvae was estimated much than *Culex* spp. in the dosages of 1 & 2 L/hectare. [32]

Alzheimer's disease

Pretreatment of neem leaves extract strengthened the reference memory, working memory and spatial learning with similar effects as Donepezil using Morris water maze test. It also significantly reversed the learning and memory in both ibotenic acid (IB) and Colchicine induced deficits. In result, neem (*A. indica*) significantly decreased the lipid peroxidase effect that was increased by both IB and Colchicine compounds. In conclusion, this study shows that neem leaf extract (*A. indica*) might effective in treatment of AD by its good antidepressant, cognition enhancement and antianxiety effects. [33]

Anticonvulsant activity

Neem was administered at dose 100 mg/kg p. o. daily in rats. Seizures intensity was recorded diminished in PTZ + Valproate and PTZ + Neem treated group as compared to PTZ induced kindling. This study suggests that use of Valproic acid and neem in epilepsy might keep safe brain from oxidative stress and anoxic (deficiency of oxygen) damage due to extended seizures. In conclusion, neem contains more protective effect as compared to Valproic acid on PTZ developed chemical kindling. [34]

Insecticidal activity

In Sudan, 3rd instar larvae of *Trogoderma granarium* were used for the evaluation of insecticidal effect of neem. The highest concentration (5%) showed high level of mortality of insects. [35] In another study, neem seed extract with acetone showed insecticidal effect against 3rd instar larvae of *Corcyra cephalonica* by diminishing its developmental stages. This extract was regarded highly toxic at dose 0.16% v/w and produced 100% mortality. [36]

Anti-allergic activity

Wheat protein was identified with possible allergens of molecular weight 7k Da, 9k Da, 15k Da, 12k Da, 17k Da, 36k Da, 45k Da and 77k Da. Neem extract exhibited high reduction of allergenic proteins in wheat protein. In conclusion, none allergic bands have been evaluated after neem treatment. [37]

Anxiolytic activity

It was evaluated using elevated plus maze (EPM) and light-dark arena model. All Groups were statistically analyzed using ANOVA followed by Tukey's test. Test drug group exhibited a statistically prominent anxiolytic effect in elevated plus maze and light-dark arena model

and compared to control group, diazepam and buspirone group. [38] In another study, anxiolytic effect of neem leaves extract was evaluated on rat behavior and compared with diazepam group using Elevated X Maze test model. In conclusion, this study exhibits that both neem & diazepam exhibited anxiolytic action in behavioral index but only neem produced anxiolytic effect without initiating motor deficiency. [39]

Patents on neem

During 50 years ago, various properties of neem have been evaluated widely. A number of National, International and World conferences on neem have been

done throughout India and across the globe. It has been globally accepted as commercial source. Most of the patents have been granted to protect applications (63%) that include- veterinary care (5%), healthcare (13%), industrial (15%), cosmetics (6%), and others (8%). [39] In 1983, Temuro Corporation got first US patent for therapeutic preparation from neem bark. Since 1995, in India there are still more than 53 patent applications pending (to be granted) because of opposition or gazette notification. [1, 40] It was started earlier in 1979 by CSIR to isolate active compounds from neem oil. Both CSIR and Hindustan Unilever Ltd. Bombay are the active participants concerning Indian patents. [41]

Table 3: List of Indian Patents [41]

S. N.	Registration No.	Title of Patents
1.	153415	Process for the isolation of active principle from neem oil evincing oviposition deterrent activity in insects
2.	171129	Therapy of neem oil
3.	171888	A process for treating (upgrading) neem oil
4.	171899	A process for treatment (upgrading) of neem oil having high free fatty acid in content
5.	172150	A process for the formulation of neem oil fatty acid distillation residue based pesticides
6.	173327	A process for the extraction of neem oil
7.	173559	A process for isolation of nimbidin from neem oil
8.	173996	A process for the formulation of an active composition containing triterpenes including Azadirachtin and its derivatives possessing insect antifeedant and growth inhibitory activity of neem
9.	173997	A process for the formulation of insecticidally active composition containing lipids from the neem
10.	173998	A process for the isolation of new triterpene derivatives of Azadirachtin from various parts of neem plant

Many neem products and processes have been patented in USA (54), Australia (23), Japan (35) & India (14). [42]

Environmental and Industrial uses of neem

There are approx. 1/3 of world's agricultural food products that often get spoiled by more than 20 thousand pest species. A large number implantation of neem fights against soil erosion, deforestations, and desertification that decrease the inordinate global warming. Neem trees undergo through rapid photosynthesis and releases a high amount of oxygen comparative to other species thus purify the environment. Various neem products also act as water purifier. In Northern India, during summer, temperature has been measured 10°C less beneath the neem tree than surroundings. Its plantation has been utilized for shade of Sahara Desert from Somalia to Mauritania. [40] World Neem Conference 2002; promoted neem as an Industrial or Commercial Plant. Neem seed oil is highly useful product in pharmaceuticals, cosmetics, disinfectants, rubbers, textiles and bio-pesticide industries. The powdered form of neem leaves & seed oil are highly incorporated in various cosmetic formulations including Nail polish, Face cream, Shampoos & Hair conditioners. Neem cake acts

as natural pesticide. Margosa oil is used in medicated bathing soap formulation. It is an important component of oral hygiene & dental care. Neem seed pulp is a major source of carbohydrate therefore it used for methane gas production by the fermentation. [1, 40] Nowadays, soap manufacturers are good supplier of neem throughout the India. They use neem due to its cheap price and easily availability. Crude oil is a good component of laundry soaps. High cost containing soaps are manufactured through saponification then distillation of neem oil before adding lye. Neem is believed as a beauty aid in India. The powdered form of neem leaves are main constituent of one facial cream. Neem oil inhibits degradation; better efficient due to its non-drying nature and used to grease the cart wheels. Timber's gravity ranges from 0.56- 0.85; aromatic in nature. Neem wood is broadly used in tool handles, agricultural designs and cart wheels. Neem oil is used as fuel in lamps. [43]

Safety Evaluation of various compounds and marketed products of neem

Nimbidin produces sub-acute toxicity in adult rats after daily administration at doses 25, 50 and 100 mg/kg up to 6 weeks. Nimbidin is a significant hypoglycemic which

evaluated in fasting rabbits. It has also spermicidal action. Nimbic acid and Nimbolide both were found much toxic in mice when administered intravenously or intraperitoneally but less toxic in hamster and rats. Azadirachtin and diacetyl nimbin are non-toxic. Margosan O showed minimal irritation in both washed & unwashed eyes of albino rabbits when applied for 7 days. A volatile NIM-76 compound was isolated from NSO that exhibited antifertility action when applied before coitus in rats, rabbits and rhesus monkeys. [3] Neem seed oil was studied for its acute toxicity at doses 14 & 24 mg/kg in rats and rabbits respectively. Neem oil at dose 0.14 mg/kg was found safe on adult human. Azadirachtin administered during pregnancy (6- 15 days) and did not show any teratogenic effect. Praneem was found safe on human at doses 1.5, 2, 2.5 & 3 ml for 3 consecutive days. [44]

CONCLUSION

Since ancient time, *Azadirachta indica* (Neem) is widely used in the cure of various human ailments. It is called Doctor Tree of village or Village Dispensary because of versatile nature. It is one of the most promising trees of 21st century. It is widely used in the processing of medicinal products in Homeopathic, Unani and Ayurveda. This is the reason; a great number of patents have done and are pending (to be granted) over neem throughout India. This research has been done to exploit some more health beneficial, traditional and pharmacological potential of neem tree along with patenting, environmental and industrial significant of various parts of neem tree with safety concerns.

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