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AN UPDATED REVIEW OF PHARMACOLOGICAL STUDIES ON *AZADIRACHTA INDICA* (NEEM)

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ABSTRACT: Neem has become valuable plant in the world which shows the solutions for hundreds to thousands problems. Neem has become important in the global context today because it offers answers to the major concerns facing mankind. Neem has been extensively used in Ayurveda, Unani and Homoeopathic medicine and has become a centre of attraction of modern medicine. *Azadirachta indica* (neem) is a rapidly growing evergreen well known tree found generally in various regions of world like America, Africa and India. The aim of this review article provides information mainly on various pharmacological activities like anti-inflammatory, antimalarial, anti-bacterial, anti-allergic, antidermatic, antiulcer, antifungal, insecticidal, larvicidal and other pharmacological activities of neem plant and medicinal uses.

INTRODUCTION: Medicinal plants are rich source of novel drugs that forms the ingredients in traditional systems of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates, bioactive principles and lead compounds in synthetic drugs. WHO pointed out that more than 80% of world's population depends on plants to meet their primary health care needs. However, overexploitation of the selected medicinal plant species lead to the reduction in number of plants in the wild and inclusion of their name in the red data book [1].

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Neem (*Azadirachta indica*) commonly called 'Indian Lilac' or 'Margosa', belongs to the family Meliaceae, subfamily Meloideae and tribe Melieae. *Azadirachta indica* has been used medicinally throughout history by many different cultures. Many compounds have been found in the exudates of the, *Azadirachta indica* plant that have been used medically by humans. Neem is a member of the Meliaceae family. The only congener is *A. excelsa*. Its sanskrit name, 'arishtha' means 'reliever of sickness' and it is considered as the 'kalpavriksh of kalyuga'. The Persian name of neem is 'Azad- Darakth- E- Hind' which means 'Free tree of India'[2].

Azadirachta indica is a fast growing evergreen popular tree found commonly in India, Africa and America [3]. It has been used in Ayurvedic medicine for more than 4000 years due to its medicinal properties.

Neem is called 'Arista' in Sanskrit a word that means 'perfect, complete and imperi-shable'[4]. Arishtha is the sanskrit name of the neem tree meaning 'reliver of Sickness' and hence is considered as 'Sarbarogaribarini'. The tree is regarded as 'Village Dispensory' in India. The importance of the neem tree has been recognised by the US National Academy of Sciences, which publish a report in 1992 entiteled 'Neem - a tree for solving global problems'[5]. Neem has become important in the global context today because it offers answers to the major concerns facing mankind. Neem (*Azadirachta indica*) is considered harmless to humans, animals, birds, beneficial insects and earthworms, and has been approved by the US Environmental Protection Agency for use on food crops [6]. Neem (*A. indica*) of family meliaceae is evergreen tree of potential medicinal value found in most tropical countries [7].

A. indica has complex of various constituents including nimbin, nimbidin, nimbolide, and limonoids and such types of ingredients play role in diseases management through modulation of various genetic pathways and other activities. Quercetin and β-sitosterol were first polyphenolic flavonoids purified from fresh leaves of neem and were known to have antifungal and antibacterial activities [8]. Numerous biological and pharma-cological activities have been reported including antibacterial [9], antifungal [10] and anti-inflammatory. Earlier investigators have confirmed their role as anti-inflammatory, antiarthritic, antipyretic, hypoglycemic, antigastric ulcer, antifungal, anti-bacterial and antitumour activities [11, 12, 13, 14] and a review summarized the various therapeutics role of neem [15].

Taxonomic Identity: [16] It has similar properties to its close relative, *Melia azederach*. The word Azadirachta is derived from the Persian azaddhirakt (meaning 'noble tree'). The taxonomic positions of neem are as follows:

Order : Rutales
Suborder : Rutinae
Family : Meliaceae
Subfamily : Melioideae
Tribe : Melieae
Genus : Azadirachta
Species : indica

Description: [17]

Tree: The neem tree (*Azadirachta indica*) is a fast growing (up to twenty feet in three years) tropical evergreen related to mahogany. It will grow where rainfall is as little as 18 inches per year and thrives in areas that experience extreme heat of up to 120ºF. They are reported to live for up to 200 years.

FIG. 1: TREE OF *AZADIRACHTA INDICA*

Leaves: Compound, alternate, rachis 15-25 cm long, 0.1 cm thick; leaflets with oblique base, opposite, exstipulate, lanceolate, acute, serrate, 7-8.5 cm long and 1.0-1.7 cm wide, slightly yellowish-green; odour, indistinct; taste, bitter.

FIG. 2: LEAVES OF *AZADIRACHTA INDICA*

Stem Bark: Bark varies much in thickness according to age and parts of tree from where it is taken; external surface rough, fissured and rusty-grey; laminated inner surface yellowish and foliaceous, fracture, fibrous; odour, characteristic; taste, bitter.

Flower, Fruits and Seeds: The tree is often covered in delicate flowers in the early summer. The flowers (white and fragrant) are arranged axillary, normally more-or-less drooping panicles which are up to 25 cm long. It has a semi-sweet, olive-sized fruit. The seed inside is rich in oil with tremendous medicinal and botanical properties.

The oil is easily obtained by pressing the kernels in a juicer. It generally begins bearing fruit at three to five years, and can produce up to 110 lbs. of fruit annually when mature.

FIG. 3: STEM BARK OF *A. INDICA*

FIG. 4: FLOWERS OF *A. INDICA*

FIG. 5: FRUITS OF *A. INDICA*

FIG. 6: SEEDS OF *A. INDICA*

Pharmacological Activities of Some Neem Compounds: Although a large number of compounds have been isolated from various parts of neem, a few of them have been studied for biological activity as shown in **Table 1**.

TABLE 1: LIST OF ISOLATED COMPOUND AND PHARMACOLOGICAL ACTIVITIES

S. no.	Coumpound name	Source	Pharmacology activity	References
1	Nimbidin	Seed oil	Anti-inflammatory	18
			Antiarthritic	19
			Antipyretic	20
			Hypoglycaemic	21
			Antigastric ulcer	22, 23
			Spermicidal	24
			Antifungal	25
			Antibacterial	25
			Diuretic	26
2	Sodium nimbidate		Anti-inflammatory	18, 19
3	Azadirachtin	Seeds oil	Antimalerial	27
4	Nimbin	Seed oil	Spermicidal	28
5	Nimbolide	Seed oil	Antimalerial	29
			Antibacterial	30,31
6	Gedunin	Seed oil	Antimalerial	31
			Antifungal	22
7	Mahmoodin	Seed oil	Antibacterial	33
8	Gallic acid, (-)epicatechin and catechin	Bark	Anti-inflammatory Immunomodulatory	34
9	Margolone, margolonone and isomargolonone	Bark	Antibacterial	35
10	Cyclic trisulphide and cyclic tetrasulphide	Leaf	Antifungal	36
11	Polysaccharides		Anti-inflammatory	37
12	Polysaccharides G1A, G1B	Bark	Antitumour	38
13	Polysaccharides G2A, G3A	Bark	Anti-inflammatory	39
14	NB-2 Peptidoglucan	Bark	Immunomodulatory	40, 41
15	Phytosterols	Fruit	Antiulcer	42

Pharmacological Activities:

Anti-inflammatory: Plants or their isolated derivatives are in the practice to treat/act as anti-inflammatory agents. A study result has confirmed that extract of *A. indica* leaves at a dose of 200 mg/kg, p.o., showed significant anti-inflammatory activity in cotton pellet granuloma assay in rats [43]. Other study results revealed that neem leaf extract showed significant anti-inflammatory effect but it is less efficacious than that of dexamethasone [44] and study results suggest that nimbidin suppresses the functions of macrophages and neutrophils relevant to inflammation [45].

Earlier finding showed immunomodulator and anti-inflammatory effect of bark and leave extracts and antipyretic and anti-inflammatory activities of oil seeds [46, 47]. Experimentation was made to evaluate the analgesic activity of neem seed oil on Albino rats and results of the study showed that neem seed oil showed significant analgesic effect in the dose of 1 and 2 mL/kg and oil has dose-dependent analgesic activity [48]. Results of the study concluded that the treated animals with 100 $mgkg^{-1}$ dose of Carbon Tetrachloride Extract (CTCE) of *A. indica* fruit skin and isolated ingredient azadiradione showed significant antinociceptive and anti-inflammatory activities [49].

Another study was made to investigate the anti-inflammatory effect of Neem Seed Oil (NSO) on albino rats using carrageenan-induced hind paw edema and results revealed that NSO showed increased inhibition of paw edema with the progressive increase in dose from 0.25 ml to 2 mL/kg body weight. At the dose of 2 ml/kg body weight, NSO showed maximum (53.14%) inhibition of edema at 4^{th} h of carrageenan injection [50]. The chloroform extract of stem bark shows effectiveness against carrageenin - induced paw aedema in rat and mouse ear Inflammation. Inflammatory stomatitis in children is treated by the bark extract. Antipyretic activity has been reported in neem oil. A methanol extract of the leaves showed antipyretic effect when it is administrated into male rabbits. Antipyretic and anti-inflammatory activities in various extracts have been reviewed [51].

Pendse *et al*., (1977) reported anti-Inflammatory, immunosuppressive and some related pharmacological actions of the water extract of neem in albino rats and immunosuppressive effect in Albino rabbits. It significantly inhibited acute inflammatory response evoked by carrageenin in a doss of 50 mg/ 100 g given orally and intraperitoneally. In chronic inflammation produced by crctcn-oil in granuloma pouch technique, 20 mg/ 100 g of the water extract significantly inhibited granulation tissue response; the reduction in exudative response and increase in the weight of adrenal glands were not significant. A significant inhibition of primary and secondary phases was observed in adjuvant induced arthritis. It significantly inhibited antibody formation by typhold "H" antigen. Mild analgesic effects of its own as well as potentiation of morphine analgesia were possessed by the extract but it was devoid of antipyretic effect [52].

Traditional Indian system of medicine mentions neem (*Azadirachta indica*) to have many medicinal properties. So the present study was carried out to access the anti-inflammatory effect of neem. Albino rats were used; they were divided into three groups. Control group treated with normal saline, standard treated with Indomethacin and test drug used was neem oil. For acute inflammation; carregennan induced rat paw edema inhibition method and for sub acute inflammation: cotton pellet granulation method. Ulcer index of Indomethacin and test compound were also studied. It is found that neem oil showed significant anti-inflammatory effect in both acute as well as chronic inflammation, it was also found to have low ulcerogenic potential compared to Indomethacin, hence can be safely used as a potent anti-inflammatory agent [53].

Antidiabetic and Antihyperlipaemic: Bopana *et al*., (1997) reported antidiabetic and anti-hyperlipaemic effects of neem seed kernel powder on alloxan diabetic rabbits. In alloxan diabetic rabbits there was a significant ($P<0.001$) increase in fasting blood glucose and urine sugar and there was a significant decrease ($P<0.001$) in body weight and total haemoglobin content. There was a significant increase in body weight and haemoglobin level, and a significant decrease in Fasting Blood Glucose (FBG) and urine sugar in diabetic rabbits treated with NP, glibenclamide, insulin and in combination of NP and glibenclamide.

Though the entire antidiabetic drugs used significantly decreased the FBG levels, combination therapy of NP (250 mg/kg) and glibenclamide (0.25 mg/kg) p to all the other groups. There was a significant (P<0.001) roduced greater reduction in FBG as compared amelioration of body weight and total haemoglobin content in the diabetic phosphatase increased considerably in alloxan diabetic rabbits compared to the normal control. Treatment with various antidiabetic agents in the above experiments significantly reduced the enzyme activity. Treatment of NP with glibenclamide produced a significant (P<0.001) decrease of HMG CoA reductase, alkaline phosphatase and serum acid phosphatise activity when compared to other experimental antidiabetic agents.

Liver glucose 6-phosphatase (G6P) and serum lactate dehydrogenase (LDH) activity significantly (P<0.001) reduced in alloxan diabetic rabbits. On the contrary, hexokinase activity significantly increased by other experimental antidiabetic agents. The most significant (P<0.001) changes were observed in the combination of NP (250 mg/kg) and glibenclamide (0.25 mg/kg). From our experiments we have found out that, though both NP and glibenclamide produced significant fall in lipid parameter and enzyme activities, the changes were more prominent when combination of NP and glibenclamide were used [54].

To study the effects of *A. indica* aqueous leaf extract on the expression of insulin signaling molecules and glucose oxidation in target tissue of high-fat and fructose-induced type-2 diabetic male rat. The oral effective dose of *A. indica* leaf extract (400 mg/kg body weight [b.wt]) was given once daily for 30 days to high-fat diet-induced diabetic rats. At the end of the experimental period, fasting blood glucose, oral glucose tolerance, serum lipid profile, and the levels of insulin signaling molecules, glycogen, glucose oxidation in gastro-cnemius muscle were assessed. Diabetic rats showed impaired glucose tolerance and impairment in insulin signaling molecules (insulin receptor, insulin receptor substrate-1, phospho-IRS-1Tyr632, phospho-IRS-1Ser636, phospho-AktSer473, and glucose transporter 4 [GLUT4] proteins), glycogen concentration and glucose oxidation. The treatment with *A. indica* leaf extract normalized the altered levels of blood glucose, serum insulin, lipid profile and insulin signaling molecules as well as GLUT4 proteins at 400 mg/kg b.wt dose. It is concluded from the present study that *A. indica* may play a significant role in the management of type-2 diabetes mellitus, by improving the insulin signaling molecules and glucose utilization in the skeletal muscle [55].

To evaluated *in-vivo* diabetic murine model, *A. indica* and *B. spectabilis* chloroform, methanolic and aqueous extracts were investigated for the biochemical parameters important for controlling diabetes. It was found that *A. indica* chloroform extract and *B. spectabilis* aqueous, methanolic extracts showed a good oral glucose tolerance and significantly reduced the intestinal glucosidase activity. Interestingly, *A. indica* chloroform and B. *spectabilis* aqueous extracts showed significant increase in glucose-6-phosphate dehydrogenase activity and hepatic, skeletal muscle glycogen content after 21 days of treatment.

In immunohistochemical analysis, we observed a regeneration of insulin-producing cells and corresponding increase in the plasma insulin and c-peptide levels with the treatment of *A. indica* chloroform and *B. spectabilis* aqueous, methanolic extracts. Analyzing the results, it is clear that *A. indica* chloroform and *B. spectabilis* aqueous extracts are good candidates for developing new neutraceuticals treatment for diabetes [56].

To examined the pharmacological hypoglycemic action of *Azadirachta indica* in diabetic rats. After treatment for 24 h, *Azadirachta indica* 250 mg/kg (single dose study) reduced glucose (18%), cholesterol (15%), triglycerides (32%), urea (13%), creatinine (23%), and lipids (15%). Multiple dose study for 15 days also reduced creatinine, urea, lipids, triglycerides and glucose. In a glucose tolerance test in diabetic rats with neem extract 250 mg/kg demonstrated glucose levels were significantly less compared to the control group, *Azadirachta indica* significantly reduce glucose levels at 15th day in diabetic rats. *Azadirachta indica* serves as an important alternative source in the management of diabetes mellitus involved in reducing increased blood glucose during diabetes which should be examined further by oral hypoglycemic therapy [57].

To evaluated the *in-vivo* hypoglycemic effect of aqueous leaf extracts of *A. indica* in alloxan-induced white male albino mice. The blood glucose lowering effect of the extract was intraperitoneally and orally bioscreened in diabetic mice in serial dilutions of the extract at 25 mg/kgbwt, 48.4 mg/kg bwt, 93.5 mg/kgbwt, 180.9 mg/kgbwt and 350 mg/kgbwt. In both routes, the extract lowered blood glucose at all dosages in a dose independent manner. The extracts contained flavonoids, tannins, sterols, saponins, anthraquinones and alkaloids. The antidiabetic activity may be attributable to these phytochemicals present in the plant extract. The study confirms the traditional use of this plant part in the treatment of diabetes mellitus. However, organic solvent extraction of the leaves of this plant should be done to compare effects of both organic and aqueous fractions [89].

Antibacterial Activity: Methanolic extract of *A. indica* (neem) leaves was tested for its antibacterial, antisecretory and antihemarrhagic activity against *Vibrio cholera* [59]. The hexane chloroform and methanol extracts of *Azadirachta indica* were screened for antibacterial activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Micrococcus luteus*, *Bacillus subtilis*, *Enterococcus faecalis* and *Streptococcus faecalis*. It was reported that methanol extract was the most effective, chloroform moderately effective and hexane extract showed low antibacterial activity [60].

Oil extracted from leaves, seeds and bark gives a wide spectrum of antibacterial activity action against gram positive and gram negative microorganisms which including *M. tuberculosis* and streptomycin resistant strains. The photo-constituents like alkaloids, spooning, steroids, tennis, crude glycosides and flavonoids of neem plants was tested for antibacterial activity against pathogenic strains of *E. coli*, *Corynebacterium bovis* and *Staphylococcus aureus* [58]. The outcomes were also supported by Hymete *et al*., (2005) they reported that flavonoids compounds have antimicrobial activity. Hafiza *et al*., (2002) reported that crude saponins also prevent the growth of the microbes. Metabolic extract and acetonic extracts of leaves of *Azadirachta indica* were screened for antibacterial activity against two different bacterial strains *i.e*. *E. coli* and *B. subtilus* and it was reported that methanolic plant extracts showed maximum antibacterial activity as compared to acetonic plant extracts [61].

El-Mahmood *et al*., 2010 observed the antibacterial effects of crude extracts of neem seed against pathogenic involved in the infection of eyes and ear. The pure, ethanol, acetone and methanol extracts of neem were screened against bacterial strains *i.e*. *E. coli*, *B. subtitles*, *Salmonella typhus*, Pseudomonas, *Staphylococcus aurous*, and *Klebsiella pneumonia* and *Staphylococcus epidermitis* for various antibacterial activities. They reported that the neem extracts of acetone showed the maximum antibacterial activity as compared to other solvent extracts [62]. Neem seed oil gives bactericidal activity against 14 pathogenic bacterial strains [63]. The solvent and crude aqueous extracts of *A. indica* (Neem) were screened against 20 pathogenic bacterial strains, wherein crude extracts shows better outcomes [64]. Ethanolic extracts of neem leaves and stick of neem plant were screened for antibacterial activity on streptococcus mutans and it was reported that neem stick extracts had higher antibacterial properties than the leaves extracts [65].

Extracts of neem tree (*Azadirachta indica*) leaves were tested against *Vibrio parahaemolyticus* and *Vibrio alginolyticus* isolated from cultured shrimp. Aqueous extract of neem leaves did not produce any inhibitory zone while the neem juice produced inhibitory zone that showed linear relationship to the concentration of neem juice on both bacteria. The Minimum Inhibitory Concentration (MIC) for *V. parahaemolyticus* and *V. alginolyticus* was 3.13 and 6.25%, respectively. The minimum bactericidal concentration (MBC) for *Vibrio parahaemolyticus* and *V. alginolyticus* was 12.50 and 25.00%, respectively. It is concluded that neem juice is an antibacterial agent and is useful for inhibition of vibrios in shrimp [66].

Methanol extract has the strongest growth inhibitory effect on both standard and clinical isolated strains of *P. aeroginosa*. Ethyl acetate and ethanol extracts, showing a growth inhibitory effect on both standard and hospital isolated strains of *S. aureus*. In the case of *E. faecalis*, ethanol and methanol extracts showed the highest growth inhibitory effect against standard and clinical strains, respectively. According to the MIC index

results, the methanol extract has a bactericidal activity against both standard and nosocomial strains of *S. aureus* and *P. aeroginosa* and bacteriostatic activity against nosocomial strain of *E. faecalis*. Ethanol extract showed bactericidal activity against both standard and nosocomial strains of *E. faecalis* and *P. aeroginosa* and bacteriostatic activity against nosocomial strain of *S. aureus*. Ethyl acetate extract had shown bactericidal activity against standard strains of S. aureus and *P. aeroginosa* and bacteriostatic against nosocomial strain of *S. aureus* and standard strain of *E. faecalis*. Neem may be a prospective therapeutic agent to combat antibiotic resistant bacteria [88].

Antifungal Activity: The aqueous and ethanolic extracts of *Azadirachta indica* leaves have been shown to have antidermatophytic activity against dermatophytes from the 88 clinical isolates with the help of agar dilution technique. In these studies, ethanolic extract showed more conspicuous activity as compared to aqueous extract [67]. Antifungal characteristics was tested using methanolic and acetone extracts of *Azadirachta indica* against two different fungal strains *i.e*. *Aspergillus niger* and *Aspergillus fumigatus* and it was reported that methanolic plant extract gives maximum antifungal activity as compared to acetonic extracts [61]. The seed and leaf extracts of *Azadirachta indica* (neem) were screened for antifungal activity against dermatophytes and the Minimum Inhibitory Concentration (MIC) of (*Azadirachta indica*) neem seed extracts was found to be lower than that of neem leaf when screened against different species of Trichophyton and *E. floccosum* [68].

Antifungal activity of aqueous ethanolic and ethyl acetone extracts of (*Azadirachta indica)* neem leaves on growth of few human pathogens. *Aspergillus flavus, Candida albicans, Aspergillus terreus, Aspergillus fumigates*, *Aspergillus niger*, and *Microsporum gypseum in-vitro* using different concentration and it was reported that these extracts prevented the growth of the test pathogenic organism and the effect gradually increased with increase in concentration [69]. Gedunin isolated from neem seed oil has been reported to have antifungal activity [70]. The compounds of sulphur such as cyclic tetrasulphide and trisulphide isolated from the stem distillate of fresh, matured neem leaves shows antifungal activity against *Trichophyton mentagrophytes* [71].

Mohanty *et al*., (2008) carried out antifungal activity of neem (*Azadirachta indica)* against *Lagenidium giganteum* and *Metarhizium anisopliae* in PYG and Emerson's YpSs agar media. The minimum inhibitory concentration of neem oil for *L. giganteum* showed higher than that for *M. anisopliae*. The minimum fungicidal concentration of neem (*Azadirachta indica)* oil in PYG medium was lower than in YpSs for both fungi [72]. *Azadirachta indica* (neem) leaf extract was taken to test its antifungal activity against three fungal species - *Aspergillus flavus*, *Alternaria solani* and Cladosporium. Ethanolic and methanolic extracts in different concentrations (25%, 50%, 75% and 100%) was prepared and tested against test organisms using disc diffusion method. Ketoconazole was used to compare the toxicity of neem leaf extract and its antifungal activity [73].

Anticarcinogenic Activity: Neem leaf aqueous extract effectively suppresses oral squamous cell carcinoma induced by 7, 12-dimethylbenz [a] anthracene (DMBA), as revealed by reduced incidence of neoplasm [74]. Neem may exert its chemopreventive effect in the oral mucosa by modulation of glutathione and its metabolizing enzymes. That neem leaf extract exerts its protective effect in N-methyl- N¢-nitro-N-nitroso-guanidine (MNNG) (a carcinogenic material)-induced oxidative stress has also been demonstrated by the reduced formation of lipid peroxides and enhanced level of antioxidants and detoxifying enzymes in the stomach, a primary target organ for MNNG as well as in the liver and in circulation [75, 76].

We examined the antioxidant system as a possible mechanism through which Neem Leaves Preparation (NLP) exerts its oncostatic potential. Female Swiss Albino mice were inoculated intramuscularly in the right thigh with Ehrlich Ascites Carcinoma (EAC) cells. NLP (500 mg/kg body weight) was injected for 20 days intraperitoneally into mice beginning on day 5 of post-EAC cell inoculation. Tumor growth, lipid peroxidation (LPx), glutathione (GSH) contents and the activity of the antioxidant scavenger enzymes were examined. Results indicated that

NLP efficiently suppressed the growth of tumors which was associated with normalization of the LPx levels and augmentation of GSH contents.

NLP enhanced the activity of the endogenous antioxidant scavenging enzymes, superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and glutathione-S-transferase (GST) in liver and tumor tissue. The effect of NLP was more pronounced when treated as early as day 5 of post-tumor cell inoculation. In conclusion, NLP induced oncostatic activity by modulating lipid peroxidation, augmenting the antioxidant defense system and protecting against oxidative stress [77].

Antimalarial Activity: Ball shaped wood scrapings which is soaked in 5% neem oil (*Azadirachta indica*) which is diluted in acetone and in 45 days the breeding of *Anopheles stephensi* and *Aedes aegypti* were controlled, when it is placed in water storage over head tanks [17]. Nimbolide isolated from neem extracts shows the antimalarial activity by preventing the growth of plasmodium falciparum [18]. Gedunin isolated from neem seed oil has been reported to show antimalarial activities [19]. Both aqueous and alcohol extracts of bark and leaves of neem are effective antimalarial agents, particularly on chloroquine resistant strains (badam *et al*., 1987) [20].

This study was designed to know the antimalarial activity of the extract of the neem leaves (*Azadirachta indica* A. Juss) on the growth stages of *P. falciparum* FCR-3. The experimental laboratoric study used "post-test only with control design". RPMI 1640 used as culture medium for cultivation of *P. falciparum*. Treated drug was the extract of neem leaves dissolved in dimethyl-sulfooxide and prepared into 7 levels concentration (3.125; 6.25; 12.5; 25; 50; 100 and 200 µg/mL). Negative control was culture medium with the malarial parasites. After cultured, synchronized, micromalarial culture were divided into control and treated groups then incubated in CO_2 Candle Jar at 37 ºC for 72 h. Each 8 h the percentage of parasitemia were measured for observing the activity of the extract on the growth stages of *P. falciparum*. After incubation, supernatant fluid was removed without disturbing the erythrocyte layer. Parasitemia was calculated by made the thin blood smear from the erythrocyte layer and stained with 10% Giemsa for 30 min. The antimalarial activity of the extract was calculated by counted the fifty percent of growth inhibition 50 (IC_{50}) using probit analysis. The result showed that the neem leaves extract can inhibit the growth of *P. falciparum* FCR-3 on mature schizont stage and the fifty percent inhibitory concentration (IC_{50}) of the extract was 3.86 µg/ml after 32 h incubating. The result indicated that the extract has an antimalarial activity on *P. falciparum* FCR-3 *in -vitro* [82].

Antiulcer Activity: The antiulcer effect was obtained with nimbidin in preventing acetyl salicyclic acid, indomethacin, serotonin-induced gastric lesions or streets as well as cysteamine induced duodenal ulcers or histamine [83], [84]. Leaf extract of *A. indica* (Neem) shows antiulcer effect was reported by Garg *et al*., and the inhibition of mucus depletion and most cell defragmentation as possible mechanism. Bandyopadhyay *et al*., isolates the phenolic glycoside as an active constituent, whose characterization and mechanism are under investigation. Therefore, *Azadirachta indica* offers another option for an effective antiulcer drug and which is safe [85].

This study was carried out to evaluate the antiulcer activity of the Aqueous Extract (AE) of the leaves of *A. indica* in Wistar rats. Gastric ulcerations were induced by pyloric ligation, aspirin, and cold restraint stress. AE was used in doses of 150, 300, and 600 mg/kg body weight per OS. Distilled water served as the control and ranitidine 20 mg/kg body weight intraperitoneal as the reference standard. The Ulcer Index (UI) and Percentage Inhibition (PI) values were determined in each model. The volume of gastric contents, free acidity, total acidity, and pH were measured in the pyloric ligation-induced ulcer model. AE showed a dose-dependent and significant ($p < 0.05$) decrease in the UI and an increase in the PI in all models employed compared to the control group. AE caused a dose-dependent decline in the gastric content volume, free acidity, and total acidity. The leaves of *A. indica* possess significant antiulcer activity and act *via* multiple mechanisms [86].

Wound Healing Activity: The wound healing properties in small animal model, the excision and incision wound models were used and water,

ethanol-water (1:1, v/v) and ethanol extracts were applied topically (15% w/w in ointment base). In the excision wound model, wound contraction, hydroxyproline content, DNA content, protein content, and nitric oxide levels were estimated after 14 days of topical treatment along with histopathological examinations. In the incision wound model, wound breaking strength was determined after 10 days of topical application of different extracts of AI. The animals treated with water extract of AI exhibited significant increment in rate of wound contraction (93.39%, $P < 0.01$), hydroxyproline content (13.31 ± 6.65 mg/g of dry tissue, $P < 0.001$), DNA content (20.99 ± 0.68 µg/100 mg of tissue, $P < 0.01$), protein content (100.53 ± 7.88 mg/g of wet tissue, $P < 0.01$) and nitric oxide level (3.05 ± 0.03 mMol/g of tissue, $P < 0.001$) as well as in wound breaking strength (289.40 ± 29.45 g, $P < 0.01$) when compared with vehicle control group which was also supported by histopathological studies. The water extract of stem bark of AI possesses significant wound healing property, validating its traditional use [87].

Herbal Cosmetics: "The cure of all ailments". Neem's role as a wonder drug is stressed as far back as 4500 years ago. Some of its health restoring benefits. Effective in skin infection, rashes and pimples, immunity booster, anti obesity, blood purifier for beautiful and healthy skin, piles, hair disorder and oral disorders [90].

CONCLUSION: By reviewing the importance of neem tree in national, regional and international perspective there is an urgent need to study its diversity and develop effect measures to store it for present and future use. At the same time it is also necessary to undertake ethnobotanical studies to link its various therapeutic uses with folklore remedies used by tribes in various areas of its occurrence. For the last few years, there has been an increase tendency and attention in neem research. Quite a significant amount of research has already been carried out during the past few decades in exploring the chemistry of different parts of neem. Several therapeutically and industrially useful preparations and compounds have also been marketed, which generates enough encouragement among the scientists in exploring more information about this medicinal plant. Neem is provides various pharmacological activities like anti-inflammatory, antimalarial, antibacterial, anti-allergic, anti-dermatic, anti-ulcer, anti-fungal, insecticidal, larvicidal and other pharmacological activities of neem plant and medicinal uses

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