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International Journal of Pharmacognosy and Chinese Medicine
ISSN: 2576-4772

A Review on Pharmacological Aspects of Arista

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Review Article

Volume 3 Issue 3

Received Date: June 04, 2019

Published Date: June 19, 2019

DOI: 10.23880/ipcm-16000167

Abstract

Arista (*Azadirachta indica*) is rapidly growing evergreen plant found commonly in India, Africa and America. Arista is the Sanskrit name of neem tree meaning "reliever of sickness'' and hence is known as "sarbarogaribarini". This contains many active chemicals *viz*., alkaloids, flavonoids, triterpenoids, phenolic compounds, carotenoids, steroids and ketones, biologically most active compound is azadirachtin. All parts of neem tree are commonly used in traditional Indian medicine for household remedy against various human diseases. This plant showed various medicinal activities such as antiallergic, antifungal, antibiotic, antidermatic, antibacterial, anti-inflammatory, insecticidal, larvicidal, antimalarial, and antiulcer. It also showed anti-cancerous and anti-HIV activity. Azadirachtin-A dose-dependently reduced hepatocellular necrosis in CCi_4 imduced hepatotoxicity. The present paper enlightens the pharmacological profile of Arista *vis-à-vis* taxonomical status, chemical constituents and some major market formulations containing Arista as an important ingredient.

Keywords: *Azadirachta Indica*; Arista; HIV Activity; Hepatoprotective; Azadirachtin-A

Introduction

Azadirachta indica is rapidly growing evergreen plant found commonly in India, Africa and America [1]. It is used in Ayurvedic medicine from more than 400 years due to its medicinal characteristics. Neem is also called as "Arista" in Sanskrit, a word that means imperishable, perfect and complete [2]. Arista is the Sanskrit name of neem tree meaning "reliever of sickness'' and hence is known as "sarbarogaribarini". In India, it is known as "Village dispensary". The importance of the *Azadirachta indica* (neem) tree has been admitted by the US National Academy of Sciences which published a report in 1992 entitled Neem-a tree for solving global problems [3].

All parts of neem tree are commonly used in traditional Indian medicine for household remedy against various human diseases [4]. Neem is native of India and naturalized in most of tropical and subtropical countries are of great medicinal value and distributed widespread in the world. The chemical constituents contain many biologically active compounds that can be extracted from neem, including alkaloids, flavonoids, triterpenoids, phenolic compounds, carotenoids, steroids and ketones, biologically most active compound is azadirachtin, it is actually a mixture of seven isomeric compounds labelled as azadirachtin A-G and azadirachtin E is more effective [5]. It gives maximum useful non-wood products [leaves, bark, gum, oil, neem cake flowers, fruits, seed] than any other tree species known to have antiallergic, antifungal, antibiotic, antidermatic, antibacterial, anti-inflammatory, insecticidal, larvicidal, antimalarial, antiulcer and other biological activities. The phytoconstituents *i.e.* alkaloids, glycosides, flavonoids and saponins are antibiotic

principles of neem plants. These antibiotic principles are actually the protective mechanism of the plants against different pathogens [6].

Origin and Distribution of Arista

Two species of Azadirachta have been reported, *Azadirachta indica* A. Juss- native to Indian subcontinent and *Azadirachta excelsa* Kack confined to Philippines and Indonesia. Neem is the member of the Mahogany family. There are estimated 25 million trees growing all over India of which 5.5% are found in Karnataka and it is in the third place next to the Uttar Pradesh (55.7%) and Tamilnadu (17.18) occupying the first two places respectively. The other states of India where neem tree is found growing includes Andhra Pradesh, Assam, Bihar, Gujarat, Delhi, Kerala, Madhya Pradesh, West Bengal along with Andamon & Nicobar Islands, the Union territory [2].

Taxonomic Classification

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

Table 1: Taxonomic Classification of Arista.

Vernacular names [7]
Hindi**:** Nim, Nimb
English: Indian lilac, Margosa tree, Neem tree
Sanskrit: Arista, Nimbah, Nimba
Punjabi: Bakam, Drekh, Nim
Bengali: Nim, Nimgachh
Guajarati: Limbado, Limbra, Limdo
Kannada: Bemu, Bivu
Tamil: Vempu
Telgue: Vepa

Botanical Description

Neem is a large tree growing about 25 m in height with semi-straight to straight trunk, 3 m in girth and spreading branches forming a broad crown. It has rough dark brown bark with wide longitudinal fissures separated by flat ridges. The leaves are compound, imparipinnate, each comprising 5-15 leaflets. The compound leaves are themselves alternating with one another. It bears many flowered panicles, mostly in the leaf axis. The sepals are ovate and about 1cm long with sweet scented white oblanciolate petals. It produces yellow drupes that are ellipsoid and glabrous 12-20 mm long. Fruits are green, turning yellow on ripening, aromatic with garlic like odour. Fresh leaves and flowers come in March-April. Fruits mature between April and August depending upon locality [2].

Chemical Constituents

Neem (*Azadirachta indica*) elaborates a vast array of biologically active compounds which are structurally complex and chemically diverse. Every part of this plant is used as herb [8]. The extracted chemical constituents of different parts of neem tree contained many biologically active compounds, including triterpenoids, alkaloids, phenolic compounds, flavonoids, carotenoids, ketones and steroid. The most biologically active compound is azadirachtin. This compound belongs to the *C*-seco limonoids which was classified as tetranortriterpenes. It is actually a mixture of seven isomeric compounds labelled as azadirachtin M and azadirachtin N [5]. The Neem oil comprised of the bitter principles which was formed from biologically active compounds that were isolated from different parts of the plant including meliacin, azadirachtin, gedunin, nimbidin, nimbolides, nimbin, salanin, meliacin and valassin [9]. Besides, the seeds also contain tignic acid responsible for the distinctive odour of the oil [10].

Pharmacological Investigation of Arista

Anti Cancerous Activity: A study was designed to examine the cellular and molecular mechanisms of azadirachtin and nimbolide for cytotoxic effects in the human cervical cancer (HeLa) cell line. The finding revealed that azadirachtin and nimbolide, dose of 250-300 mg/kg extensively suppressed the viability of HeLa cells in a dose dependent manner by inducing cell cycle arrest at G1/G2 phase accompanied by p53-dependent p21 accumulation and down regulation of the cell cycle regulatory proteins [11].

In addition to this, dose of 500 mg/kg of ethanolic NLE was found to induce apoptosis in 4T1 breast cancer cell [12]. NLE also plays role in the induction of dose-dependent reduction in chronic lymphocytic leukaemia cell viability with significantly observed apoptosis, and the extract causes loss of mitochondrial outer membrane permeability and nuclear translocation of apoptosis inducing factor [13].

Treatment with extract inhibited N-methyl-N-nitrosourea-induced mammary tumor progression and treatment was also extremely efficient in dropping mammary tumor burden and in suppressing mammary

tumor progression even after the stop of treatment [14]. Another study was performed to examine the effect of leaf extract on PI3K/Akt and apoptotic pathway in prostate cancer cell lines. Result of the study demonstrated that extract gives 50% inhibition at a dose of 100 µg/ml in both PC-3 and LNCaP cells and extract decreased the protein expression of PI3K as well as p-Akt and the mRNA expression of Akt-1 and Akt-2 in both the cells [15].

The treatment of MCF-7, HeLa, and normal cells with leaf extract differentially suppresses the growth of cancer cells in a dose and time-dependent manner through apoptosis. Moreover, lower dose combinations of leaf extract with cisplatin resulted in synergistic growth inhibition of the cells compared to the individual drugs. The limonoids of neem have proven its role in the target of oncogenic signaling kinases and transcription factors mainly and JAK/STAT signaling pathways. Moreover, limonoids target several pathways that are abnormal in cancer and are ideal candidates for cancer chemoprevention and therapy [16].

Antibacterial Activity: The petroleum ether, methanol and aqueous extracts of the leaves of *Azadirachta indica* were screened for their anti-microbial activity using the cup plate agar diffusion method. They were tested against six bacteria; two Gram positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and four Gram-negative bacteria (*Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Salmonella typhi*). The susceptibility of the microorganisms to the extracts of these plants was compared with selected antibiotics. The methanol extract of *Azadirachta indica* exhibited pronounced activity against *Bacillus subtilis* [17]. Gram Positive bacteria showed higher susceptibility as compared to gram negative bacteria.

The antibacterial activity is performed by using cup plate agar & diffussion disc method. The minimium inhibitory concentration of ethanol extract of *A.indica* against *Staphylococus aureus* were 0.87 mg/ml &1.74 mg/ml. For *Bacillus subtilis* were 0.36 mg/ml & 0.72 mg/ml and for *E.coli* they were 1.26 mg ml & 2.52 mg/ml, respectively. The investigation shows that the ethanolic extract of *A.indica* has great potential against Gram positive bacteria [18].

NLEs have been found to show zones of inhibition further confirming that they contain antimicrobial properties, and the extract showed significantly greater zones of inhibition than 3% sodium hypochlorite [19]. The effects of the neem limonoids such as azadirachtin, salannin, deacetylgedunin, gedunin, 17-hydroxyazadiradione, and deacetylnimbin on *Anopheles stephensi* were evaluated. Azadirachtin, salannin, and deacetylgedunin showed high bioactivity at all doses. In addition, azadirachtin was the most potent in all experiments and produced almost 100% larval mortality at 1 ppm concentration [20]. Antiviral activity of neem bark extract confirmed that bark extract extensively blocked HSV-1 entry into cells at 50–100 µg/ml concentration [21].

Antidiabetic Activity: Diabetes was induced in animals by intraperitoneal injection of streptozotocin (50 mg/kg body weight) dissolved in 0.01M citrate buffer (pH 4.5). Streptozotocin induced diabetes in rats by degradation of β-cells. 72h after streptozotocin injection diabetes was confirmed in rats showing blood sugar level 262 ± 17 mg/dl. *A.indica* leaf extract at a fixed dose (500 mg/kg) which was found to be the working dose from our previous experiments was fed daily to stable hyperglycemic rats (72h after stz. injection) for 7 days consecutively. The normal control and stz induced diabetic control animals received normal saline in place of leaf extract. Total cholesterol, total lipids and triglycerides of serum were estimated using standard methods. The values of serum lipid parameters were near to normal in case of animal receiving *A. indica* leaf extract [22].

Diabetes was induced by Alloxan monohydrate (100 mg/kg b.w). The neem root extract was given in the doses of 200, 400 & 800 mg/kg. The doses 200 and 400 mg/kg showed reduction in blood sugar level, but it was not statistically significant. When the neem root extract was given in the dose of 800 mg/kg showed significant ($p<0.05$) reduction in blood sugar level by 54% after 4 hours as comparison to control [23].

Anti-HIV/AIDS Activity: In HIV/AIDS patients, a 12-week oral administration of acetone water neem leaf extract had a significant influence *in vivo* on CD4 cells (which HIV reduces) without any adverse effects in the patients. Of the 60 patients who completed treatment, 50 were completed laboratory-test compliant. The mean levels of CD4 cells increased by 159% in 50 patients, which is a major increase; the number of HIV/AIDS pathologies decreased from the 120 baseline to 5; and significant increases were experienced in body weight (12%), hemoglobin concentration (24%), and lymphocyte differential count (24%) [24]. The crude extract of neem exhibited strong HIV-1Reversed transcriptase inhibitory activity. At concentration of 50 &100µg/ml of the extract significantly reduced 0.005% polymerase activity of the recombinant HIV-1 RT with the peak inhibition of 92.4% at 100µg/ml [25].

Hepatoprotective Activity: Medicinal plants and their ingredients play a pivotal role as hepatoprotective without any adverse complications. A study was performed to investigate the hepatoprotective role of azadirachtin- A in carbon tetrachloride (CCl_4) induced hepatotoxicity in rats and histology and ultrastructure results confirmed that pretreatment with azadirachtin-A dose-dependently reduced hepatocellular necrosis. Furthermore results of the study show that pretreatment with azadirachtin-A at the higher dose levels moderately restores the rat liver to normal [26].

Azadirachta indica seed oil was evaluated for its hepatoprotective effect. Liver damage was induced using CCL_4; hepatotoxicity was induced by the administration of 1.0 ml/kg of CCL_4 subcutaneously to 72 healhty rats of both sexes with wt. range 145-315g. The seed oil of *Azadirachta indica* was orally administered daily in various doses of 0.25 ml/kg, 0.5ml/kg &1.0 ml/kg for 14 days. At higher doses 0.5 ml/kg & 0.1 ml/kg, showed a healthy liver, at low dose 0.25 ml/kg neem treatment showed only moderate accumulation of fatty tissues [27].

Treatment of Periodontitis: Neem leaf extract can help reduce bacteria and plaque levels that cause the progression of periodontitis. In 2004, the International Journal of Dentistry published a study showing that subjects using neem gel experienced periodontal improvement when compared to a control group. A study published the same year in the Journal of Ethno pharmacology revealed similar findings. To take advantage of this herb's bacteria-reducing properties, uses a mouthwash made with several drops of neem leaf extract mixed in water and uses it twice daily [28].

Antifertility Activity: The Neem seed oil (NSO) and leaf extracts act as powerful spermicide and significantly inhibited spermatogenesis, decreased sperm motility, count and cessation of fertility. These conditions were reversed by the withdrawal of neem products 4 - 6 weeks later. No significant effect on loss of libido or potency. Furthermore, NSO possess anti-implantation and abortifacient properties found spermatozoa of human and rhesus monkey were immotile and die within 30 min of contact with NSO in an intravaginal dose of 1 mL. Vaginal biopsy revealed no side effect, while radio-isotope studies indicate non-absorption in the vagina and non-antiovulatory [29].

Anti Trypanosomal Activity: Some investigators have studied the efficacy of extracts of *A. indica* against different species of *Trypanosomes*, a protozoal organism responsible for incidence of sleeping sickness (trypanosomiasis) and nagana disease in man and animals. Using Microtiter Plate Bioassay demonstrated that fractions of chloroformic extracts of *A.indica* leaves markedly inhibited growth of *Trypanosoma cruzi epimastogotes* with ultra-structural changes such as cell division disruptions [30]. Similarly, the phytochemical in neem, azadirachtin a tetranortriterpenoid, when administered as a single dose (2.5mg/kg) through blood meal, blocked the development of *T. cruzi* and induced a permanent resistance of the vector against reinfection with *T. cruzi* [31].

Molluscidal Activity: Molluscidal activity refers to the ability of a substance to kill one or more members of the Snail family, through direct effect on the adult organism or any of the stages in the life cycle. Using criteria such as feed intake, cessation of crawling, mucus secretion, lack of response to mechanical stimuli, decomposition and even enzyme profiles, the molluscidal effect of *A. indica* products on several species and sub-species of snails has been evaluated [32]. At concentration of 350, 500 and 700 mg/kg extracts of neem seed oil showed no significant effect but those of the bark, roots and leaves produced mortality at 500 and 700 mg/kg after exposure of *Limicolaria aurora*, for 48–72 h [33].

Anti-Inflammatory Activity: Anti-inflammatory effect of neem plants has been reported by various studies. In an experimental study based on rat models, nimbidin from neem trees was used orally to evaluate its anti-inflammatory response. It was confirmed that the phagocytosis was inhibited, and further, the migration of macrophages to their peritoneal cavities was significantly inhibited in response to inflammatory stimuli. Moreover, *in vitro* exposure of rat peritoneal macrophages to nimbidin also inhibited phagocytosis [34].

The anti-inflammatory activities of neem fruit skin and its specific ingredient, azadiradione, have also been evaluated. The results have concluded that the animals treated with 100 mg/kg dose of this fruit skin extract and azadiradione exhibited significant anti-inflammatory activities [35].

Furthermore, the anti-inflammatory effect of neem seed oil has been examined on rats using carrageenan-induced hind paw edema. The result has confirmed that this oil showed increased inhibition of edema with the progressive increase in dose from 0.25–2 ml/kg body weight. Using the dose of 2 ml/kg body weight, this oil showed maximum inhibition of edema at the 4th hour of carrageenan injection [36].

Immunomodulatory Effect: Neem oil is also used as a nonspecific immunostimulant as it plays a role in the

activation of cell-mediated immune mechanisms to elicit an enhanced response to subsequent mitogens Besides this, neem infusion has been found to successfully improve the antibody titer growth performance when used at the level of 50 ml/l of fresh drinking water [37].

Larvicidal & Nematicidal Effects: Larvicidal and nematicidal properties are the underlying bases for the use of neem products for control of agricultural pests. These effects have been reported for methanolic extracts of defatted neem seed kernels. In eggs, immature and adult stages of *Hyalomma anatolicum excavatum* at concentrations of 1.6, 3.2, 6.4 and 12.8%, observed a significant increase in the hatching rate during the first 7 days post treatment, giving incompletely developed and dead larvae, and after 15 days, it resulted in hatching failure, induced a significant increase in mortality rates of newly hatched larvae, unfed larvae and unfed adults [38]. Similarly, azadirachtin extracted from neem seed and ethanolic extract of grounded seed blended into cow manure or administered orally to cattle, exhibited effects similar to those of insect growth regulators as they were found to be larvicidal against hornfly *(Haemotobia irritans, L),* stable fly *(Stomoxys calcitrans)* and house fly *(Musca domestica)* [39]. The larvicidal effect of *A. indica* on *Aedes aedes aegyptica* (Linnaeus) and *Culex quinequefaciatus* third instar larvae of *Drosophila melanogaster* and fifth instar larvae of *Manduca sexta* have been demonstrated [40].

There are also reports that aqueous extract of de-oiled neem seed kernel caused 100% mortality in the fourth instar larvae and pupae at the concentration of 100 ppm with no significant effect on the development period of *Culex quinquefasciatu* and anopheline pupae [41].

Anti-Ulcerogenic Activity: The effect of neem extracts on gastric secretion and gastro-duodenal ulcer. In albino rats found that stem bark extracts of *A. indica* significantly inhibited gastric ulceration induced by indomethacin (40 mg/kg b.w) when administered orally at a dose of 100–800 mg/kg b.w or intraperitoneally at a dose of 100–250 mg/kg b.w. This action was found to be accompanied by a dose-dependent decrease in total gastric acidity, and when administered in combination with histamine (1 mg/kg b.w) and cimetidine (0.12 mg/kg b.w) in situ, *A. indica* at 250 mg/kg b.w, significantly inhibited the basal and histamine-induced gastric acid secretion.The anti-ulcerogenic effect of *A. indica* has indeed been demonstrated in clinical trials involving humans. In that trial, which involved administration of lyophilized aqueous extracts to Indian patients suffering from acid-related problems and gastroduodenal ulcers for 10 days at daily twice dose of 30 mg, it was observed that neem bark extract not only has therapeutic potential for controlling gastric hypersecretion and gastroesophageal and gastroduodenal ulcers, but can also heal the duodenal ulcers as monitored by Barium Meal X-ray and endoscopy. Using important blood parameters for organ toxicity, these investigators further established the relative safety of the extracts when administered at 30–60 mg/kg b.w for 10 weeks [42].

Cardioprotective Effect: As a folk medicine, the neem tree extract is well known for its cardioprotective properties as well. In this regard, *A. indica* extract at a dose of 250–1000 mg/kg significantly restores most of the hemodynamic, biochemical, and histopathological parameters. The study further concluded that neem extract shows equipotent cardioprotective activities as compared to Vitamin E [43].

Marketed Formulations of Arista

S.No	Marketed Products	Active Ingriedents	Manufactured	Uses
1.	Tooth Paste-Total care	Calcium carbonate glycerin, acetic acid, sodium lauryl, sodium benzoate, neem leaf	Manufactured by Mountain 8 Tooth Material Co., Ltd	To prevent plaque formation & strengthening the gums
2.	Face-wash: Khadi Neem Face Wash	Aqua, neem oil, wheat germ oil, tea tree oil	Manufactured by M.O.H.D173 Ambala, Haryana	To prevent reoccurrence of pimples & acne
3.	Face-wash: Himalaya Neem Face wash	Turmeric & neem leaves, aqua, stearic acid, sodium lauryl, disodium EDTA	The Himalaya Drug Company Makali, Banglore	Nourishes the skin & cleanses all impurities
4.	Soap: Neem Soap	Sodium palmate, neem oil, talc, perfume, aqua, hard paraffin, vitamin E, glyceryl monosterate	Jyothy Laboratories Ltd., Kerala	Moisturizing the skin & brightening the skin

5.	Tablet: Herbal Neem Tablets	Azadirachtin, Nimbin, Nimbidin, Nimbolides	Shriji herbal products ltd. in boroveli, Mumbai	Control skin diseases, itching, reduces rashes, effect on piles, effective in D.M
6.	Syrup: Himalaya Neem Syrup	Nimba (62.5mg), methyl paraben sodium, propyl paraben sodium, sodium benzoate	The Himalaya Drug Company Makali, Banglore	Control long standing skin allergies & infection
7.	Body Cream: Biocare Neem Cream	Aqua, isopropyl palmitate, glycerin, stearic acid, tocopheryl acetate, neem extract, lemon oil, methyl paraben, fragrance	Gold Street Middx. OJO, England	Moisturizing the skin & lightening the skin
8.	Shampoo: Lever Ayush Antidandruff Neem Shampoo	Neem (11mg), amla (4.4mg), rosemary (20mg), shampoo base q.s, methyl iso thiazolinone	Herbal Concepts Health Care pvt.ltd. Ranipur, Haridwar (Uttarakhand)	Promoting hair growth & dandruff free hair & scalp
9.	Skin Cream: Soothing Neem Cream	Aqua, ceto-stearyl alcohol, sweet almond oil, sunflower oil, beeswax, rosemary, neem leaf extract	A. Vogel Bioforce Pvt. Ltd., Switzerland	Used for eczema, psoriasis, athelete's foot, ringworm, scabies
10.	Powder: Neem Leaf Powder	Neem leaf powder 100gms	Isha Agro Developers Pvt. Ltd., Lonavala, Pune	To cleanse the body system, promote immunity, for healthy blood sugar

Table 2: Formulations containing Arista available in the market.

Conclusion

Neem has become valuable plant in the world which shows the solutions for hundreds to thousands problems. *Azadirachta indica* (Neem) is a rapidly growing evergreen well known tree found generally in various regions of world like America, Africa and India. Most of the varied, but desirable biological and pharmacological activities of the plant extracts and purified bioactive compounds are observed at doses within the estimated safe doses. It provides information mainly on various biological activities like antibacterial, anti-inflammatory, insecticidal, larvicidal, anticancer, antiulcer, cardioprotective activity and other biological activities of neem plant and medicinal uses. Neem tree such as root, bark, leaf, flower, seed and fruit together possesses biological activities. Various compounds have been obtained from various parts of neem. Biological activities of few of them have been studied. Neem has become valuable plant in the world which possesses significant therapeutic activity. There may be present numerous *Azadirachta* species in the nature, but mainly work has been carried out only two species *Azadirachta indica* and *Azadirachta excels*. It is a high time to explore more Azadirachta species with their therapeutic profile that not only will be a quality research work rather it will be beneficial to the society and mankind.

References

1. Pingale S (2010) Hepatoprotection study of leaves of *Azadirachta indica*. Juss. Internationl Journal of Pharmaceutical sciences review and research 3(2): 37-42.

2. Girish K, Bhat SS (2008) Neem –A green treasure. Electronic journal of Biology 4(3): 102-111.

3. Kausik B, Chattopadhya ishita, Banerjee Ranjiit k, Uday B (2002) Biological activities and medicinal properties of neem. Current science 82(11): 1336-1345.

4. Drabu S, Khatri S (2012) Neem: Healer of all ailments. Res J Pharma Biol Chem Sci 3(1):120-126.

5. Verkerek RHJ, Wright DJ (1993) Biological activity of neem seed kernel extract and synthetic azadirachtin against larvae of plutella xylostella L. Pesticide science 37(1): 83-93.

6. Faiza A, Muhammad S, Muhammad A (2009) Antibacterial Activity of Various Phytoconstituents of Neem. Pak J Agri sci 46(3): 23-35.

7. Shankara P, Tomar L, Bansal V (2008) Review on Neem: Thousand Problem One Solution. International Research Journal of pharmacy 2(12): 97-102.

8. Seddiek SA, Khater HF, El Shorbagy MM, Ali AM (2013) The acaricidal efficacy and ivermectin against Sarcoptes scabiei var. cuniculi in experimentally infested rabbits. 112(6): 76-79.

9. Amitava G, Piyali C, Partha R, Somnath B, Tanushree N, et al. (2009) Bioremediation of heavy metals from neem *(Azadirachta indica)* leaf extract by chelation with dithizone. Asian J Pharm Clin Res 2(1): 87-92.

10. Sharma P (2011) Review on neem *(Azadirachta indica*): Thousand problems one solution. IRJP 2(12): 97-102.

11. Priyadarshini RV, Murugan RS (2010) The neem limonoids Azadirachtin & nimbolide induce cell cycle arrest & mitochondria-mediated apoptosis in human cervical cancer cells. Free Radic Research 44(6): 624-634.

12. Othman F, Motalleb G, Rahmat A, Fakurazi S, Pei Pei C, et al. (2011) Extract of *Azadirachta indica* leaf induces apoptosis in 4t1 breast cancer in mice. Cell Journal 13(2): 107-116.

13. Chitta KS, Khan AN, Masood A, Paulus A, Qadeer A, et al. (2014) Neem leaf extract induces cell death by apoptosis & autopagy in B-Chronic lymphocytic leukemia cells. Leuk Lympoha. Asian journal of Pharmacology 55(3): 652-661.

14. Arumugam A, Agullo P, Boopalan T, Nandy S, Lopez R, et al. (2014) Neem leaf extracts inhibits mammary carcinogensis by altering cell proliferation, Apoptosis & angiogenesis. Cancer Biol Therapy 15(1): 26-34.

15. Gunadharini DN, Elumalai P, Arunkumar A (2011) Induction of apoptosis & inhibition of P13K/Akt pathway in PC-3 & LNCaP prostate cancer cells by ethanolic neem leaf extract. Journal Ethnopharacol 134(3): 644-650.

16. Nagini S (2014) Neem limonoids as anticancer agents: Modulation of cancer hallmarks & oncogenic signaling. Enzymes 36: 131-147.

17. Shravan KD, Santosh KM (2011) In-vivo Antidiabetic evaluation of Neem leaf extract in STZ induced rats. Journal of applied pharmaceutical sciences 1(4): 100-105.

18. Prashar pratibha, Pruthi Hitesh (2012) In vitro antibacterial activity of *Azadirachta indica* against pathogenic bacteria. Journal of Pharmacy Research 5(1): 363-364.

19. Ghonmode WN, Patil AK, Balsaraf OD, Tambe VH, Saujanya KP, et al. (2013) Comparison of the antibacterial efficiency of neem leaf extracts & 3% sodium hypochlorite against *E. feacalis*-An in vitro. Journal International oral health 5(6): 61-66.

20. Nathan SS (2005) Effects of neem limonoids on the malaria vector Anopheles stephensi Liston. Acta Trop 96(1): 47-55.

21. Tiwari V, Darmani NA, Shukla D (2010) In vitro antiviral activity of neem bark against herpes simplex virus type-1 infection. Phytother Res 24(8): 1132-1140.

22. Zlatkis A, Zak B, Biyle AJ (1953) A new method for the direct determination of serum cholesterol. Journal of Laboratory & Clinical Medicine 41(3): 486-492.

23. Patil P, Mane A, Verma S (2013) Antidiabetic activity of alcoholic extract of neem root bark. National Journal of Physiology Pharmacy & Pharmacology 3(2): 142-146.

24. Mbah AU, Nubila T, Shu EN, Chijioke CP, Nubila T, et al. (2007) Fractioned neem leaf extract is safe & increases CD+ Cell levels in HIV/AIDS patients. Am J Ther 14(4): 369-374.

25. Awah FM, Rutherford J (2011) In vitro anti-HIV/AIDS potentials of *Azadirachta indica* leaf extract. African Journal of Parmacy & Pharmacology 5(11): 1353-1359.

26. Baligar NS, Ahmed M (2014) Hepatoprotective activity of the neem based constituent azadirachtin-A in carbon tetrachloride intoxicated Wistar rats. Canadian Journal of Physiology & pharmacology 44(1): 64-68.

27. Gomase PV, Rangari VD, Verma PR (2011) phytochemical evaluation & hepatoprotective activity of fresh juice of young stem bark of *Azadirachta indica.* International Journal of pharmacy & pharmaceutical sciences 3(2): 55-59.

28. Reddy Dwarakanadha P, Satyanaryana T (2010) Local drug delivery of herbs for Treatment of Periodontitis. International research journal of Pharmacy 1(5): 245-251.

29. Sinha P, Tomar L, Sharma V (1984) Exploiting Neem Resources for Improving the quality of life in Taraba State, Nigeria. International Journal of Agriculture & Biology 24(2): 530-532.

30. Yanes A, Finol HJ (2004) Effects of *Azadirachta indica* extracts from leaves on *Trypanosoma cruzi* growth & ultrastructure. American journal of insecticide science 36(2): 149-154.

31. De Azambuja P, Garcia ES (1992) Effects of azadirachtin on *Rhodnius prolixus*: immunity & Trypanosoma interaction. International Journal of Pharmacy 87(5): 69-72.

32. Rao IG, Singh A, Singh DK (2003) Effect of single & binary combinations of plant derived molluscides on different enzyme activities in the nervous tissue of *Achatina fulica*. Journal of apply Toxicol 23(1): 19-22.

33. Ebenso IE (2004) Molluscidal effects of neem extracts on edible tropical land snails. Pest Management Science 60(2): 178-182.

34. Kaur G, Sarwar Alam M, Athar M (2004) Nimbidin suppresses function of macrophages & neutrophills. Relevance to its anti-inflammatory mechanisms. Research journal of Pharmacology 18(5): 419-424.

35. Ilango K, Maharajan G (2013) Anti-inflammatory activities of *Azadirachta indica* fruit skin extract & its isolated constituent azadiradione, Research journal of Pharmacology 27(16): 1463-1467.

36. Naik MR, Bhattacharya A (2014) Study of anti-inflammatory effect of neem seed oil on infected albino rats. Journal Health Research Review 1(3): 66-69.

37. Durrani FR, Chand N, Sultan A (2008) Immunomodulatory & growth promoting effects of neem leaves infusion broiler chicks. Sarhad J Agric 24(4): 655-659.

38. Abdel Shafy S, Zayed AA (2002) In vitro larvicidal effect of plant extract of neem seed oil on egg, immature, adult stages of *Hyalomma anatolicum excavatum*. Vet Parasitol 106(1): 89-96.

39. Miller JA, Chamberlain WF (1989) Azadirachtin as a larvicide against the horn fly, house fly. J Econ Entomol 82(5): 1375-1378.

40. Mitchell MJ, Smith SL, Morgan ED (1997) Effects of the neem tree compounds azadirachtin, salanin, nimbin on ecdysone 20- monooxygenease activity. Arch Insect Biochem Physiol 97(1-2): 916-923.

41. Rao DR, Reuben R (1995) Development of combined use of neem & water management for the control of culicine mosquitoes in rice fields. Med Vet Entomol 9(1): 25-33.

42. Bandyopadhyay U, Biswas K, Sengupta A, Moitra P, Dutta P, et al. (2004) Clinical studies on the effect of neem bark extract on gastric secretion & gastodudenal ulcer. Life Sciences 75(24): 2867-2878.

43. Peer P, Trivedi PC, Nigade PB, Ghaisas MM, Deshpande AD (2008) Cardioprotective effect of Azadirachta indica on isoprenaline induced myocardial infarction in rats. Int J Cardiol 126(1): 123-126.