

***Azadiarachta indica*, A natural Pharmaceutical Agent**

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ABSTRACT

Since the origin of mankind, the use of plants and their derivatives remains an important aspect of human life to cure various ailments. Such pharmaceutical uses of plants are the cheaper and safe sources for disease management against the expensive allopathic drugs with various side effects. At present the use of traditional medicines is not gaining favors from masses but the rapidly increasing pharmaceutical industry is also shifting itself from the synthetic chemicals towards the natural extracts. The *Azadiarachta indica* is one of the most important and extensively used medicinal plants. Its uses as antiseptic agent and as cure and preventive remedy have been known since remote past. The extracts of *A. indica* have a proven anti-diabetic, anti-oxidant, bactericidal, anti-termite, pesticide activities. This plant can be used to treat various intestinal ailments. It has a proven wound healing capacity. Various types of tumors are being treated by the phytochemicals derived from this miracle tree. Its leaves bark and fruit constitute very useful natural components that can be used to cure various ailments. The oil of *Azadiarachta* has a significant importance in cosmetic industry. Biologically active compounds are isolated from different parts of *A. indica* like meliacin, nimbidin, gedunin, salanin, nimbolides, valassin, nimbin and Azadirachtin are present in *A. indica* oil.

Key Words: *Azadiarachta indica*, leaf extracts, Medicinal plant, ethnobotany, anti-oxidant

1 Introduction:

The plant derivatives are of vital importance for mankind especially in the management of integrated diseases as well as for the cure and prevention of human and cattle ailments. There are many proven facts regarding to the different properties of plants and their roles in the enhancement of antioxidant activities in humans and other animals, modulation of genetic pathways, and role in disease prevention. The plant products have fewer side effects and are cheaper when used as therapeutic agents as compared to expansive pharmaceutical drugs. (T. Efferth and E. Koch., 2011). All the modern medicines and drugs have been derived from the natural sources. (Krishnaiah., et al., 2011). More than 50% the drugs in modern clinical approaches are originated from the naturally synthesized products. Different bioactive compounds are present in the *A. indica* tree which can be extracted from it. (Seddiek SA, et al., 2013).

All over the Asian and African subcontinent *Azadirachta indica* is the most important and widely cultivated tree which produces different types of drugs related to therapeutics and pharmacological industries. *A. indica* is an ever green, fast growing tree with hard, moderately thick and straight trunk and it has long spreading branches. Its bark is longitudinally fissured and rough. The mature tree of *A. indica* may attain the height of 7-15 m (23-50 feet). However this plant is widely cultivated in West Africa and but it is quite native to Asia (Velusamy, P., et al., 2015). All parts of *A. indica* have some medicinal properties. So all of its parts are used to treat several diseases (GRIN, 2017; Velusamy, et

al., 2015). In Nigeria malaria and related diseases are cured by the use of different parts of *A. indica*. Its use may also cause some toxicological and other adverse effects. (GRIN, 2017). The common names of this plant are 'neem', 'Indian iliac' or *A. indica* tree. In Ethnology *A. indica* tree name is derived from Sanskrit 'Nimba' which is a Hindi noun. (Compact Oxford English Dictionary, 2013). *A. indica* tree is categorized in the genus *Azadirachta* of *Meliaceae* family. It is the well-known species of this genus which is commonly present in Pakistan, Sirilanka, Maldives, India and Bangladesh. Typically it is widely cultivated in the tropical regions of the world but its cultivation in the semi-tropical regions and islands of southern Iran is also common. Neem oil is the valuable by-product of *A. indica* which is produced by its all body parts. (GRIN, 2017)

2 Ecological features of *A. indica*:

The ecological feature of *A. indica* is that it is drought resistant. In normal life it can live in areas which can thrive life in sub-humid to sub-arid conditions with an average rain fall up to more than 47 inches. It can grow in the soils having different textures but the soil having sandy texture with its deep and well drained conditions is best for its cultivation. It can tolerate high temperature in the tropical and subtropical regions which have existed at the annual mean temperature of twenty-one degree Celsius to thirty-two degree Celsius. But the temperature of about four degree Celsius is not favorable for this plant (Compact Oxford English Dictionary, 2013). *A. indica* is not sensitive to the water quality, so this tree can fulfill its water uptake demand by taking the merest trickle of water which may be present in that region. This tree is commonly growing for obtaining shade in schools, temples, streets and in other public places (Compact Oxford English Dictionary, 2013).

3 Phytochemical values of *A. indica*:

Biologically active compounds are isolated from different parts of *A. indica*. Major biologically active compounds are meliacin, nimbidin, gedunin, salanin, nimbolides, valassin, meliantriol, nimbin and Azadirachtin. These compounds make the principal taste of its oil. Seeds of *A. indica* also have a compound called tignic acid, contributing towards the distinctive odour. The kernel also contain 30%-50% of the oil and many other active ingredients which are altogether called as the tri-terpenes or limnoids and are mainly used for the formation of soaps, pesticides and in the pharmaceutical industries. (Djenontin, 2012). These compounds make it insecticidal, pesticidal, anti-feedants, insect repellent, growth inhibitors, attractants of different organisms, or as chemosterilant (Hashmat. et al., 2012). Including antibacterial, antifungal and anti-inflammatory activities the pharmaceutical activities have been reported which are due to different compounds extracted from *A. indica*. The biological compounds which are present in *A. indica* such as Azadirachtin M and N showed their effects on arthropods, besides other major activities such as anti-protozoal and anti-typanosomal activities. Analytical study of *A. indica* plant explores the presence of tetra-nortriterpenoids. (Kusari, et al., 2012).



Figure 1: Graphical representation of *A. indica* Abstract

4 Medicinal importance of leaves:

Azadirachta indica leaves are useful to treat various foot fungi, as immunity booster, to relieve neuromuscular pains and as anti- termites. Leaves are also used as natural remedy for acne, and cure of acquired immune deficiency syndrome (AIDS), chicken pox (Debjit, et al. 2010). The aqueous extract of leaves possess the significant amount of hypo-lipidemic, hypoglycemic, hepato-protective, hyposensitive anti-fertility activities. (Sunarwidhi, et al., 2014; Koul et al., 2014). Leaves are also effective in cure of diabetics, udder-infection remedy and against bleeding, fever, lice, hypoglycemic and antiglycemic effects. For the elevation of immunity against the malarial attacks, dental problems, against headache, skin diseases, gastrointestinal disorders, and malaria, in appetite stimulation, febrile illness and as insect-repellents *A. Indica* plant parts are used in Indian continent (W. Sujarwo et al., 2016). But on the other hand, Bali (Indonesia) people use the same leaves against the headache, hurt-burn and as diuretic and for the stimulation of appetite. (Sujarwo et al., 2016; Melati et al., 2019).

5 Ethnobotanical importance of *A. indica* oil:

Its oil contain different principal compounds which are used for the formation of pesticides, soap, face washes, creams, spreys, and other nature derived products and in pharmaceutical industry (Djenontin, 2012; Rosaline, et al., 2013). *A. indica* oil shows antiplaque activity (Elavarasu, et al., 2012; Kusari, et al., 2012).

6 Importance of roots and bark in ethnobotny:

A. indica rootbark is used for the control of ticks and fleas of pets, against infections such as acne, eczema, AIDS, psoriasis, heart diseases, allergies, ulcer, hepatitis, Dental care and in cure of several

other diseases. Extract of *A. indica* bark is used against the inhibition of microbes which cause different dental problems due to the presence of antioxidant properties. (Rahmani and Aly, 2015).

7 Ethnobotanical importance of *A. indica*:

Different biologically important compounds are present in different parts of *A. indica* such as leaves, fruit, seeds, bark and roots. These all compounds play an important role in ethno-botany. (Saddiek SA et al., 2013; Sing A et al., 2014)

7.1 Pesticidal activity of *A. indica*:

The principal importance of *A. indica* based on three main aspects. **A:** Its efficacy which has been reported against a wide range of mites, insects, nematodes, snails and fungi; **B:** It is considered as harmless to beneficial birds, insects earth worms and for humans. The US EPA powers also approve the use of *A. indica* tree on food yielding crops as it is also harmless to food crops.(EPA, 2012). **C:** it not generates the resistance in affected pests. (EPA, 2012).

7.2 Antibacterial activity of *A. indica*:

The leaf extract expresses antibacterial activities. A study reveals that *A. indica* leaf extract show zone of inhibition of bacterial colony as compared to the 3% of sodium hypochlorite. The leaf extract also have the capability to inhibit the biofilm formation of *Pseudomonas aeruginosa* (Harjai, et al., 2013). The *A. indica* oil which is extracted from the different parts has anti-plaque properties and it is very useful for living organisms to eliminate plaques at vital places and organs (Elavarasu, et al., 2012). Another study has revealed that the *A. indica* leaf extract show antibacterial effects on *Enterococcus faecalis* and *Candida albicans*. Oil from *A. indica* also show effective responses against the wide variety of bacteria Viz., *E. cerus*, *B.coli*, *P. vulgaris* *S. aureus*, *pumilus*, *S. dysenterae*, *K. pneumoniae*, *E. faecalis*, *S. salivarius*, *S mutant*, *S. mitis*, *S. sanguis*, *M. tuberculosis*, *S. resistant* strains.(Rosaline, et al., 2013).The methanolic extract of *A.indica* has the remarkable efficacy to inhibit the production and growth of *B. subtilis*.(Rosaline, et al., 2013).

7.3 Role of *A. indica* extract on dental caries and bacterial strains

A. indica bark is used against the antibacterial activities in a number of tooth pastes and tooth powders and in other oral care industries. (Balappanavar,et al., 2013; Chava, et al., 2012). The *A.indica* bark is used for the tooth and gum health as it has many active and safe therapeutical ingredients (Kaushik, et al., 2012). The earlier studies have confirmed that the chewing sticks have higher antibacterial actions against the *S. mutant*. But the *S. salivarius*, *S. mitis*, and *S. sanguis* showed less response to the antibacterial action of *A. indica* and make colonies on the dental areas in mouth (Chava, et al., 2012). The chloroform extract and petroleum ether extract also have the strong antimicrobial activities. At its higher concentration *A. indicacan* inhibit the growth of many strains of bacteria (Lekshmi, et al., 2012; Chatterjee, A. et al., 2011; Vinothkumar, et al., 2013)

Several in vitro studies revealed the importance of *A. indica* prepared medicament which are valuable for elimination of *C. albicans* and *E. faecalis* and their mixed state. *A. indica* extract also used as oral hygienic medicament and is used with proper professional maintenance. (Ghonmode, et al., 2013).

7.4 Use of flowers in the preparation of eyeliner:

The soot of *A. indica* flower with animal fat is used to make eye-liner, which is used in Pakistan, India, Egypt and other eastern areas of the world.

7.5 Anti-carcinogenic and oncogenic properties of *A.indica* extract:

The natural plant products show an important role in tumor growth inhibition. (Rahmani, 2015). There are various mechanisms such as cell mediated immunity, boosting up of lymphocytic activities, natural killer cells and many other mechanisms. These all are able to destroy the cancer cells along with other living cells such as viruses and bacteria. *A. indica* extract can also protect the body by controlling the liver damage through increasing antioxidant levels of body against carcinogenic agents. (Debjit, et al., 2010; Chitta, et al., 2014). Nimbolide- fruit of *A.indica* shows apoptosis. Its activities which mainly showed anticancer effect (Elumalai, et al., 2012). The extract has capability to inhibit mammary tumor progression. It was shown that the 50% cancer cells are inhibited by using the dose of *A. indica* extract in a quantity of 100 µg/ml. It has the capability to suppress the protein and mRNA expression in cancerous and normal cells. (Gunadharini, et al., 2011). The leaf and cisplatin combination in inhibition of cancer lines have been proved to be effective in cancer positive organisms (Sharma et al., 2014; R. Pual, et al., 2008). The supersession of oncogene expression can be done by the use of pre-decided dose of *A. indica* leaf extract. (Othman, et al., 2012). *A. indica* fruit extract induces different effects in the signaling of transcription factors and the regulation of pathways of oncogenic signaling kinases. (Nagini S., 2014).

7.6 Role of *A. indica* extract as free radical scavenger

Free radicals and reactive oxygen species are the main offenders in the development of different diseases. However, the diseases can be prevented by the neutralization of free radical activities through antioxidant. (Nunes, et al., 2012). *A.indica* plant extract played a role as antioxidant and free radical scavenger in many organisms. *A. indica* causes antioxidative enzyme activation which then causes the prevention of destructive damage by ROS. (Rahmani and Aly, 2015). Nimbolides, ascorbate and Azadirachtin show the dose dependent properties in free radical scavenging. The ethanolic extract of the *A.indica* oil has the higher scavenging capability in relation to other plant parts (Nahak, et al., 2011).

7.7 Effect of *A. indica* constituents in angiogenesis

A complex process that is essential for the metastasis and growth of tumors and formation of new blood supply is called angiogenesis. It is regulated by the differential effects of regulators and activators. (Alzohairy 2016; Metwally FM, et al., 2014) Studies have reported that many plants and their components cause the modulation of tumour suppressor genes, apoptosis, cellular proliferation and various other pathways which cause the inhibition of malignant cell growth. (Rahmani, et al., 2015). The results of another study also revealed angiogenesis effect of *A. indica* by using the treatments of various concentrations of methanolic extract of root fractions in the water soluble form on zebra fish embryos. (L.P.B. Lavanya, et al., 2015).

7.8 Role of *A. indica* in hepato-protection

Natural products which are extracted from the medicinal plants played a major role in hepato-protection. The hepatocellular necrosis can be reduced by pretreatment with Azadirachtin-A. In dose dependent manner it not only causes reduction of hepatotoxicity but it can also restore liver to normal functioning besides other major constituents of *A. indica*, nimbolides also play a protective role against CCl₄, induced liver toxicity in rats. (Abdel Moneim, et al 2014).

7.9 Use of *A.indica* seed oil as anti-inflammatory ingredient

The use of *A. indica* seed oil is common in dose dependent manner, as anti-inflammatory purposes is common Asian and African sub continents. (Naik, et al. 2014). In combination with carbon tetrachloride

the *A.indica* seed oil showed anti-inflammatory, anti-pyretic, anti-nociceptive and analgesic properties.(Ilango, et al., 2013; Abdul Moneim et al., 2014).

7.10 As Anti-malarial agent

Ancient people use the *A. indica* plants in the preparation of antimalarial medicines due to the presence of different active ingredients in different parts since centuries. They use different parts especially leaves twigs and bark etc, of *A. indica* in making drugs, for making smoke which act as the best insect and mosquitoes repellents and help for escaping from malaria. (Akin-Osanaiya, et al.2013).

7.11 Anti-nephrotoxic effect

The methanolic extract of *A. indica* has proved very helpful as anti-nephrotoxic agent. In the nephrotoxicity use of different parts of *A. indica* plant play an important role in its controlling (Abdel Moneim, et al., 2014).

7.12 Wound-healing effect

Besides other medical properties, *A. indica* leaves are known to use in the process of wound healing.(Singh A., et al., 2014). Another study revealed the anti-inflammatory and neovascularizing properties of *A. indica* extract which could cause wound healing actions. (Osunwoke, et al., 2013).

7.13 Effects of *A. indica* in neuro-protection

The standardized extract of *A. indica* revealed the significant decrease in the allodynia, hyperalgesia, motor nerve conduction and coordination in peripheral neuropathy, oxidative, nitrosative stress inflammatory mediators and mRNA of Bax and iNOS were also significantly (Kandhare, et al., 2017). Neuro-protective properties of *A. indica* were investigated by leaf extract dose before and after the CP injection revealed the presence of well-preserved brain tissues in neurotoxicity induced rats. (Abdel Moneim, 2014).

7.14 Antifertility potential of *A. indica* plant

The alcoholic *A. indica* flower extract was used in study of fertility, ovulation, fetal morphology, estrous cycle and the results confirmed the marked changes by the *A. indica* extract. Prolonged diestrus phase and alteration of estrous cycle with the reduction in shedding of ova was the prominent results by the induction of *A. indica* flower extracts (AbdelMoneim, 2014).

7.15 Insect repellent properties of *A. indica*

A. indica has many biologically active compounds which have capabilities to distress the insects. Azadirachtin –a powerful insect anti-feedants compound causes disruption on metamorphosis of moth larvae to elaborate its insect repellent properties. The synthetic chemicals such as N, N-diethyl –m-toluamide, a potentially carcinogenic repellent. The sensitive strains of malarial parasites and chloroquine resistant strain of *P. falciparum* larvae are affected by *A. indica* seed extract at both their sexual and asexual stages. The study about Azadirachtin revealed its potential in control of ectoparasites of ornamental fish. (AbdelMoneim, 2014).

7.16 Role of *A. indica* in gastro-protection

All the non-neoplastic and neoplastic disorders of biliary system, gastrointestinal tract. Liver, anus, pancreatic issues are cured by the *A. indica* extract since centuries.(Abdel Moneim, 2014).

7.17 Anti-fungal effect of *A. indica*

A. indica have potential anti-fungal properties (K Anjali, et al., 2013). Ethanol and methanol extracts have been used against the growth of different fungal strains (Shrivastava, et al., 2014). Growth in seed born fungi *Rhizopus*, *Aspergillusniger*, *alternariasolani* and *Aspergillus* were significantly controlled by use of greater amount of extract. *A. indica* extract in the mixture of ethyl acetate (Jabeen, et al., 2013; Septiyanti, et al., 2019).

7.18 Health and Personal Care products of *A. indica*

The products such as shampoo, creams, face-washes, tooth-paste, soap, tea, lotions etc, used in health and personal cares are derived from seeds, leaf and other parts of *A. indica* (Brototi et al., 2011).

7.19 Larvicidal Activity explored by *A. indica*

The insect larvae causes the crop damage. To compensate this larval active use of *A. indica* extracts in different concentrations. It may cause 70-90% mortality of larvae of different arthropods. (Aditi, et al., 2011).

7.20 Anti-hypercholesteremic as well as Antihypertensive properties of *A. indica*:

The extract of *A. indica* in a study was used with the collaboration of DOCA salt application prevent the hypertension in laboratory reared rats. It decreases the blood and serum cholesterol without intervention in serum proteins, uric acid and urea in rats which demonstrated the anti-hypercholesteremic activity of *A. indica* (Ogbuewu, 2011).

8 Ld50 values of *A. indica* in its Safety and Toxicity

The management and measurement of toxicity in the natural compounds is crucial before their application. *A. indica* product on animal models and in the clinical trials showed its positive response, but they also exhibit the presence of the adverse effect in high doses. *A. indicaleaf* extract is very helpful in cure of diabetics but it also reduces blood glucose level if taken in large quantity. Several studies were reported which explored the poisoning of *A. indica* oil causing vomiting, metabolic acidosis, disturbance in liver metabolism, and other issues in children. The study based on rats model elaborate low dose effect of *A. indica* extract. Anti-anxiety and encephalopathy were reported in low dose toxicity by *A. indica* (Alzohairy., 2016). A study was performed by use of chicks to elaborate the toxic effects of *A. indica* and results showed that the dose dependent clinical sign of intra-peritoneal LD50 value of 4800mg Kg⁻¹ of the *A. indica* leaf caused toxicity in chicks (Deng, et al., 2013). The LD50 values of leaf and seeds of *A. indica* were taken by using spectrophotometer. The leaf showed 6.2mL/Kg and seeds showed 9.4 mL/Kg values. (S. A. Bakr, 2013). This showed the LD50 value of stem extract as 489.9mg kg⁻¹, leaf extract had 31.62g per kilograms and *A. indica* oil had 31.95g per kilograms of the body weight (Akin-Osanaiya, et al., 2013).

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