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AZADIRADIONE: A MULTI-TARGETS COMPOUND WITH NEW THERAPEUTIC APPROACH

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ABSTRACT

Azadirachta indica is known for its use in the traditional treatment of malaria, leprosy, cancer, intestinal helminthiasis, respiratory disorders, inflammation, constipation, blood morbidity, diabetes, rheumatism, biliary infections, dermatological complications, itching, ulcers and more. Azadiradione (AZD), as a major constituent in the seed of *A. indica*, was found to have many different biological activities related to the traditional uses of *A. indica*. It was found effective against inflammation peptic ulcer, Huntington's disease, mycobacteria, diabetes, cancer, malaria along with other activities as bone cells differentiation and mineralization, anti-nociceptive, anti-fungal, cytotoxic and insect anti-feedants activities. Azadiradione may present a potential multi-targets with new therapeutic approach.

KEYWORDS

Azadiradione, *Azadirachta indica*, Anti-diabetes, Anti-inflammatory, Huntington's disease, Anti-malarial and Multi-target agent.

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INTRODUCTION

In 1960, the structure of limonin was determined[1], since then huge number of naturally occurring limonoid derivatives (Figure No.1) have been isolated and characterized structurally. Azadiradione (AZD, Figure No.2) is a tetra cyclic triterpenoid isolated from the evergreen tree, *Azadirachta indica* (neem plant, miracle tree)[2]. Neem is well known for its medicinal properties. It has been largely used in ayurveda, unani and homeopathic medicine for various ailments[3,4]. Neem oil, bark and leaf extracts have been

therapeutically used as folk medicine in the treatment of malaria, leprosy, cancer, intestinal helminthiasis, respiratory disorders, inflammation, constipation, blood morbidity, diabetes, rheumatism, biliary infections, dermatological complications, itching, ulcers and more[2,5]. Most of the mentioned activities have been related to AZD.

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STRUCTURE AND CHEMICAL FEATURES of AZD

As showed in Figure No.2 AZD contains α, β-unsaturated C3 ketone and4, 4-dimethyl moiety in A-ring. It also possesses critical furan ring attached to the D-ring along with another ketone[6] and acetyl group at ring B. There are also two α and β methyl moities between rings B and C and C and D, respectively.

AZD exist in *Azadirachta indica* seeds as a major terpenoid[6,7,8] and fruit coat[6] along with other triterpenoids[2]. Also, AZD was isolated from *Chisocheton siamensis* seeds[9]. The detailed chemical synthesis steps of AZD was described by Corey and Hahl[10].

BIOLOGICAL ACTIVITIES OF AZD

AZD and neem were found to have numerous biological and therapeutic properties which have been identified since ancient times and are extensively used in ayurveda, unani, and homoeopathic medicine. Literature reveals that neem possess anti-inflammatory, anti-arthritic, antipyretic, hypoglycemic, antigastric, antifungal, antibacterial, and antitumor properties as described below:

AZD and Anti-fungal activity

AZD showed moderate anti-fungal activity against *Puccinia arachidis* (groundnut trust) with comparison with cedrelone (a tetranortriterpenoids isolated from *Toona ciliate*) which showed high activity against *P. arachidis*. The modification of A or B ring (Figure No.1) or the change of the functional groups in cedrelone reducing the effectiveness of the anti-fungal activity for the AZD[11].

AZD and Anti-inflammatory activity

AZD showed significant anti-inflammatory activity against acute paw oedema induced by carrageenan at the doses of 50 and 100 mg/kg with comparable results to that of diclofenac sodium as a positive control in rats[12].

AZD and Anti-nociceptive

AZD showed significant anti-nociceptive effects in mice at doses 50 and 100 mg/kg by writhing reflex and hot-plate methods. The authors related this inhibition to the inhibition of synthesis of arachidonic acid metabolites[12].

AZD and Anti-malarial activity

Antimalarial activity was evaluated against the parasite *Plasmodium falciparum* (K_1, multidrug resistant), using the method of Trager and Jensen (1976)[13]. AZD showed significant anti-malarial activity with IC_{50} 2.91µg/mL comparing with 0.784µg/mL for the crude extract of *Chisocheton siamensis* from which AZD was isolated[9].

AZD and Cytotoxic activity

AZD showed moderate cytotoxic activity against breast cancer (MCF-7), human small cell lung cancer (NCI-H187) and oral human epidermal carcinoma (KB) cell lines[9]. Low concentrations of AZD were found to be non-toxic to AR42J (pancreas) cell line but effectively inhibit the activity of secreted alpha amylase which could be helpful in the management of diabetes[6].

AZD and Anti-diabetic activity

AZD was found to inhibit human and porcine pancreatic alpha amylase same as other structurally similar limonoids. Some structure features of AZD might be responsible for the inhibitory activity of AZD including; α, β-unsaturated C3 ketone and4, 4-dimethyl moiety in A-ring[6].

AZD and Anti-mycobacterial activity

AZD was most effective against *Mycobacterium tuberculosis* compared with other limonoids isolated form *Chisocheton siamensis*[9].

AZD and Osteoblast differentiation and mineralization activity

Azadirachta indica terpenoids including AZD were found to promote osteoblast differentiation and mineralization in vitro and *in vivo*[2]. Osteoblast differentiation is further marked by the formation of mineralized nodule composed of inorganic hydroxyapatite (HA) (Ca_{10} $(PO_4)_6$ $(OH)_2$ and the organic component type 1 collagen[14].

AZD and peptic ulcer

Peptic ulcer disease, including gastric and duodenal ulcer, affects many populations around the world which caused by *Helicobacter pylori* (the leading cause of ulceration). Azadiradione was found to have protective and treating effects against peptic ulceration *in vivo* models. AZD showed protection against cold restraint induced ulcer, pyloric ligation induced ulcer and aspirin induced ulcer in rats. On the other hand, AZD showed significant anti-ulcer activity against ethanol induced ulceration. AZD also reduced the free acid and total acid significantly and upregulatedmucin secretion. A proton pump is a membrane bound enzyme that catalyzes H+ transport by breaking of ATP hydrolysis. Thus, the inhibition or the blockade of H+ K+-ATPase may account for suppressed acid secretion. The anti-secretary mechanism of AZD is through the inhibition of H+ K+-ATPase. AZD was also found to improve the levels of prostaglandin which known to have a positive impact upon the secretion of mucus and bicarbonate by the gastric and duodenal epithelial cells[5].

AZD and Huntington's Disease

Huntington's Disease (HD) is an inherited autosomal disorder caused by a mutation in huntingtin gene, the resulting mutant huntingtin protein goes through proteolysis resulting in a repeated polyglutamine resides (the amino terminal of the mutant protein) which results in impairment of cellular protein quality control system and deterioration of brain functions. The prolonged treatment of HD model mouse by AZD was proven effective in the improvement in the disease pathology which manifested as an improvement in the progression of body weight and motor functions deterioration along with the increase the of life span. AZD, also, decreased the mutant protein aggregate accumulation in HD rats[15,7].

OTHER ACTIVITIES OF AZD

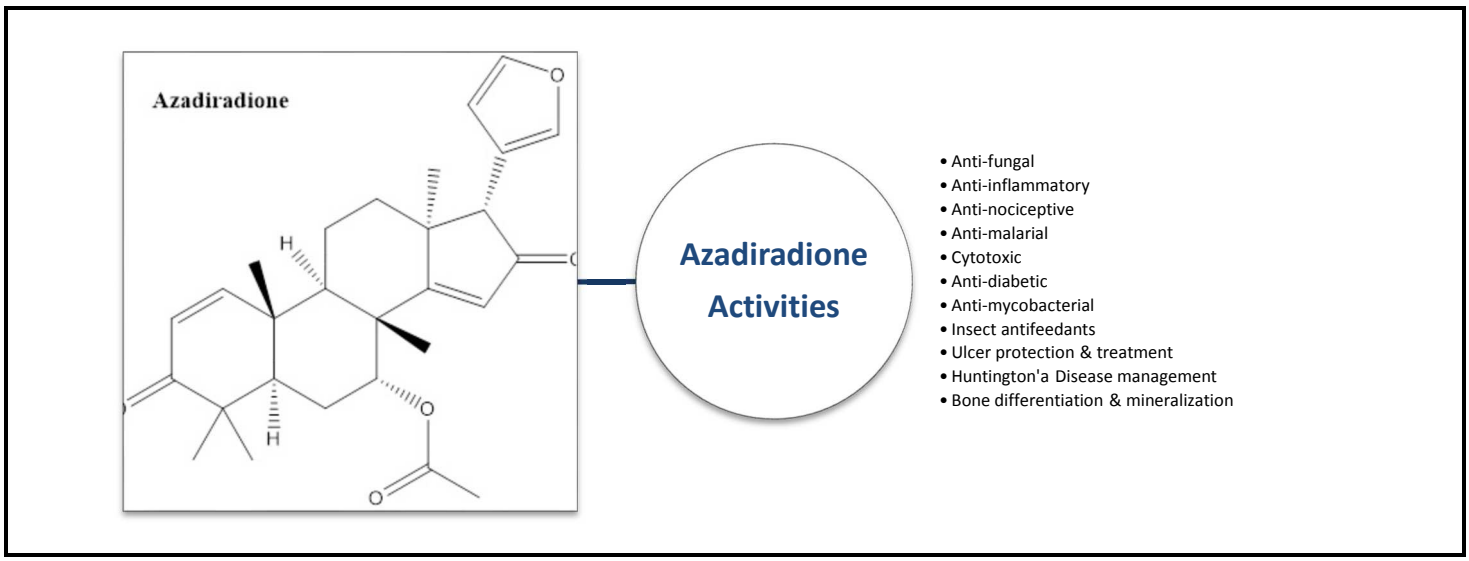
Limonoids are known for their insect anti-feedants activities[16] on the top of these compounds is AZD and Havanensin. This could replace the currently known insecticides for being bios elective, biodegradable, and very active at low concentration[17]. The fragment responsible for activity was sensitized with overall yield of 9% for AZD[16]. The detailed synthesis steps are described by Fernandez *et al.*[16,17].

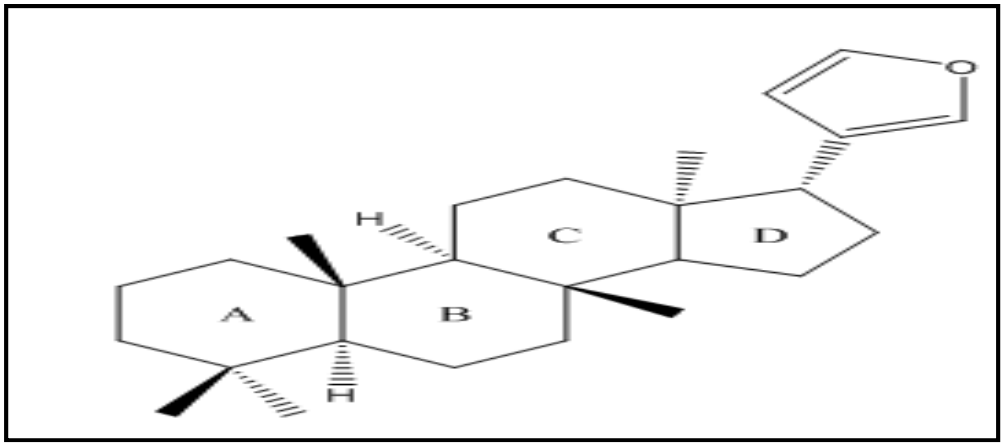
FUTURE PRESPECTIVE

Recently, liposomal nanoform of AZD was successfully prepared in Fab-Lab (liver Research Lab, Mansoura University, Egypt).The high zeta potential (-38.13 ± 1.89) of liposomal nanoform of AZD indicated the repulsion between the particles preventing the aggregation. Liposomal AZD showed an average size of 323.4 ± 9.79 and a narrow size distribution (0.594 ± 0.0331). In addition, AZD loaded liposomes had a zeta potential value of -38.13 ± 1.89. Furthermore, the encapsulation efficiency of the drug (EE %) was determined by using high performance liquid chromatography. The analysis showed that EE% was around 82.02 ± 9.01%. Additionally, the morphology of the particles was examined by scanning electron microscope. The results revealed that the nanoparticles have a roughly spherical shapes. In conclusion, the employed method produced a liposomal encapsulated form of the biologically active AZD which worse further analysis for the determination of the bioavailability and tissue distribution of AZD Vs liposomal nanoparticles *in vivo* in order to increase the activity of AZD as anticancer potential drug[18].

AZD could be considered as a multi-target agent and could be used in several therapeutic models as cited by Badria *et al.*(2018)[19].

GRAPHICAL ABSTRACT





FigureNo.1: Basic Limonoid skeleton

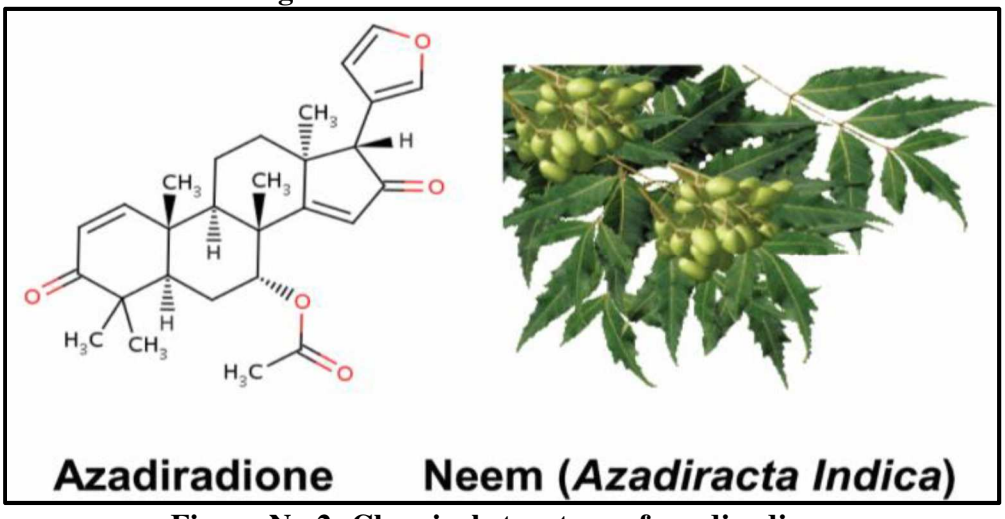


Figure No.2: Chemical structure of azadiradione

CONCLUSION

Azadiradione (one of the major constituent in the seed of *A. indica*) is found to have many different biological activities related to the traditional uses of *A. indica*. It was found effective against inflammation peptic ulcer, Huntington's Disease, mycobacteria, diabetes, cancer, malaria along with other activities as bone cells differentiation and mineralization, anti-nociceptive, anti-fungal, cytotoxic and insect anti-feedants activities.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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