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A Mini-review on the Phytochemistry and Pharmacobiology of *Azadirachta indica* A. Juss. (Meliaceae): Towards future research directions

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Mini-review Article

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ABSTRACT

Medicinal plants are suppliers of molecules used in both modern and traditional therapy. One of these plants is *Azadirachta Indica* (also known as the neem tree).Originally from Asia (India), this plant is currently widespread and cultivated in several countries in the world, including in Africa, because of its extraordinary therapeutic properties. A survey carried out on the Internet revealed that *A. indica* contains various secondary metabolites such as: Azadirone, Nimocimol,

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Azadiradione, Epoxyazadiradione, nimbinin, salannin, nimbanal, salannol acetate, nimbandiol, tannins, saponins, cardiac glycosides, steroids, gedunin, nimbinene, nimbolide, mahmoodin, margolonone, isomargolonone, azadirachtin, epicatechin, catechin, phenols, alkaloids, flavonoids, steroids, triterpenoids, anthraquinone, anthocyanins. The main structures of these different molecules were drawn using the ChemBioDraw Ultra 12.0 software package. As a result, it has been demonstrated that these compounds confer several pharmacological properties on the neem tree, including anticancer, antifungal, antidiabetic, antibacterial, antiviral, antiplasmodial, and anthelmintic activities. Because of its high anthocyanin content, *A. indica* could be an interesting candidate for the development of an anti-sickle cell drug.

Keywords: Azadirachta indica; neem tree; medicinal plants; biological activities; anthocyanins.

1. INTRODUCTION

Medicinal plants play a very important role for people around the world, especially in developing countries [1]. Since time immemorial, man has resorted to the therapeutic values of plants to alleviate various ailments to which he is exposed [2]. According to the World Health Organization (2002), nearly 90% of the population in developing countries relies on medicinal plants for healthcare [3].The pharmacological properties of traditional medicine have received a renewal of interest from researchers throughout the world because of increasing knowledge [4-6]. *Azadirachta Indica*, also called neem tree, is one of these medicinal plants with therapeutic properties.This plant belongs to the Meliaceae family [7, 8]. It has been known since ancient times [9, 10] through its extraordinary medicinal properties that earned it the name of the divine tree [10]. Literature reports that all parts of neem (flower, leaf and bark) contain very interesting secondary metabolites with therapeutic purposes [7, 11].

It has been shown that this plant contains compounds such as Azadirone, Nimocimol, Azadiradione, nimbinin, salannin, nimbanal, steroids, gedunin, nimbinene, isomargolonone, azadirachtin, epicatechin, catechin, phenols, alkaloids, saponins, flavonoids, steroids, triterpenoids, anthraquinone, anthocyanins [12-14]. These compounds are responsible for the outstanding therapeutic properties of *A. indica* [10].

From India, where A. indica originates [15, 16], to Sub-Saharan African countries, this plant is used in different pharmacopoeias to treat many diseases [10]. It is proved that *A. indica* is endowed with several pharmacological properties such as anticancer, antifungal, antidiabetic, antibacterial, antiviral, antiplasmodial, anthelmintic activities [13, 14, 17-21]. Apart from its usefulness as a source of therapeutic molecules, *A. indica* is particularly known for its repellency against insect pests of crops and, as such, is an environmentally friendly insecticide [21, 22].

However, the anti-sickle cell activity of *A. indica* has not yet been demonstrated. Previous research has shown that anthocyanins are among the compounds that play a major role in normalizing sickle cell disease [23, 24]. In this regard, *A. indica* is also rich in anthocyanin compounds [25, 26]. Thus, these possibilities could be investigated by researchers to assess the anti-sickle cell properties of *A. indica*.

2. METHODS

2.1 Search Strategy and Eligibility Criteria

In order to find appropriate and pertinent data for our survey, we used search engines for scientific items such as Google Scholar, PubMed, Sciences Direct, Hindawi. Only free and downloadable papers were taken into account. The keyword *Azadirachta indica* or neem tree was used on each search site to find the relevant papers. This keyword was often associated with terms referring to the biological activities of this plant. To be selected, the year of the item's publication had to be between 2000 and 2021. Papers published before 2000 were systematically eliminated, regardless of the relevance of their information. Then, only items that focused on at least one biological activity and/or on the chemical composition of *A. indica* were selected. Finally, the selected papers were divided and classified according to the type of biological activity.

3. RESULTS AND DISCUSSION

3.1 Botany Description

A. indica is a tree reaching a high of 15 to 35 meters. The long compound and imparipennate

leaves measure 20 to 40 centimeters, with 5 to 15 leaflets. The bark is rough and dark brown and fissured vertically. Young fruits are green, and become yellow when they are ripe. The flowers are white and aromatic, and they are axillary, with panicles that are more or less hanging and can reach a length of 25 centimeters. The inflorescences are branched and carry from 150 to 250 flowers. An individual flower is about 6 millimeters long and 10 millimeters wide [22, 27-29].

*The f*lowers, leaves and seeds of *Azadirachta indica* are shown in Fig. 1.

3.2 Origin and Geographic Distribution

It is accepted that *A. indica* is Indian originally. But nowadays, this plant is spread over the world, such as Australia, African countries, Asia and South America [8,10,30].

3.3 Ethno-botanical Uses

Bhowmik et *al*. [28] reported that *A. indica* is largely used by Indian people to treat several diseases. For example, a paste obtained by grinding leaves is applied to the eyes as a remedy for night blindness and conjunctivitis. They also claim that this plant has the ability to cure skin disorders such as eczema, and that it can be applied to the skin to relieve the itching and pain caused by the disorder. Boiling the leaves and using them to wash the body can help to eliminate acne-causing bacteria.

Many organs of neem are used in the treatment of diseases. Twigs are used for dental health and the leaves are used to treat skin disorders. Placed on beds, neem leaves repel insects in the household. Additionally, the Indian population employs decoction of the leaves, which is an effective remedy for various ailments [10].

Gupta et *al*. [2] confirmed that Nigeria people employ A. indica to treat malaria. The use of *A. indica* oil as a remedy against some bacterial strains was reported in the DRC [31].

3.4 Phytochemistry of *Azadirachta indica*

In this plant, all parts are used as a remedy in different folk medicines [32]. Thus, literature reported various secondary metabolites isolated from *A. indica* such as Azadirone, Nimocimol, Azadiradione, Epoxyazadiradione, nimbinin, 6-Deacetylnimbin, salannin, nimbanal, 3-Deacetylsalannin, salannol acetate, nimbandiol, tannins, saponins, cardiac glycosides, steroids, gedunin, cyclic trisulfide, nimbinene, 6-Deacetylnimbinene, nimbolide, mahmoodin, margolonone, isomargolonone, azadirachtin A, azadirachtin B , NB-II peptoglycan, gallic acid, epicatechin, catechin, phenols, alkaloids, saponins, flavonoids, steroids, triterpenoids, anthraquinone, aminoacids, anthocyanins [12-14, 28, 29, 33]. Babatunde et al. [34] isolated several compounds from crude oil extracts of A. indica leaves, including Eicosane (9.7662%), Diacenaphtho (1,2-j:1 ', 2 '-l)] fluoroanthene (11.301%), Phenol, 4- [4-methoxyphenyl]- (11.84%) and (3Ar, 6S, 9ar)-1,2,3,4,5,6,7,9a-octahydro-8-methyl-3a,6-methano-3ah-cyclopentacycloocten-10-one (36.883%) in steam extracted oil; Eicosane (10.259%), Diacenaphtho [1,2-j:1], 2 -lanthene (13.51%), and Butanamide,-1,2,3,4,5,6,7,9a-octahydro-8-methyl-3a,6-methano-3ah-cyclopentacycloocten-10-one (10.72%), n-Hexadecanoic acid (14.688%) and 9,12,15-Octadecatrienoic acid, (Z,Z,Z)- (34.719%).

The chemical structures of some compounds isolated from A. indica are given in Fig. 2.

3.5 Biological activities of *A. indica*

3.5.1 Anthelmintic activity

Ethanolic and aqueous extracts of three plants (*Calotropis procera*, *Azadirachta indica* and *Punica granatum*) were evaluated for their anthelmintic activity. The LC-50 A. indica values were 21.02 mg/ml ± 4.6. The mean mortality index (MI) of *A. indica* was 0.90 for both ethanolic and aqueous extracts. After 4 hours of exposure, the above mentioned extracts demonstrated significant anthelmintic effects [13].

3.5.2 Anticancer activities

Jeba Malar et *al*. [14] carried out the anticancer activity of two methanolic extracts of *A. indica* and *M. azaderach* using MCF cell lines at concentrations of 50, 100, 150, 200 µg/ml. The results indicated the highest anticancer effect of *A. indica* methanolic extract at the concentration of 200 µg/ml with 65.5% of inhibition and the lowest percentage of viability activity was 60.4%. Additionally, the IC50 value was 165.5629 µg/ml.

Another study was conducted to determine the anticancer activity of the supercritical extract of

fresh *A. indica* leaves against LNCaP-luc2 (prostate cancer cells). The results demonstrated the high activity of the supercritical extract by causing inhibition of dihydrotestosterone-induced androgen receptor and prostate-specific antigen levels. Additionally, integrin β1, calreticulin, and focal adhesion kinase activation in LNCaP-luc2 and PC3 prostate cancer cells were suppressed [35].

3.5.3 Antimicrobial activity

3.5.3.1 Antibacterial activity

Rajendaran et *al*. [36] carried out a study on the synthesis of different groups of silver nanoparticles (AzI-CO, AzIACO, AzI-MCO and AzI-MACO) from leaves of *A. indica*. Their antimicrobial activity against gram positive and gram negative pathogens as well as Aspergillus Niger fungal species was evaluated. The results showed that AzI-MACO nanoparticles had the best activity against all the mentioned pathogens.

Chinnasamy et *al*. [37] reported antibacterial activity using aqueous extracts of *A. indica* leaves to synthesize silver nanoparticles (AI-AgNPs). Silver nanoparticles concentration (1,000 mg/mL) demonstrated high antibacterial activity against Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus. The minimum inhibitory concentration and minimum bactericidal concentration values were 390 and 780 mg/mL respectively.

Arévalo-Hijar et *al*. [38] purchased methanolic extracts of two plants (*Azadirachta indica and Moringa oleifera*) were evaluated and their antibacterial and cytotoxic properties were determined in vitro using strains of Enterococcus faecalis (ATCC 29212). The results show that at a concentration of 25 g/ml, the antibacterials were effective for the first 24 and 48 hours, and the minimum inhibitory concentration (MIC) was 75 g/ml. Low concentrations did not show toxicity against cell lines.

Leaf extract of *A. indica* was used to synthetize MoO3 (MO) microrods. While *A. indica* leaves modified MoO3 (AzI-MO) microrods, photocalytic activity was elucidated by the MB (Methylene blue) dye. Antimicrobial effects of both products were conducted. Results show the highest activity of AzI-MO against bacterial strains (Staphylococcus aureus and Escherichia coli) and against fungal strain (Aspergillus flavus, Candida albicans) [39].

Recently, Mulla et al. [40] reported biosynthesized selenium nanoparticles (SeNPs) from the aqueous leaves extract of *A. indica*. The results showed a high concentration dependent effect of SeNPs against all bacterial strains. However, concentrations of 20 and 40 µg/mL completely killed all bacterial strains after 80 minutes of contact.

Pai et *al*. [41] evaluated the antimicrobial activity of a dental gel from *A. indica* leaf extract against some bacterial strains (*Streptococcus mutans* and *Lactobacilli species*) associated with plaque formation. Results suggest that mucoadhesive gel reduced significantly bacterial strains ($P < 0.05$).

Thakur et *al*. [42] synthetized nanoparticles of titanium dioxide (TiO_2) from *A. indica* leaf extract and tested its antibacterial effects. It was demonstrated that TiO_2 has a high activity against *E. coli*, Bacillus subtilis, *S. typhi* and *K. pneumonia* with a minimum inhibitory concentration (MIC) of 10.42 µg/mL against *Salmonella typhi* and *Escherichia coli,* while the minimum bactericidal concentration (MBC) was 8.33 µg/mL against *Klebsiella pneumoniae*.

3.5.4 Antifungal activity

The authors Álvarez-Caballero and Coy-Barrera [16] assessed the antifungal activity of some plant materials such as leaves, fruits, and seeds from 40 trees of *A. indica* against *Fusarium oxysporum* conidia. Thus, 84 ethanolic extracts were prepared, and their total limonoid content was determined. The findings indicated that the antifungal activity was effective. The IC_{50} values of extracts derived from *A. indica* varied from 0.08 to 44.8 µg/mL.

3.5.5 Antidiabetic activity

An aqueous extract of *A. indica* flowers was used to treat the functional recovery of a sciatic nerve crush injury in rat models of diabetes mellitus. According to the findings, the extract significantly improved sensory functions. Additionally, malondialdehyde levels, superoxide dismutase activity and axon density have been highly reduced by the extract at the doses of 750 mg/kg and 500 mg/kg animal body weight respectively [43].

3.5.6 Insecticidal activity

The authors Roel et *al*. [44] assessed the insecticidal effects of sublethal doses of *A. indica*

oil on the midgut of *S. frugiperda* (Lepidoptera), one of the major pests of corn production. The main results showed that the dose of *A. indica* oil mixed with *S. frugiperda* food resulted in their total death at the dose of 0.4% while they were still in the early stages.

The insecticidal effects of water and ethanol leaf extracts, and the oil extract of the seeds of *A. indica* were carried out. The results showed that both extracts and oil extracts significantly reduced *Pyricularia oryzae in vitro* radial growth as well as the development and spread of blasts in greenhouse rice plants. Oil extracts demonstrated the best activity on the pathogen and subsequent disease, followed by ethanol, cold water and hot water extracts. Neem oil, ethanol, and cold water extracts were more effective than carbendazim at 0.1% [45].

3.5.7 Antiviral effect

The virucidal activity of two polysaccharides (P1 and P2) isolated from the leaf of *A. indica* and their chemically sulfated derivatives (P1S and P2S) were tested against the herpetic virus HSV-1. It was found that simultaneous use of P1S and P2S showed better activity. However, at the concentration of 200 µg/mL, P1S showed a better inhibitory effect (91.8%) when compared to P1 (50%), P2 (71.1%) and P2S (70%) [20].

Fig. 1. Different parts of *A. indica* (A: Flowers; B: Leaves; C: Seeds)

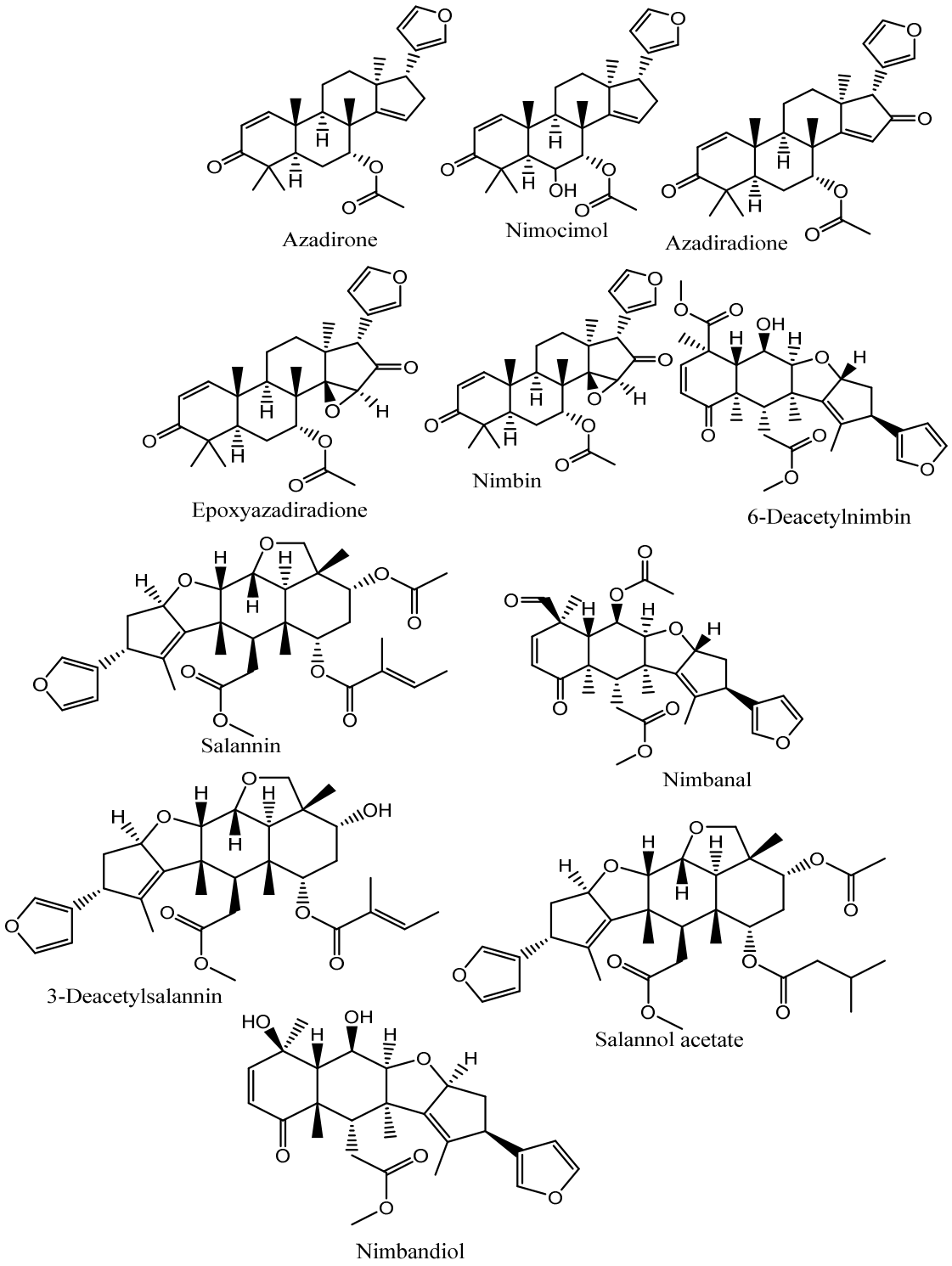

Fig. 2. Chemical structures of Compounds isolated from *A. indica*

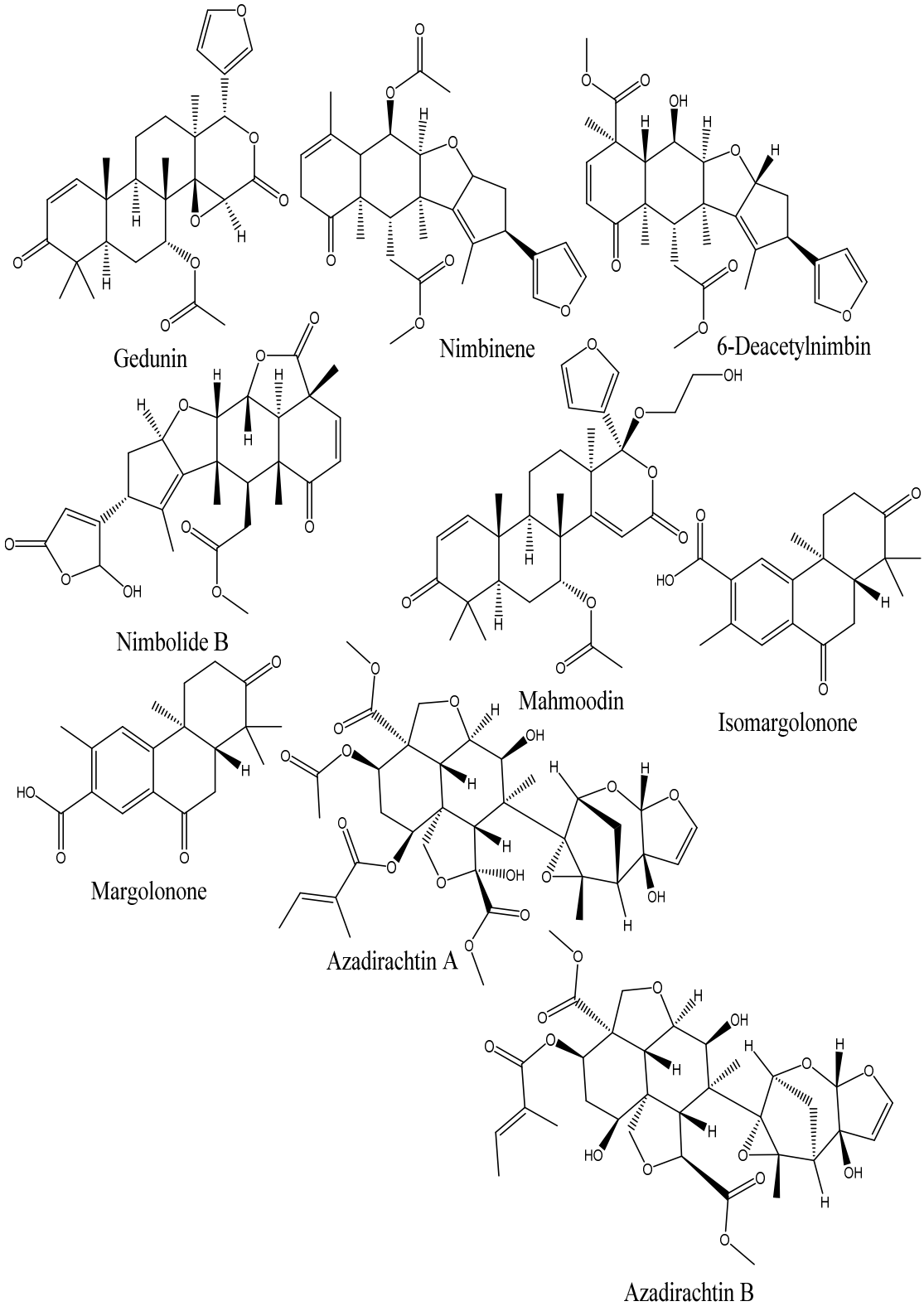

Fig. 2. Chemical structures of Compounds isolated from *A. indica* (continued)

Table 1. Summary of bioactivity of *Azadirachta indica* and model system used

Reference	Part used	Solvent for extraction	Biological activity	Model system	Concentration	Period	Main result
[13]	Leaves	Ethanol and water	Anthelmintic activity	worms (*Gastrothylax indicus*)	5-5000 µg/ml	4 h	Extracts showed high anthelmintic activity, and mortality was observed 4 hours after contact between the extract and the worms.
[14]	Aerial part	Ether, petroleum, methanol, hexane and water	Antibacterial and Anticancer activity	MCF cell lines	50 µg/ml		MCF cell lines were inhibited at concentrations of 50, 100, 150, 200 µg/ml for the methanolic extract. The IC50 values were 165.5629 µg/ml. There was a 65.6% rate for 200 µg/ml of methanolic extract. K. pneumoniae was highly sensitive to 50 µg/ml of methanolic extract (14 mm).
[17]	Leaves s	Water	Anticancer activity	Male Laca mice	300 mg/kg body weight	22 weeks	Administration of aqueous extract of *A. indica* leaves to DMBA/TPA-treated animals showed good cancer chemopreventive action by causing a lowering of collagen and GAG levels and a decrease in serum CEA levels.

[52]	Seeds	Water	Anticancer activity	Wistar Rats	3mL/kg body weight	12 weeks	It has been shown that regular consumption of A. indica oil has protected rats against DMBA-induced mammary hyperplasia. Thus, A. indica oil may prevent breast cancer.
[53]	Seeds	Methanol	Anticancer activity	Human osteosarcoma (HOS) cells.	1 mg/ml	2 h	The Sonication extract of *A. indica* showed the highest effectiveness in inducing apoptosis in human osteosarcoma cells (HOS).
[54]	Leaves	Ethanol, ethyl acetate, dichloromethane	Anticancer activity	Breast cell lines and Drosophila melanogaster	1.0 µg/mL and 0.03125 µg/mL	24 and 48 h	In vivo assays demonstrated that ethanolic extracts of *A. indica* leaves caused fewer tumors at a higher concentration of doxorubicin (DXR).
[35]	Leaves	Water	Anticancer activity	Mice	5-25 µg/mL	24h	Oral administration of supercritical extract of *A. indica* leaves significantly reduced LNCaP-luc2 xenograft tumor growth in mice with the formation of hyalinized fibrous tumor tissue, reduction in the prostate-specific antigen, and increase in AKR1C2 levels.

[18]	Stem bark	Ethanol	Anti-diabetic activity	Rats	15-240 µg/mL		It was indicated that butanol and ethyl acetate, both fractions of the ethanol extract of *A. indica* stem bark, had high anti-diabetic activity with an IC50 of 0.0154 µg/mL and an IC50 of 0.23 µg/mL respectively and reduced hyperglycemia.
[55]	Leaves	Hexane, chloroform and methanol	Antidiabetic	Diabetic rats	300 mg/kg	28 days	Chloroform extract exhibited significant inhibitory activity against advanced glycation end product formation with an IC_{50} average range of 79.1 mg/ml.
[56]	Leaves	Water	Antidiabetic		400 mg/kg	30 days	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.
[43]	Flowers	Water	Antidiabetic	Rats	250, 500 or 750 mg/kg	21 days	Administration of *A. indica* flower extract at a high dose (750 mg/kg animal BW) significantly increased SFI on postoperative days 18 and 21 ($P < 0.05$ and $P < 0.00l$, respectively). Administration of A. indica flower extract at a medium dose (500 mg/kg animal BW).

[57]	Leaves	Ethanol	Antimalarial activity	Mice	300, 500, and 1,000 mg/kg	5 days	After treatment, it was demonstrated that at the highest dose (500 mg/kg), the extract reduced neuroinflammation, the severity of brain oedema was decreased, and pyramidal neurons were protected from apoptosis.
[58]	Leaves	Ethanol	Antimalarial activity	*Anopheles coluzzii*	250 ppm	7 days	Ethyl acetate fraction of ethanolic extract from *A. indica* leaves, at 250 ppm in blood from gametocytaemic donors and membrane fed to *An. coluzzii* mosquitoes. The NLA reduced oocyst prevalence by 59% and oocyst intensity by 90%.
[19]	Seeds (ripe fruit and fruit)	Methanol	Antimalarial activity	Mice	150 mg/kg	4 days	Methanolic extract from *A. indica* seed reduced approximately 30% of erythrocytes infected with the malaria parasite in C57BL/6 mice in the 4 days suppressive test.
[59]	Leaves	Ethanol/water (70:30)	Antimalarial activity	Mice	75, 150, and 300 mg/kg	4 days	The most efficient doses of extracts for female and male mice were 300 mg/kg/day (68 ± 1.1%-69.3 ± 1.4%).
[60]	Leaves		Antimalarial activity	Balb/3T3 cells (mouse embryonic fibroblast cell line)		72h	Essential oils from *A. indica*, was very active, with half maximal inhibitory concentration (IC50) values of 15.21 µg /mL.

[37]	Leaves	Water	Antimicrobial activity	Mice	1,000 mg/mL	1 week	The antibacterial activity of AI-AgNPs was confirmed by a disc diffusion assay with zone of inhibition against B. cereus (17.7 mm), E. coli (18.7 mm), P. aeruginosa (10.3 mm), and *S. aureus*, theC and MBC values for AI-AgNPs ranged between 390 and 780 mg/mL.
[38]	Leaves	Methanol	Antimicrobial activity	Strains of E. faecalis (ATCC 29212)	From 1.56 to 75 µg/ml	48 h	MIC was 75 µg/ml, and bactericidal effect of the *A. indica* extract was found at a concentration of 25 µg/ml.
[62]	Leaves	Water	Antimicrobial activity	E. coli O157:H7 (EcO157)	1000 µg/mL	10 days	The ethyl acetate extractable fraction was inhibitory to the growth of EcO157 in LB broth. Azadirachtin, a neem product with insect antifeedant properties, failed to inhibit EcO157.
[39]	Leaves	Water	Antimicrobial activity	Bacterial strains (Gram positive and Gram negative) and fungal strain	from 0.02 g/L to 0.10 g/L	24h	*A. indica* leaves modified MoO3 (AzI-MO) microrods were very efficient against gram positive, gram negative and fungal strains.
[42]	Leaves	Water	Antimicrobial activity	Bacterial strains (*E. coli, B. subtilis, S. typhi and K. pneumonia*)	200-0.78 µg/mL	24 h	TiO2 nanoparticles inhibited the growth of all the tested microorganisms. The antibacterial effect was more pronounced in the case of TiO2 nanoparticles as compared with the TiO2 compound.

[41]	Leaves	Ethyl alcohol	Antimicrobial activity	*S. mutans* and *Lactobacilli* species	25 mg/g	6 weeks	The extract significantly (P 0.05) reduced the control group's plaque index and bacterial count.
[40]	Leaves	Water	Antimicrobial activity	Gram-positive and Gram-negative bacterial strains	20 and 40 µg/mL	24 and 48 h	Biosynthesized SeNPs showed promising antibacterial activity against selected Gram-positive and Gram-negative bacterial strains.
[20]	Leaves	Water	Antiviral activity	HEp-2 cell	25, 50, 100 and 200 µg/mL	40 h	Synthesis of viral protein showed a dose-dependent response and the nucleic acid synthesis was inhibited by up to 25 µg/mL, by P1 and P1S and by up to 50 µg/mL, by P2 and P2S.
[46]	Leaves	70% Ethanol	Hepatoprotective activity	Rat	500 mg/kg, p.o.)	7 days	Administration of *A. indica* extract increased the concentration of GSH in the liver and glutathione in the blood and liver Na+K+-ATPase activity significantly.
[47]	Leaves	Methanol	Hepatoprotective activity	Rat	500mg/Kg bwt	5 days	After treatment extract, the histological damage and apoptosis induction caused by cisplatin were improved. Malondialdehyde and nitric oxide were significantly decreased.

[48]	Leaves and seeds	Hexane, ethanol and water	Immunostimulatory activity	Leishmania parasitized RAW 264.7 acrophages and mice	500 µg/ml	7 days and 2 weeks	Ethanolic fraction of leaves and seeds exhibited leishmanicidal activity in a time- and dose-dependent manner (IC50 34 and 77.66 µg/ml, respectively) and exerted appreciable anti-amastigote potency (IC50 17.66 and 24.66 µg/ml, respectively). In vivo therapeutic was efficacy (87.76% and 85.54% protection in liver and 85.55% and 83.62% in spleen, respectively).
[49]	Leaves	Methanol	Immunostimulatory activity	Vero cells and mice	100, 50, 25, 12.5, 6.25 and 3.125 µg/ml	120 h	The IC50 for antiparasitic activity was 11.5 g/mL. Optimal efficacy was 72 %. The optimal efficacy of the compounds against promastigotes was 78.0 µg /mL.
[21]	Seeds	N-hexane	Insecticidal activity	*Anopheles gambiae*	From 100 to 500 ppm.	3 days	Larvicidal activity was significant across the concentration of the emulsified Azadirachta oil (91.6-100%) while the control experiment gave 5-15%. A total larval mortality (100%) of mosquito (A. gambiae) was recorded within three days at 500 ppm.

[45]	Leaves and seeds	Water and ethanol	Insecticidal activity	*Pyricularia oryzae*(larval)			Water and ethanol leaf extracts, and the oil extract of the seeds, significantly reduced the in vitro radial growth of *P. oryzae.*
[63]	Seeds	Water	Insecticidal activity	*Spodoptera frugiperda* (caterpillars)	125, 250, and 500 ppm	24 h	The total number of hemocytes in insects exposed to neem oil was 21% lower than in the control group. The mean diameter of cell lysis halos was reduced only at concentrations of 125 and 250 ppm.
[64]	Leaves	Methanol	Insecticidal activity	*Aedes aegypti* (larvae)	From 21 to 63 and 41.4 to 83 ppm	24 h	The two triterpenoids isolated demonstrated toxicity against *Aedes aegypti* larvae with LC50 values of 21 and 83 ppm, respectively.
[51]	Leaves	Water	Neuroprotective activity	Rats	200 and 400 mg/kg	28 days	Treatment with *A. indica* significantly reduced neural apoptosis and reactive oxygen species levels.
[50]	Leaves	Water	Neuroprotective activity	Rats	300 mg/kg	28 days	A. indica exhibited anxiolytic activity in the open field test in Col lesion animals and significantly alleviated IB and Col-induced anxiety.
[12]	Leaves	Water	Anti-parasitic activity	Chickens	100mg/kg, 200mg/kg, and 400mg/kg	5 days	The aqueous extracts of *A. indica* leaves were ameliorative in chickens infected with coccidiosis.

3.6 Immunostimulatory Effects of *A. Indica*

Hepatoprotective activity of *Azadirachta indica* leaf extract against paracetamol induced hepatic damage in rats has been reported. Results showed that administration of Azadirachta indica leaf extract increased liver GSH and blood glutathione concentration and liver Na+K+-ATPase activity significantly when compared to the paracetamol-treated control group [46].

A Methanolic extract of neem leaves was used on rats to assess its protective activity. Cisplatin was used to induce hepatotoxicity in these rats. The histological damage and apoptosis induction caused by cisplatin were corrected by treatment with methanolic extract at a dose of 500mg/Kg.In addition, it was demonstrated that malondialdehyde and nitric oxide were significantly decreased and the antioxidant system, ie. glutathione content, glutathione transferase, glutathione peroxidase, catalase and superoxide dismutase activities were also significantly improved [47].

3.7 Immunostimulatory Activity of *A. indica*

The authors Chouhan et *al*. [48] reported the *in vitro* and *in vivo* antileishmanial and immunomodulatory activity of ethanolic fractions of *Azadirachta indica* leaves and seeds. The final result showed that at the concentration of 500 µg/ml, both ethanolic fractions of *A. indica* exhibited time- and dose-dependent leishmanicidal activity with change in promastigote shape and with induction of apoptosis. ALE and ASE showed good anti-amastigote activity associated with strong therapeutic action in vivo.

In the same year, Jumba et al. [49] carried out in vivo and in vitro immunostimulatory activity of two plants, *A. indica* and *R. communis* in BALB/c mice as the mouse model. The combination of both plants resulted in significant lesions being reduced.

The antiparasitic action of *A. indica* on amastigote (with a 50 % inhibitory concentration) was 11.5 µg/mL, whereas association therapy produced the best result (IC50 9.0 µg/ml) compared to the standard drugs.

3.8 Neuroproperties Effect of *A. indica*

The authors Raghavendra et *al*. [50] assessed *Azadirachta indica's* potential against Alzheimer's disease in rats. The final result showed that *A. indica* exhibited an anxiolytic effect in the open field test in animals with a lesion of the cervix. In the cross maze test, *A. indica* significantly decreased the anxiety induced by IB and Col. IB- and Col-induced depression was attenuated by *A. indica*. The increase in lipid peroxidase activity caused by IB and Col was significantly reversed by *A. indica* while the growth of superoxide dismutase and a decrease in physical activity were stabilized. The growth of lipid peroxidase activity induced by IB and Col was significantly reversed by *A. indica* with stabilization of the superoxide dismutase growth and a downward trend in acetylcholine esterase (AChE) activity was noticed with IB and Col lesions.

The neuroprotective effect of *A. indica* was evaluated in male Wistar rats (with peripheral neuropathy induced by partial sciatic nerve ligation) at the doses of 100, 200 and 400 mg/kg. Results showed an important improvement in rats' behavior (motor coordination and motor nerve conduction velocity) at doses of 200 and 400 mg/kg, inducing a reduction of neural apoptosis and reactive oxygen species levels [51].

The biological activities of *Azadirachta indica* and model system used are summarized in the Table 1.

4. CONCLUSION AND SUGGESTIONS

The aim of this mini review was to identify data related to the plant *Azadirachta Indica* (neem tree) on the Internet, using search engines to download free scientific papers. Phytochemical compounds and biological activities of this plant were reported. Several compounds, including azadirone, nimocimol, azadiradione, nimbinin, salannin, nimbanal, salannol acetate, nimbandiol, tannins, saponins, steroids, gedunin, nimbinene, nimbolide, isomargolonone, azadirachtin, catechin, phenols, alkaloids, flavonoids, steroids, triterpenoids, anthraquinone, anthocyanins, were isolated from this plant, while their biological activities were also reported. The results indicate that the neem tree possesses anticancer, antifungal, antidiabetic, antibacterial, antiviral, antiplasmodial and anthelmintic activities provided by its secondary metabolites. Due to its

anthocyanin content, future research on its anti-sickle cell potential would be very interesting for a new formulation of a phytodrug against sickle cell disease.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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