Sapporo Medical Journal
Volume 55, Issue 01, January, 2021

Constituents, pharmacological and toxicological effects of Melia azadirachta- A review

Assist. Prof. Wajdy J. Majid[1], Tayseer A. Talab[2], Assist. Prof. Dheyaa Khalf Al Omer [3]

[1]Department of biochemistry, [2]Dept of Pharmacology and [3]Dept. of Internal medicine,
College of Medicine, University of Thi-Qar- Iraq.

Abstract— The phytochemical analysis of different parts of Melia azedarachshowed that the plant contained alkaloids, carbohydrates, fixed oil and fats, protein and amino acids, saponins, sterols, triterpenoids, esters, thiols, cynogenic glycosides, tannins, flavonoids and phenolic compounds. The pharmacological studies revealed that Melia azedarach possessed antimicrobial, antiparasitic, anticancer, antioxidant, antiinflammatory, analgesic, antipyretic, reproductive, hepatoprotective, dermatological, antidiabetic, immunological, antilithiatic, hypolipidemic, butyrylcholinesterase inhibitory activity and melanogenesis stimulation effects. The current review highlighted the constituents, pharmacological and toxicological effects of Melia azedarach.

Keywords: Melia azedarach, constituents, pharmacology, toxicology

Introduction:

Recently years, the field medicinal plant studies has received much attention as this brings to light the numerous little known and unknown medicinal virtues especially of plant origin which needs evaluation on modern scientific lines such as chemical analysis, pharmacological investigations and clinical trials. Melia azedarach (Family: Meliaceae) was widely used in the traditional medicine for the treatment of intestinal worms, skin diseases, stomach ache, nausea, vomiting, paroxysmal fever, sciatica, lumbago, piles, asthma, wounds, diabetes, post labor pain , ammenorrhoea and leucoderma. The phytochemical analysis of different parts of Melia azedarachshowed that the plant contained alkaloids, carbohydrates, fixed oil and fats, protein and amino acids, saponins, sterols, triterpenoids, esters, thiols, cynogenic glycosides, tannins, flavonoids and phenolic compounds. The pharmacological studies revealed that Melia azedarach possessed antimicrobial, antiparasitic, anticancer, antioxidant, antiinflammatory, analgesic, antipyretic, reproductive, hepatoprotective, dermatological, antidiabetic, immunological, antilithiatic, hypolipidemic, butyrylcholinesterase inhibitory activity and melanogenesis stimulation effects. The current review highlighted the constituents, pharmacological and toxicological effects of Melia azedarach. In the current review, databases including Web Science, PubMed, Scopus and Science Direct, were used for searching for the chemical constituents and pharmacological effects of Melia azedarach**.**

Plant profile:

Synonyms:

Azedara speciosa, Azedarach commelinii, Azedarach deleteria, Azedarach fraxinifolia, Azedarach odoratum, Azedarach sempervirens, Azedarach sempervirens var. glabrior, Azedarach sempervirens f. incisodentata, Azedarach sempervirens f. longifoliola, Azedarach sempervirens f. subdentata, Melia angustifolia, Melia australis, Melia azedarach var. glabrior, Melia azedarach var. intermedia, Melia azedarach var. subtripinnata, Melia azedarach var. toosendan, Melia birmanica, Melia bukayun, Melia chinensis, Melia cochinchinensis, Melia

dubia, Melia japonica, Melia japonica var. semperflorens, Melia orientalis, Melia sambucina and Melia toosendan[1].

Taxonomic classification[2]:

Kingdom:Plantae

Subkingdom:Viridiplantae

Infrakingdom:Streptophyta

Superdivision: Embryophyta

Division:Tracheophyta

Subdivision: **Spermatophytina**

Class:Magnoliopsida

Superorder:Rosanae

Order:Sapindales

Family:Meliaceae

Genus:Melia

Species:Melia azedarach

Common names:

Arabic:Zanzelkhat,Sebahbah, Neem, Jarood, Sebahi;**Afrikaans**: bessieboom syringe, arbre à chapelets; **Chinese**: chuan liang zi, lian; **English**: Cape-lilac, chinaberry, chinaberry-tree, Persian-lilac, Sichuan pagoda-tree, syringa berrytree, Texas umbrella-tree, tulip-cedar, umbrella-cedar, umbrella-tree, white-cedar; **French:** arbre à chapelets, lilas des Indes; **German**: indischer Zedrachbaum,persischer Flieder;**Hindi**: betain,deikna, dek, drek, bakain, mallan, nim, bakarja; **Indonesian**: marambung, mindi, gringging; **Italian**: Albero dei paternostri; **Japanese**: sendan; **Korean**: meolguseulnamu,**Portuguese**: amargoseira-do-Himalaio; **Spanish**:melia, paraíso; **Swedish**: zedrak[3].

Distribution:

It is native to Indochina, Pakistan, India, Australia, and Southeast Asia[4].However, the plant was distributed in **Asia** (China, Bhutan, India, Pakistan, Nepal, Sri Lanka, Indonesia, Laos, Thailand, Vietnam, Indonesia, Philippines, Japan, Cyprus), **Australasia** (Australia), **Europe** (Croatia, Italy, France), **Northern America**(Mexico,United States) and**Southern America**(West Indies, Guatemala, Nicaragua, Guyana, Suriname, Venezuela, Brazil, Ecuador, Argentina, Chile, Paraguay, Uruguay)[3].

Description:
-The plant is a deciduous tree, may reach up to 45 m tall, and up to 30-60 (max. 120 cm) in diameter, with a spreading crown and sparsely branched limbs.
-Bark is smooth, greenish-brown when young, turning grey and fissured with age. – Leaves are alternate, 20-40 cm long, bipinnate or occasionally tripinnate.
-Leaflets are 3-11, serrate and with a pungent odour when crushed.
-Inflorescence is axillary panicle up to 20 cm long.

-Flowers are fragrant, numerous on slender stalks, white to lilac; sepals 5-lobed, 1 cm long, petals 5-lobed, 0.9 cm long, pubescent; staminal tube deep purpleblue, 0.5 cm long, 1 cm across.
-Fruits are small, yellow drupe, nearly round, about 15 mm in diameter, smooth and becoming a little shrivelled, slightly fleshy.
-Seeds are oblongoid, 3.5 mm x 1.6 mm, smooth, brown and surrounded by pulp[5].

Traditional uses:

It was used traditionally in the treatment of intestinal worms, skin diseases, stomach ache, nausea, vomiting, paroxysmal fever, sciatica, lumbago, piles, asthma, wounds, diabetes, post labor pain , ammenorrhoea and leucoderma[6-7].It was said that the plant was beneficial in the treatment of leprosy, inflammation, scrofula, anthelmintic, antilithic, diuretic, deobstruent and cardiac disorders[8].Leaf extract was given orally twice a day for pyrexia[9], to relieve headache, locally applied in the treatment of burn and other skin diseases, as laxative, and prepared as mouth wash for gingivitis. Leaves and seed were used as insecticide. Stem bark infusion was used in gonorrhea[10-11].The seed oil of Azadirachta indica was used in traditional medicine as antidiabetic, antifertility, antibacterial, and for wound healing[12]

Parts used medicinally:

Leaf, flower, seed, oil, root, young branches, fruit and bark were used medicinally[10,13].

Physicochemical parameters:

Physicochemical parameters of Melia azedarach leaves were: total ash value: 5.19%, water soluble ash value 3.47%, acid insoluble ash value 1.72%, alcohol soluble extractive value 3.26%, water soluble extractive value 7.83% and moisture content 4.64%[14].Physicochemical properties of Melia azedarach seed oil were: moisture 6.86%, protein 20.13%, fiber 15.40%, carbohydrate 19.45%, acid value 2.25 mgKOH/g, iodine value 9.14, saponification value 84.15 mgKOH/g, unsaponifiable matter 0.71%w/w, total saturated 9.02% and total unsaturated fatty acids 90.97%[15].

Chemical constituents:

Preliminary phytochemical analysis showed that the plant contained alkaloids, carbohydrates, fixed oil and fats, protein and amino acids, saponins, sterols, triterpenoids, esters, thiols, cynogenic glycosides,tannins, flavonoids and phenolic compounds[9,14,16-20].
The fresh leaves hexane extract contained 2-undecanol; methyl 4, 6-decadienyl ether; 13-docosenoic acid; 7, 8-dihydrocarpesterol; glutaric acid, dimethyl ester; nonanoic acid, 1, 2, 3-propanetriyl ester; glycerol 2-acetate 1, 3-dipalmitate; docosenoic acid and 1 methyl-butyl ester[4].

While, five compounds: 3,7,11,15- tetramethyl-2-hexadecen-1-ol; ethanol, 2-(9-octa decenyloxy)-,(Z)-; phytol; carotene; 1,1'2,2'-tetrahydro-1,1'-dimethoxy- and rhodoxanthin were isolated from the ethanolic extracts of Melia azedarach leaves[20].
However, forty eight compounds were identified in the methanolic leaf extract of Meliaazedarach by GC-MS included: 2, 3-dihydro-3,5-dihyroxy-6-methyl-4H-pyran-4-one (aromatic flavoring agent); 2,3-dihydrobenzofuran (essential oil); 5-hydroxypipecolic acid (imino acid); ethoxytriethylsilane (dibasic esters); 4-methyl-2-hexanone (aromatic flavoring agent); pentadecane (n-alkanes); limonene (monoterpenes); pyrazol-5(2H)-one (flavonoids), 1-hexadecene (alpha-olefins); nonadecane (saturated aliphatic hydrocarbon); caryophyllene oxide(flavor and fragrance agents); 1-Acetyl-4-hydroxy-pyrrolidin-2-one (pyrrolidones); n-tetradecanoic acid (saturated fatty acid); 1,2-dihexylcyclopropene-3-carboxylic acid (n-alkanoic acids); 9-eicosyne (saturated aliphatic hydrocarbon); 14,10,6- tTrimethyl-2-pentadecanone (essential oil); E-6-octadecen-1-ol acetate (fatty acids); citronellyl propionate

(flavor and fragrance agents); hexadecanoic acid, methyl ester (methyl ester); carvacrol (monoterpenoid phenol); palmitic acid (saturated fatty acid) ; 1,5-anhydro-2-deoxyhex-1-enitol (nsaturated sugars); linolenic acid, methyl ester (poly unsaturated fatty acid); phytol (diterpene); methyl linoleate (polyunsaturated fatty acid); 15,12,9-octadecatrienoic acid (n-alkanoic acids); stearic acid (n-alkanoic acids); 10, 6, 2- trimethyl,14-ethylene-14-pentadecne (olefins); 2-propenoic acid, 2-methyl-, 2-dimethylamino) ethyl ester (ethyl ester); 16, 12, 8, 4-tetramethylheptadecan-4-olide (isoprenoid); 5, 3, 1- trisilacyclohexane (saturated hydrocarbon); palmitic acid (monoglyceride); tetracosanoic acid, 3-oxo-methyl ester (methyl ester); hexacosane (unsaponifiable matter); stearic acid chloride (unsaturated fatty acid); quercetin (flavanoids); 13-docosenamide (alkyl amides); squalene (triterpene) 8, 2- dimethyl-2-4,8,12-trimethyltridecyl)-6-chromanol; gamma- tocopherol; 1-eicosanol (triterpene); beta-carotene, alpha-tocopherol-beta-D-mannoside, Kamphferol (Flavanoids); beta-sitosterol(phytosterol); stigmasterol (phytosterol); campesterol (phytosterol) and tetramethyl-2-hexadecen-1-ol (terpene alcohol)[18].

Melianone, meliandiol, melianoninol, melianol, vanillin and vanillic acid were isolated from the fruits of Melia azedarach[21].

Tirucallanes (3-alpha-tigloylmelianol, melianone, 21-beta-acetoxy-melianone, and methyl kulonate); tirucallane triterpenoids: [(21S,23R,24R)-21,23-epoxy-21,24-dihydroxy-25-methoxy tirucall- 7-en-3-one, (3S,21S,23R,24S)-21,23-epoxy-21,25-dimethoxytirucall-7-ene-3,24-diol, (21S,23R,24R)-21,23-epoxy-24-hydroxy-21-methoxytirucalla-7,25- dien-3-one, and (21S,23R,24R)-21,23-epoxy-21,24-dihydroxytirucalla-7,25-dien-3-one, along with 16 analogues] were also isolated from the fruits of Melia azedarach[22-23].

Fatty acid identified in the seeds oil of Melia azedarach were: palmitic acid 5.68%, linoleic acid 74.57%, oleic acid 16.39% and stearic acid 3.33%[15].
Mineral content (mg/100g) of Melia azedarach seed oil were calcium 1230, magnesium 990, phosphorous 213, potassium 121, zinc 3.12, manganese 3.4 and iron 19.52[15].
The total proanthocyanidinsin the methanolic leaves extracts of Melia azedarachwas 330 ±15 mg/ml, total phenolics 92± 5 mg/g gallic acid equivalent and total flavonoids 286± 10 mg/g rutin equivalent[24].Flavonoids isolated from Melia azedarachwere included: 4', 5-Dihydroxy flavone-7-O-u-Lrhamnopyranosyl-(1→4)-β -D-glucopyranoside; apigenin-5"O-β-D-galactopyranoside; kaempferol-3-0-β-rutinoside kaempferol-3-L-rhamno-D-glucoside and rutin[25]

Pharmacological effects:
Antimicrobial effect:
The leaves and stem barks crude extracts and their chloroform, petroleum ether, acetate ethyl, butanol, and aqueous fractions was evaluated against Streptococcus mutansusing seven different concentrations. The crude extracts and the petroleum ether fraction from showed significant antibacterial activity[26].

Antimicrobial effects of Melia azedarach leaf extracts were investigated against six human pathogens (Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae and Proteus vulgaris). Melia azedarachleaf extract possessed maximum zone of inhibition against Staphylococcus aureusand minimum zone of inhibition against Escherichia coli. The zone of inhibition was concentration dependent[24].
The in vitro antibacterial activities of the ethanolic extract of Melia azedarach fruit were studied against Bacillus cereus (ATCC11778), Staphylococcus aureus (ATCC25923), Salmonella typhimurium (ATCC 14028) and Escherichia coli (ATCC 25922). The extract inhibited the growth of all the tested bacteria. The lowest MIC (40 mg/ml) and MBC (80 mg/ml) were recorded against Salmunella typhimurium,which showed sensitivity more than other bacteria[27].
The antibacterial activity of petrol, ethyl acetate, methanol, benzene, and aqueous extracts of the seeds of Melia azedarach, at five different concentrations (1, 2, 5, 10 and 15 mg/ml) was

investigated against eighteen hospital isolated human pathogenic bacterial strains(Staphylococcus aureus, Staphylococcus aureus ATCC 25923,Staphylococcus epidermidis, Group-A Streptococcus, Group-B Streptococcus,Enterococcus faecalis, Bacillus subtilis, Escherichia coli, Edwardsiella tarda, Klebsiella pneumonia, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhi, Shigella boydii, Shigella dysenteriae, Shigella flexneri and Plesiomonas shigelloides). All seeds extracts demonstrated significant antibacterial activity against the tested pathogens. Ethyl acetate extract revealed the highest inhibition of bacterial growth[28].

Antimicrobial activity of methanol, ethanol, petroleum ether and water extracts of the leaves ofMelia azedarach was examined against eight human pathogens (Bacillus cereus, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Aspergillus niger, Aspergillus flavus, Fusarium oxisporumand Rhizopus stolonifer) All the extracts showed significant activity against all pathogens, but the alcoholic extract of Melia azedarachleaves extract showed the maximum zone of growth inhibition and the minimum inhibitory concentration against the tested microorganisms. However, the minimum zone of inhibition and greater inhibitory concentration were recorded for the petroleum ether and aqueous extract of Melia azedarachagainst all the experimental strains[29].

Five crude leaf extracts of Melia azedarach (methanol, ethanol, dichloromethane, ethyl acetate and aqueous) at five different concentrations were tested for antibacterial effect against eight strains of Gram-positive: Micrococcus glutamicus, Lactobacillus bulgaris, Streptococcus faecalis, Staphylococcus aureus, Bacillus stearothermophilus, Staphylococcus pyogenes, Micrococcus luteus, Bacillus cereus and Gram negative bacteria: Escherichia coli and Pseudomonas aeruginosa. Dichloromethane leaf extract of Melia azedarachwas effective against Gram positive than Gram negative bacteria. Ethanol extract inhibited the growth of all the tested bacterial strains, with maximum inhibition zone against the Gram negative bacteria. Methanolic extract was effective against all the tested bacteria. All the tested bacterial were sensitive to the ethyl acetate extract, while, aqueous leaf extract showed moderate activity against all tested bacterial strains[30].

The ethanolic extract of the leaves of Melia azedarachwas tested for antibacterial activity against Escherichia coli, Salmonella typhi, Shigella dysenteriae, Staphylococcus aureus, Staphylococcus epidermidis. The ethanolic extract showed antibacterial activity against all the tested bacterial strainswith zone of inhibition ranging from 8.40 mm to 10.39 mm and 11.56 mm to 15.87 mm for 250 and 500 µg/disc of extract respectively[31].

The antibacterial activity of the ethanolic leaf extract of Melia azedarach was studied against E. coli (ATCC 8739), Enterococcus faecalis (Ec P07)and Bacillus subtilis (Bs), and the antifungal activity was examined against Alternaria alternate, Fusarium solani, Fusariumoxysporum sp. melonis, F. oxysporum f. sp. lycopersici, F. sambucinum and Botrytis cinerea. The results showed that IC_{50} of ethanolic leaf extract against E. coli was 6.6 µg/ml, Enterococcus faecalis 1 µg/ml, Bacillus subtilis 1.3 µg/ml, Alternariaalternate 1.0 µg/ml and Fusarium solani53 µg/ml. The ethanolic leaves extracts exhibited a significant ($P \leq 5\%$) inhibitory effects on growth of tested fungal pathogens by disc-methods [32].

The antifungal effects of Melia azedarach flowers extracts was investigated against Aspergillus niger, Aspergillus fumigatus, Aspergillus flavus. The methanolic extract of theflowers showed the highest antifungal activity against Aspergillus flavus fungus with zone of inhibition of 19.6±0.66 mm. Dichloromethane, ethyl acetate and n-butanol extracts also possessed significant antifungal activity with 18±0.57 mm, 18.6±0.88 mm and 18±0.66 mm zone of inhibition, respectively. N-butanol extract showed the least antifungal activity against Aspergillus niger with 13.6±0.88 mm zone of inhibition. Dichloromethane and methanolic extracts exhibited excellent MIC against Aspergillus flavus (13.909±1.5 µg/ml)[16].

Meliacine peptide isolated from the leaves inhibited the multiplication of foot and mouth disease virus (FMDV) in BHK-21 cells. The meliacine -inhibitable process was occurred within the first hour of the viral reproductive cycle. Meliacine didn't affect adsorption and penetration of the virus in cells. It prevented the process of uncoating of FMDV in BHK-21 cells by inhibiting vacuolar acidification[33].

Meliacine, also exhibited antiviral activity against herpes simplex virus type 1 (HSV-1) by inhibiting specific infected-cell polypeptides produced late in infection which involved in DNA synthesis and in the assembly of nucleocapsids. It also affected the late event in the multiplication cycle of HSV-1. It diminished the synthesis of viral DNA and inhibited the spread of infectious viral particles[34].

Limonoid 1-cinnamoyl-3,11-dihydroxymeliacarpin isolated from the ethyl acetate extract of leaves of Melia azedarach showed IC_{50} values of 6 microM and 20 microM against vesicular stomatitis (VSV) and herpes simplex (HSV-1) viruses, respectively[35].

Antiparasitic effect:

Ethanolic extracts from the kernels of ripe fruits of Melia azedarach(0.0033 to 0.05 g%) were assayed against larvae of Aedes aegypti. The extracts of the seed were lethal for third to fourth instar larvae. Non-fed Aedes aegyptilarvae were more susceptible to the extracts. Under a more realistic environmental situation (25 and 30C), the death rate caused by the extract was higher[36].

The larvicidal activity of aqueous extracts of different parts(50, 100, 500, 1000, 1500 and 2000 ppm) of Melia azedrach was investigated against Culex quinquefasciatus. The extracts increased the mortality of 3rd and 4th instar larvae, the effect was concentration dependent. 1.6±2.2% mortality was caused by the fruit extract (50 ppm), while, leaves extract caused 17.60±6.0% and bark extract caused 17.60±7.3% mortality. The $LC_{50}$of the fruits extract was 2035.13ppm, while that of leaves extract 612.250ppm and bark extract 368.3ppm[37].

The antiparasitic effect of ethanolic extracts of Melia azedarach was examined against the larval stages of Anopheles stephensi, Culex quinquefasciatus and Aedes aegypti. The results showed that the extracts of seed and leaf caused significant larval mortality in all larval stages of the three mosquito species. The fruit extract (50 ppm) produces 81% larval mortality on the 4th instar larvae of An. stephensi and 79% larval mortality in Cx. quinquefasciatus and Ae. aegypti. It appeared that the first and second instar larvae of An. stephensi and Cx. quinquefasciatus were more susceptible to all concentrations of leaf and fruit extracts[38].
The activities of ripe fruit extract and fruit oil of Melia azedarachwere studied against the head louse Pediculus humanus capitis. Theoil and extract, individually or combined, caused high mortality of adult lice (62.9% and 96.5%). The highest mortality rate was recorded when 20% ripe fruit extract was combined with 10% ripe fruit oil[39].

The anthelmintics effect of Melia azedarachwas investigated against Haemonchus contortus. The ovicidal and larvicidal activity of Melia azedarachextracts on Haemonchus contortus was investigated bylarval development and egg hatching tests. The seed ethanol extract was the most active on eggs (LC_{50}=0.36mgml) and the leaf ethanol extract showed the best inhibition of larval development (LC_{50}=9.18mg/ml)[40].

The antiparasitic effect of Meliae cortex (Melia azedarachLinne. var. japonica) was investigated on the growth and fine structure of Trichomonas vaginalis. Meliae cortex decreased the viability of T. vaginalis dose-dependently. One to two hours after adding of Meliae cortex extract, the movement of flagella and axostyle was decreased, but the cell death didn't occur. After 30 min to 2 hour of the treatment with the extract of Meliae cortex, the fine structure of the cytoplasm was changed. The number of polyribosome was decreased, whereas the number of single ribosomes in the cytoplasm was increased[41].
The antimalarial activities of the extracts of Albizia gummiffera, Aspilia mossambicensis, Melia azedarachand Azadirahchta indica were evaluated against laboratory adapted isolates

of Plasmodium falciparum using an in vitro radioisotopic uptake technique. The antimalarial activity (IC_{50}) of Melia azedarach was 299.7±202.0 ug/ml[42].

Anticancer effect:

Four tirucallane triterpenoids, isolated from the fruits, along with 16 analogues, were evaluated for their cytotoxicities against HepG2 (liver), SGC 7901 (stomach), K562 (leukemia), and HL60 (leukemia) cancer cell lines. One of the tirucallane triterpenoids analogues possessed strong cytotoxicity against HepG2 and SGC7901 cancer cells with the IC_{50} values of 6.9 and 6.9 μm, respectively[23].

Thirty one limonoidsand tirucallane-type triterpenoid isolated from the fruits of Melia azedarachwere tested for their cytotoxic activities against HL60, SK-BR-3, A549 and AZ521 human cancer cell lines. Meliarachin C (IC_{50} 0.65 μM) and 3-O-deacetyl-4'-demethyl-28-oxosalannin (IC_{50} 2.8 μM) exhibited potent cytotoxic activity against HL60 cells, attributed to their apoptotic effects[43].

Triterpene, 3-alpha-tigloylmelianol isolated from the fruits of Melia azedarach showed cytotoxicity against the human lung adenocarcinoma epithelial cell line A549mined[22].

The anticancer activity of Melia azedarach was studied against cancer [HT-29 (human colon adenocarcinoma), A-549 (non-small cell line carcinoma), HepG2 (hepatocellular carcinoma) and MCF-7 (human breast adenocarcinoma)] and normal cell line. The results showed that the extract of Melia azedarachseed kernel possessed high cytotoxic activity and selectivity to cancer cell lines (IC_{50} range of 8.18- 60.10 μg/ml)[44].

Antioxidant effect:

The water, ethanol and methanol extracts of dried leaves of Melia azedarach were investigated for antioxidant activity using DPPH radical scavenging assay. The result revealed that the extract, contains high amount of phenolic compounds and exhibited potent antioxidant activity[45].

The antioxidant effect of the Melia azedarachwas studied ethanol-induced erythrocyte damage in rats. Chronic administration of ethanol increased the level of lipid peroxidation, decreased the activity of superoxide dismutase and catalase and reduced the content of glutathione. The ethanol- induced changes was inhibited with co- administration ofMelia azedarach (500mg/kg, orally)[46].

The antioxidant activity of Melia azedarach leaf extracts was studied using DPPH radical scavenging activity. The result revealed that 5mg plant extract showed highest (65.4%), and 1 mg showed the lowest inhibition activity (45.04%). The inhibition activity of the plant extract was comparatively lower than that bpossessed by ascorbic acid[24].

The ethanolic extract of the leaves of Melia azedarach was tested for antioxidant, using DPPH scavenging assay. Ethanolic extract of the leaves demonstrated antioxidant activity in vitrowith IC_{50} value of 19 μg/ml [31].

The antioxidant activities of the ethanol leaf extract of Melia azedarach and its protective effect was also studied against H_2O_2-induced cellular damage in cultured lymphocytes. The ethanol extract of Melia azedarach (20, 40, 60, 80, 100 mg/ml) exhibited significant dose dependent radical scavenging effects, and their IC_{50} values were: DPPH radical (30.55±0.32 mg/ml), hydroxyl radical (26.50±0.26 mg/ml), nitric oxide radical (48.00±0.48 mg/ml), superoxide anion (30.00±0.32 mg/ml), and reducing power (22.00±0.22 mg/ml). The extract 60 mg/ml protected from the increased DNA damage at 500 μM H_2O_2-treated cultured lymphocytes[47].

The antioxidant activity of Melia azedarach flowers extracts was measured using DPPH free radical scavenging assay. Only ethanolic extract of the flowers revealed antioxidant

activity with $IC_{50}$of 50±2. Dichloromethane, ethyl acetate, n-butanol and methanol extracts showed no antioxidant activity[16].
The antioxidant activity of Melia azedarach was evaluated in depression induced in rat by stress procedures. The leaves aqueous extract (50 and 150 mg/kg bw, orally for 30 days) showed significant increase in the levels of protein, cholesterol and significant decrease in LPO level in depression induced rats[17].

Antiinflammatory, analgesic and antipyretic effects:
The anti-inflammatory activity of hexane extract of the seeds of Melia azedarach was investigated in rats, using carrageenan induced paw oedema and formalin induced inflammation test. The extract at doses of 100 and 200 mg/kg bw, reduced the paw edema induced by carrageenan by 52.77 and 91.66%, respectively. While, it reduced the formalin induced inflammation by 15.21 and 20.86% at the same doses, respectively[48].

The anti-inflammatory effect of the ethanolic leaf extract of Melia azedarach was studied using carrageenan-induced hind paw edema in female rats. The extract of Melia azedarach(150 mg/kg)possessedthe high antiinflammatory activity (25%) compared with indomethacin (32%) at 10 mg/kg after 2 hours of treatment[32].
The ethanolic extract of the leaves of Melia azedarachwas tested for analgesic activity using acetic acid induced writhing test in mice.The extract demonstrated 45.45% ($P<0.001$) and 67.05% ($P<0.001$) writhing inhibition at the doses of 250 and 500 mg/kg bw respectively[31].
The antipyretic activity of Melia azedarach leaves hydromethanol extract was investigated using the yeast induced pyrexia method in rabbits.The extract at 500 mg/kg dose, significantly ($P<0.0001$) reduced yeast-induced elevated temperature as compared with that of paracetamol[9].

Reproductive effect:
The follicular development in cyclic female albino rats wereinvestigated after oral administration of polar (PF) and non-polar (NPF) fractions of Melia azedarachseed extract at 24 mg/kg bw/day for 18 days. There was a significant reduction ($P = 0.05$) in the number of normal single layered follicles in females treated by M. azedarach. In addition, the extracts significantly reduced the total number of normal follicles (13.00 ±3.58 and 14.60 ± 2.25 after 24 mg/kg NPF and PF) treatments compared to control (216.00 ± 15.72 and 222.20 ± 19.52, respectively)[12].

The antifertility activity of ethanolic bark extract of Melia azedarach (200 and 400mg/kg, once daily for 15 days) was investigated in male rats. The male rats were allowed to mate with sexually active female of same strain and the percent of pregnancy, number of implantation and number of viable fetuses were observed. Both doses of Melia azedarach significantly decrease the percent of pregnancy, number of implantation and number of viable fetuses in the treated female rats compared to control rats[49].

Hepatoprotective effect:

The hepataprotective effect of leaf methanolic extract was investigated in paracetamol induced hepatic damage in rats. Rats received paracetamol showed decreased activity of antioxidative enzymes (GPx, GST, SOD and CAT) in liver and increase the serum enzymes (SGOT, SGPT and alkaline phosphate), bilirubin and decrease the total proteins content. Theleaf extract restored the activity of antioxidant enzymes and serum enzymes to the normal level[50].
The hepatoprotective effect of the leaves ethnolic extract of Melia azedarach (300 and 500 mg/kg) was also studied against simvastatin induced hepatotoxicity in rats. The leaf showed significant hepatoprotective activity which could be due to its antioxidant property. It significantly reduced the increased serum glutamate pyruvate ransaminase, glutamate oxaloacetate transaminase, alanine phosphatase and bilirubin[51].

The ethanol extract of the leaves of Melia azedarach was significantly decreased the elevated levels of serum glutamic pyruvate transaminase, serum glutamic oxaloacetic transaminase, alkaline phosphatase in rats intoxicated by carbon tetrachloride[52-53].

Dermatological effect:

A herbal cream containing a methanolic HPLC-standardized extract of Melia azedarach flowers was tested in skin diseases. The preparation possessed potent effect against bacterial skin diseases like cellulitis, pustules and pyogenic infections, in children. The obtained results were comparable to those of neomycin[54].

Antidiabetic effect:

The antidiabetic effect Melia azedarach was studied in streptozotocin induced diabetic rats. The ethanol extract of Melia azaderach significantly decreased blood glucose 14.8% ($P< 0.01$)[55].

Immunological effect:

Melia azedarach leaf extract inhibited the phagocytosis of opsonized sheep erythrocytes. This inhibition was time and dose- dependent, it was reverted after 48 hrs of removing the extract from the culture medium. Chemiluminescence in treated cells was also impaired[56].

Melanogenesis stimulation effect:

The effect of a 70% ethanol extract of Melia azedarach on melanogenesis was studied with investigation of the underlying mechanisms using A B16F10 mouse melanoma cell line. Melia azedarach extract(10, 20 and 40 µg/ml) increased melanogenesis through the upregulation of tyrosinase and tyrosinase-related protein-1 protein expression by post-transcriptional control in B16F10 cells[57].

Antilithiatic effect:

The antilithiatic effect of the aqueous extract was investigated against ethylene glycol-induced nephrolithiasis in male albino rats. Administration of aqueous extract (250 mg/kg bw, orally, for 28 days) with ethylene glycol (0.75%) reduced urinary calcium, oxalate, phosphate, and elevated urinary magnesium level. It also increased the urine volume, and reduced the tendency for crystallization. Histopathologically, the microcrystal deposition was reduced after treatment with the extract[58].

Hypolipidemic effect:

The antihyperlipidemic effect of ethanol extract of leaves of Melia azedarach was investigated in hyperlipidemia induced by high-fat diet supplemented with propylthiouracil for 15 days. The ethanol leaves extract (300, 600 and 1200mg/200 g bw), decreased total cholesterol and LDL levels 37.78% and 35.57% (300mg/200g bw), 45.99% and 40.39% (600mg/200g bw), and 56.29% and 52.42% (1200mg/200g bw). ED_{50} value of ethanol extract was 869 mg/200 g bw for total cholesterol and 1086.84 mg/200 g bw for LDL reduction[59].

Hypotensive effect:

The antihypertensive effect of ethanolic extract of the leaves of Melia azedarach (180, 360 and 720mg/ 200g bw) was studied in doca-salt (deoxycorticosterone acetate) induced hypertension in rats. Blood pressure was measured at day 0, 8, and 14. There was a significant difference in blood pressure before and after induction ($P<0.05$) in rats received the extract at a dose of 180mg/ 200g bw[60].

Butyrylcholinesterase inhibitory activity:
Aqueous, potassium phosphate buffer (pH 7.2), hydroethanolic solution 70:30 and hydroethanolic solution 50:50. extracts of Melia azedarach leaves were investigated for the inhibitory effect on butyrylcholinesterase activity in homogenates rat livers. The introduction of Melia azedarachextracts in the reaction mixture produced a variety of inhibitions (> 45 to 100%), independent on its concentration (0.5 to 2.0 mg/ml) and extract type[61].

Toxicity and side effects:

The acute oral toxicity study of Melia azedarach showed no mortality upto 610 mg/kg[50].The effects of n-hexane, ethyl acetate, n-butanol, chloroform, and aqueous fractions of the methanolic extract of Melia azedarach fruits (50 mg/kg bw, orally for 40 days) on serum glucose, lipid profile, GPT, ALP and creatinine were investigated in normal rabbits. All the extracts decreased the serum glucose, cholesterol, triglycerides and LDL concentrations significantly, and significantly increased serum HDL levels. All extracts (except the aqueous extract) significantly elevated the serum levels of GPT, ALP and creatinine. Of the tested extracts, only the aqueous fraction was found safe, as it caused no significant alterations in the serum levels of GPT, ALP and creatinine[62].

The toxicological studies performed on poultry, sheep, goat, swine and cows showed that the swine was the most susceptible and showed two main groups of symptoms. The first was gastrointestinal adverse effects(nausea, vomiting, violent colic, tympanites, diarrhoea and thirst). The second was neurological and respiratory adverse effects (coma, depressed respiration, marked dyspnoea, labored and irregular breathing, gasping, cyanosis and tachycardia).Different parts of the plant caused different reactions on the same species. Oral administration of aqueous extract of the fruit in rabbits caused gastrointestinal symptoms, while, subcutaneous injection caused dyspnoea, tremor, convulsions and death. The toxic principle would appear to be an alkaloid azaridine, tannin, bakacactone, and certain oils and proteins[63-64].

Melia azedarach poisoning was recorded in dog. Clinical signs of poisoningwere developed within hours and were manifested by gastrointestinal and CNS disturbances. However, the clinical signs appeared initially, were variable, but usually included tremors and a moderate limp in the dog's back leg, which evolved to a more severe condition in the following hours[65-66].
Administration of Melia azedarach at single doses (5 to 30 g/kg bw)in calves revealed that animals dosed with 15, 25 and 30 g/ kg bw were died. Clinical signs includedruminal stasis, anorexia, diarrhea, depression, incoordination, muscle tremors, difficulty to stand, sternal recumbence, hypothermia and dyspnea. Serum AST and CPK were increased. Signs were appeared after 4 to 24 h of dosing and the clinical signs continued for 20 to 72 h. Macroscopic signs wereincluded congestion of the intestine, with liquid content in rumen and intestines, focal or diffuse yellow discoloration of the liver, and brain congestion.The liver sections showed swollen and vacuolated hepatocytes, scattered throughout the parenchyma or concentrated in the periacinar zone. Degenerative and necrotic changes were recorded in the epithelium of the forestomachs. There was also necrosis of lymphoid tissue. Skeletal muscles had hyaline degeneration and fiber necrosis[67].

An African woman was died after using a decoction of the bark as an enema. A poisoning was also occurred after drinking a decoction of the leaves, the symptoms being severe included stomatitis, marked oliguria and sanguinous vomiting. Eating fruits was also caused poisoning in children. Death was also recorded in adult female after intake of a concoction prepared from the bark of a tree. On examination, the patient was found to be comatose. All reflexes were absent. The pupils were dilated and fixed. Pulse was 100/min and blood pressure 110/80. Later, the patient collapsed and her blood pressure was not recordable. She was also gasping and three days later the patient died[64,68-69].

Conclusion:

The current review discusses the chemical constituent, pharmacological, therapeutic and toxicological effects of Melia azedarach as promising herbal drug because of its wide pharmacological effects.

References:

[1] The plant list, Melia azedarach, http://www.theplantlist.org/tpl1.1/record/kew-2505106

[2] IT IS report, Melia azedarach, https://www.itis.gov/servlet/SingleRpt/ Single Rpt? search_topic=TSN&search_value=29024

[3] U.S. National Plant Germplasm System, Melia azedarach L., https://npgsweb.ars-grin.gov/gringlobal/taxonomydetail.aspx?id=23936

[4] Habib R, Mohyuddin A, Khan Z and Mahmood T. Analysis of non-polar chemical profile of Melia azedarach L Scientific Inquiry Rev 2017; 1(1):1- 7.

[5] Melia azedarach (Meliaceae), Persian lilac, http://docplayer.net/39432895-L-meliaceae-melia-azedarach-persian-lilac.html

[6] Sharma PC, Yelne MB and Dennis TJ. Data base on medicinal plants used in Ayurveda, Documentation and Publication Division, Central Council for Research in Ayurveda and Siddha, New Delhi, 2001: 389-406.

[7] Warrier PK, Nambiar and Ramankutty VPK. Indian Medicinal Plants, A Compendium of 500 Species, Hyderabad, Orient Longman Limited 1995.

[8] Descalzo AM and Coto C. Inhibition of the pseudorabies virus (Scisherpesvinyl) by an antiviral agent isolated from the leaves of Melia azedarach. Rev Argent Microbiol 1989; 21:133–140.

[9] Sultana S, Akhtar N and Asif HM. Phytochemical screening and antipyretic effects of hydro-methanol extract of Melia azedarach leaves in rabbits. Bangladesh J Pharmacol 2013; 8: 214-217.

[10] Khan AV, Parveen G, Alam MM and Singh VK. Ethnomedicinal uses of Neem in rural areas of Uttar Pradesh, India. Ethnomed and Pharmacog. II Rec. Prog. In Med Plants 2002; 7: 319-326.

[11] Seedl eaflets, Melia azedarach L. https://curis.ku.dk/ws/files/20496638/melia_ azadarach.pdf

[12] Roop JK, Dhaliwal PK and Guraya SS. Extracts of Azadirachta indica and Melia azedarach seeds inhibit folliculogenesis in albino rats. Braz J Med Biol Res 2005; 38(6) : 943-947.

[13] Azam MM, Mamun-Or-Rashid ANM, Towfique NM, Sen MK and Nasrin S. Pharmacological potentials of Melia azedarach L -A review. American Journal of BioScience 2013; 1(2): 44-49.

[14] Sumathi A. Evaluation of physicochemical and phytochemical parameters of Melia

azedarach L. leaves (Family: Meliaceae). Int J Pharm Pharm Sci 2013; 5(2): 104-107.

[15] Bachheti RK, Dwivedi H, Rana V, Rai I and Joshi A. Characterization of fatty acids in Melia azedarach L. seed oil. International Journal of Current Res and Rev 2012; 4(3):108-114.

[16] Abbas MK, Ahmad M and Barkat K. Antifungal, antioxidant and phytochemical screening of Melia azedarach flower extracts by using different solvents. Journal of Pharmac Res Internat 2017; 20(1): 1-12.

[17] Leelavathi AA and Doss VA. Evaluation of antioxidanat activity of Melia azedarach on depression induced rat brain tissue. Int J of Scie and Res 2014; 3(8): 224-229.

[18] Sen A and Batra A. Chemical composition of methanol extract of the leaves of Melia azedarach. Asian J of Pharmac and Clin Res 2012; 5: 42-45.

[19] Khan M, Kihara M and Omolosa A. Antimicrobial activity of Horsfieldia helwigii and Melia azedarach. Fitoterapia2001;72: 423-427.

[20] Krishnaiah GM and Prashanth GK. Phytochemical Studies and GC-MS Analysis of the Leaf Extracts of Melia azedarach Linn.Int J Adv Eng Tech Manag App Sci 2014; 1(6): 48-54.

[21] Han J, Lin WH, Xu RS, Wang WL and Zhao SH. Studies on the chemical constituents of Melia azedarach L. Yao Xue Xue Bao 1991;26(6):426-429.

[22] Ntalli NG, Cottiglia F, Bueno CA, Alché LE, Leonti M, Vargiu S, Bifulco E, Menkissoglu- Spiroudi U and Caboni P. Cytotoxic tirucallane triterpenoids from Melia azedarach fruits.Molecules 2010;15(9):5866-5877.

[23] Zhou F, Ma XH, Li ZJ, Li W, Zheng WM, Wang ZB, Zeng XM, Sun KH and Zhang YH. Four new tirucallane triterpenoids from the fruits of Melia azedarach and their cytotoxic activities.Chem Biodivers 2016;13(12):1738-1746.

[24] Pokhrel B, Raut S and Rijal S. Phytochemical screening , antimicrobial and antioxidant activity of Melia azedarach leaves in methanol solvent. World Journal of Pharmacy and Pharmaceutical Sciences 2015; 4(7):1562-1575.

[25] Rishi K and Singh R. Chemical components and insecticidal properties of Bakain (Melia azedarach L.)- A Review. Agri Rev 2003; 24(2): 101-115.

[26] Della Bona A and Nedel F. Evaluation of Melia azedarach extracts against Streptococcus mutans.J Med Food 2015;18(2):259-263.

[27] Kelati HA, Sani AM, Zadeh M and Yaghooti F. In vitro antibacterial activity of ethanolic extract from Melia azedarach fruit. IJBPAS 2015; 4(6): 4007-4015.

[28] Khan AV, Ahmed QU, Mir MR, Shukla I and Khan AA. Antibacterial efficacy of the seed extracts of Melia azedarach against some hospital isolated human pathogenic bacterial strains. Asian Pac J Trop Biomed 2011; 1(6): 452–455.

[29] Sen A and Batra A. Evaluation of antimicrobial activity of different solvents extracts of medicinal plant: Melia azedarach L. Int J Curr Pharm Res 2012; 4(2):67-73.

[30] Ramya S, Jepachanderamohan PJ, AlaguchamyN, Kalayanasundaram M and

Jayakumararaj R. In vitro antibacterial prospective of crude leaf extracts of Melia azedarach Linn against selected bacterial strains. Ethnobotanical Leaflets 2009;13: 254-258.

[31] Asadujjaman, Abu Saed, Hossain A and Karmakar UK. Assessment of bioactivities of ethanolic extract of Melia azedarach(Meliaceae) leaves. Journal of Coastal Life Medicine 2013; 1(2): 118-122.

[32] Akacha M, Lahbib K, Remadi MD and Boughanmi NG. Antibacterial, antifungal and anti-inflammatory activities of Melia azedarach ethanolic leaf extract. Bangladesh J Pharmacol 2016; 11: 666-674.

[33] Wachsman MB, Castilla V and Coto CE. Inhibition of foot and mouth disease virus (FMDV) uncoating by a plant-derived peptide isolated from Melia azedarach L leaves. Arch Virol 1998;143(3):581-590.

[34] Alché LE, Barquero AA, Sanjuan NA and Coto CE. An antiviral principle present in a purified fraction from Melia azedarach L. leaf aqueous extract restrains herpes simplex virus type 1 propagation. Phytother Res 2002; 16(4): 348-352.

[35] Alché LE, Ferek GA, Meo M, Coto CE and Maier MS. An antiviral meliacarpin from leaves of Melia azedarachL. Z Naturforsch C J Biosci2003;58(3-4):215-219.

[36] Wandscheer CB, Duque JE, da Silva MA, Fukuyama Y, Wohlke JL, Adelmann J and Fontana JD. Larvicidal action of ethanolic extracts from fruit endocarps of Melia azedarach and Azadirachta indica against the dengue mosquito Aedes aegypti. Toxicon 2004;44(8):829-835.

[37] Ilahi I, Khan I, Tariq M and Ahmad I. Larvicidal activities of different parts of Melia azedarach Linn. against Culex quinquefasciatus Say. (Diptera: Culicidae). Journal of Basic & Applied Sciences 2012; 8: 23-28 23.

[38] Selvaraj M and Mosses M. Efficacy of Melia azedarach on the larvae of three mosquito species Anopheles stephensi, Culex quinquefasciatus and Aedes aegypti (Diptera: Culicidae). European Mosquito Bulletin 2011;29: 116-121.

[39] Carpinella MC, Miranda M, Almirón WR, Ferrayoli CG, Almeida FL andPalacios SM. In vitro pediculicidal and ovicidal activity of an extract and oil from fruits of Melia azedarachL.J Am Acad Dermatol 2007;56(2):250-256.

[40] Mac ie MV, Morais SM, Bevilaqua SML, Camurca-Vasconcelos ALF, Costa CTC and Castro CMS. Ovicidal and larvicidal acivity of Melia azedarach extracts on Haemonchus contortus.Veterinary Parasitology 2006;140(1-2):98-104.

[41] Lee YS, Chung IB, Choi WH, Cho YJ, Chu JP, Min BI and Shin EH. Inhibitory effects of Melia azedarach L. extracts on the growth of Trichomonus vaginalis- Ultrastructural changes of Trichomonu vaginalis by Melia azedarach L. J Protozool Res 2007;17: 16-24.

[42] Ofulla AV, Chege GM, Rukunga GM, Kiarie FK, Githure JI and Kofi-Tsekpo MW.In vitro antimalarial activity of extracts of Albizia gummifera, Aspilia mossambicensis, Melia azedarach and Azadirachta indica against Plasmodium falciparum.Afr J Health Sci 1995;2(2):309-311.

[43] Akihisa T, Pan X, Nakamura Y, Kikuchi T, Takahashi N, Matsumoto M, Ogihara E, Fukatsu M, Koike K and Tokuda H. Limonoids from the fruits of Melia azedarach and their cytotoxic activities.Phytochemistry 2013;89:59-70.

[44] Jafari S, Saeidnia S, Hajimehdipoor H, Ardekani MRS, Faramarzi MA, Hadjiakhoondi A and Khanavi H. Cytotoxic evaluation of Melia azedarach in comparison with, Azadirachta indica and its phytochemical investigation. DARU Journal of Pharmaceutical Sciences 2013; 21:37-43.

[45] Nahak G and Sahu RK. In vitro antioxidative acitivity of Azadirachta indica and Melia azedarach leaves by DPPH scavenging assay. Nature and Science 2010;8(4): 22-28.

[46] Ahmed MF, Ahmed MA, Thayyil H, Zameeruddin K and Ibrahim M. Antioxidative activity of Melia azedarach Linn leaf extract. IJPT 2008; 7(1): 31-34.

[47] Marimuthu S, Balakrishnan P and Nair S. Phytochemical investigation and radical scavenging activities of Melia azedarach and its DNA protective effect in cultured lymphocytes. Pharmaceutical Biology 2013; 51(10): 1331-1340.

[48] Jain G, Pandit D, Gupta P and Jharia V. Evaluation of anti-inflammatory activity of seeds of Melia azedarach (Linn) in albino Wistar rats. Intern J of Sci & Engin Res 2015; 6(1): 1837-1846.

[49] Nivedhana Arthi P, Yasodha S and Agarwal A. Effect of Melia azedarach bark extract on bark extract on reproductive functions in male Wistar albino rats. Scholars Academic Journal of Biosciences 2017; 5(1):29-31.

[50] Ahmed MF, Srinivasa Rao A, Thayyil H, Ahemad SR and Ibrahim M. Role of Melia azedarach leaf extract in paracetamol induced hepatic damage in rats. Pharmacognosy Journal 2011; 3(21): 60-64.

[51] Rao AS, Ahmed MF and Ibrahim M. Hepatoprotective activity of Melia azedarach leaf extract against simvastatin induced hepatotoxicity in rats. Journal of Applied Pharmaceutical Science 2012; 02 (7): 144-148.

[52] Sumathi A. Hepatoprotective activity of Melia azedarach L. against carbon tetrachloride induced hepatic damage in rats. International Journal of Pharma Sciences and Research 2012; 3(5): 387-388.

[53] Ahmed MF, Rao AS, Ahemad SR and Ibrahim M. Phytochemical studies and hepatoprotective activity of Melia azedarach Linn, against CCl4 induced hepatotoxicity in rats. Journal of Pharmacy Research 2012;5(5): 2664-2667.

[54] Saleem R, Rani R, Ahmed M, Sadaf F, Ahmad SI, ul Zafar N, Khan SS, Siddiqui BS, Lubna, Ansari F, Khan SA and Faizi S. Effect of cream containing Meliaazedarach flowers on skin diseases in children.Phytomed 2008;15(4):231-236.

[55] Khan MF, Rawat AK, Khatoon S, Hussain MK, Mishra A and Negi DS.In vitro and in vivo antidiabetic effect of extracts of Melia azedarach, Zanthoxylum alatum, and Tanacetum nubigenum. Integ Med Res2018, http://creativecommons.org/licenses/by-nc-nd/4.0/

[56] Courrèges MC, Benencia F, Coto CE, Massouh EJ and Coulombié FC. In vitro antiphagocyticeffect of Melia azedarach leaf extracts on mouse peritoneal exudates cells. J Ethnopharmacol 1994;43(2):135-140.

[57] Yao C, Jin CL, Oh IG, Park CH and Chung JH. Melia azedarach extractstimulates melanogenesis through increase of tyrosinase-related protein 1 expression in B16F10 mouse

melanoma cells. Int J Mol Med 2015;35(6):1761-1766.

[58] Christina AJM, Najumadeen NAH, Kumar SV, Mainikandan N, Tobin GC, Venkataraman S and Murugesh N. Antilithiatic effect of on Melia azedarach ethylene glycol-induced nephrolitiasis in rats. Pharmaceutical Biology 2006; 44(6): 480 - 485.

[59] Herlina H, Untari B, Solihah I and Santia M. Antihyperlipidemic activity of ethanol extract mindi's leaves (Melia azedarach Linn.) in male Wistar rats induced propiltiouracil.Science and Technology Indonesia 2019; 4: 222-227.

[60] Andansari P, Candrasari A, Sutrisna EM, Rahma UF and Wahyuni NT. The effect of mindi leaf (Melia azedarach L.) from Indonesia on blood pressure in wistar white rats (Rattus norvegicus) induced by doca-salt (deoxycorticosterone acetate). J Bio Innov 2017;6 (5): 651-658.

[61] Marek CB, Itinose AM, Jorge TCM, Parizotto RA, Tebaldi NR and Reichert AM. Influence of leaf extracts from Melia azedarach L. on butyrylcholinesterase activity in rat liver. Journal of Medicinal Plants Research 2012;6(22):3931-3938.

[62] Ilahi I, Qureshi I and Ahmad I. Effects of fractions of Melia azedarach (L.) fruit extracts on some biochemical parameters in rabbits. Arch Biol Sci, Belgrade 2014; 66 (4):1311-1319.

[63] Nath B. Chemical examination of the heartwood of Melia azedarach. Chemical Abstracts 1955; 49:4942.

[64] Watt JM and Breyer-Brandwijk MG. Medicinal and poisonous plants of South and Eastern Africa. E and S Livingstone, Edinburgh and London, 2nded 1962.

[65] Hare WR, Schutzman H, Lee BR and Knight MW. Chinaberry poisoning in two dogs.J Am Vet Med Assoc 1997; 210(11):1638-1640.

[66] Ferreiro D, Orozco J, Mirn C, Real T, Hernndez-Moreno D, Soler F and Pérez-Lopez M. Chinaberry tree (Melia azedarach) poisoning in dog: A case report. Top Companion Anim Med 2010; 25: 64-67.

[67] del Mendez MC, Elias F, Aragao M, Gimeno EJ and Riet-Correa F. Intoxication of cattle by the fruits of Melia azedarach. Vet Hum Toxicol 2002;44(3):145-148.

[68] Carratala RE. Fatal intoxication by fruit from Melia azedarach Linn. Chemical Abstracts 1939; 33: 6951.

[69] Kiat TK. Melia azedarach poisoning. Singapore Medical Journal 1969; 10(1): 24-28.