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Nelumbo Nucifera (Lotus): A Review on Ethanobotany, Phytochemistry and Pharmacology

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ABSTRACT

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Nelumbo nucifera Pharmacological activities Phytoprinciples Traditional uses Nelumbo nucifera Gaertn (Nymphaeaceae), a perennial aquatic plant, has been used as a medicinal herb in China and India. It has been recorded in the most famous medicinal book in China for more than 400 years. Different part of plant (leaves, seeds, flower, and rhizome) can be used in traditional system of medicine. In traditional system of medicine, the different parts of plant is reported to possess beneficial effects as in for the treatment of pharyngopathy, pectoralgia, spermatorrhoea, leucoderma, smallpox, dysentery, cough, haematemesis, epistaxis, haemoptysis, haematuria, metrorrhagia, hyperlipidaemia, fever, cholera, hepatopathy and hyperdipsia. Following the traditional claims for the use of *N.nucifera* as cure of numerous diseases considerable efforts have been made by researchers to verify it's utility through scientific pharmacological screenings. The pharmacological studies have shown that *N.nucifera* posseses various notable pharmacological activities like amti-ischemic, antioxidant, anticancer, antiviral, antiobesity, lipolytic, hypocholestemic, antipyretic, hepatoprotective, hypoglycaemic, antidiarrhoeal, antifungal, antibacterial, antiinflammatory and diuretic activities. A wide variety of phytoprinciples have been isolated from the plant. The present review is an effort to consolidate traditional, ethnobotanic, phytochemical and pharmacological information available on N.nucifera.

1. Introduction

Nelumbo nucifera, now placed in the mono-generic family Nymphaeaceae, has numerous common names (e.g. Indian lotus, Chinese water lily and sacred lotus) and synonyms (Nelumbium nelumbo, N. speciosa, N. speciosum and Nymphaea nelumbo)[1][•] Worldwide, there are only two species of Nelumbo: N. lutea Willd. (synonyms: N. pentapetala (Walter) Fernald and Nelumbium luteum Willd.) and N. nucifera (synonyms: N. speciosa Willd, Nelumbium speciosum Willd, Nelumbium N. Druce and Nymphaea N. L)[2,3]. N. nucifera Gaertn., the Indian or sacred lotus, is found throughout Asia and Australia, whereas N. lutea, the American lotus or water chinquapin, occurs in eastern and southern North America[4]. N. lutea is considered to be a subspecies of N. nucifera[5]. In India, N. nucifera, commonly known as lotus, kamala or padma, is an aquatic

species, requiring plenty of space and full sun in order to thrive. It has stout, creeping, yellow rhizomes and green fruits. Leaves are large, of both types, aerial as well as floating orbicular 20-90 cm. in diameter, abruptly acute to form a short tip, petiolate, entire glaucous, non-wettable, strong cupped in case of aerial leaves and flat in case of floating ones. Fruit is an aggregate of indehiscent nut-lets. Ripe nutlets are ovoid, roundish or oblongish upto 1.0 cm long 1.5 cm broad, with hard smooth, brownish or grayish black pericarp which is faintly longitudinally striated, pedunculated and one seeded. Seeds fill in the ripe carpel [6].There are two varieties of 'kamala': one has white flowers and is commonly called 'pundarika' or 'sveta kamala'; the other has pink or reddish-pink flowers and is called 'rakta kamala'[7]. The whole plant with flowers is known as 'padmini', the rhizomes as

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'kamalkand', the tender leaves as 'sambartika', the peduncle as 'mrinal' or 'visa', the stamens as 'kirijalaka', the torus as

upon padma is known as 'makaranda' or 'padma- Madhu'[8]. The sepals, petals and stamens are spirally arranged, passing gradually one into another [9]. The plant is often cultivated for its elegant sweet scented flowers, which are the national flower of India. The present review is a comphrensive account of traditional uses and ethnobotonacial, phytochemical and pharmacological investigations carried out on the plant, which may explain the multifaceted role of this medicinal herb.

1.2 Uses described in traditional medicine

Plants have been used as source of medicine by mankind since ancient times. The indigenous knowledge of many tradition communities has been formulated, been documented and eventually become organized systems of medicine such as ayurveda, siddha, unani, and other systems out of India[.] In Ayurveda this plant is used as a diuretic and anthelmintic and in the treatment of strangury, vomiting, leprosy, skin diseases and nervous exhaustion[1,10,11]. In popular medicine it is used in the treatment of tissue inflammation, cancer, skin diseases, leprosy and as a poison antidote [12,13]. Rhizomes are prescribed as demulcents for haemorrhoids and are beneficial in dysentery, chronic dyspepsia, and have nutritive, diuretic and cholagogue activities[14,15]. The stem is used in indigenous Ayurvedic medicine as a diuretic, anthelmintic, to treat strangury, vomiting, leprosy, skin disease and nervous exhaustion. The leaves are used for the treatment of haematemesis, epistaxis, haemoptysis, haematuria, metrorrhagia and hyperlipidaemia[16]. The flowers are useful in the treatment of diarrhoea, cholera, fever and gastric ulcers.^[12] The seeds and fruits are used as a health food in Asia and to treat many ailments, including poor digestion, enteritis, chronic diarrhoea, insomnia, palpitations, spermatorrhoea, leucorrhoea, dermatopathy, halitosis, menorrhagia, leprosy, tissue inflammation, cancer, fever and heart complaints, and as an antiemetic. poisoning antidote. diuretic and refrigerant[12,17,8,18]. Lotus seedpods are sometimes used as a traditional medicine for haemostatic function [19]. The seed powder mixed with honey is useful in treating cough [10]. Embryos of lotus seed are used in traditional Chinese medicine to overcome nervous disorders, insomnia, high fevers (with restlessness) and cardiovascular diseases (e.g. hypertension, arrhythmia)[20].

1.3 Chemical constituents

A wide variety of chemical constituents are isolated from various parts of *N.nucifera*. The structures of major chemical constituents of plant are shown in figure.

I. Fruits and seeds

The seeds of *N. nucifera* are rich in asparagin, fat, protein, starch and tannin[22]. The lotus seed is composed of three parts – integuments, plumule and cotyledons, which comprise 3.74%, 3.03% and 93.23% of the mass, respectively. The average weight of 100 seeds is 87.35 g. A large amount of glutathione is

'padmakosa', the seed as 'karnika' or 'padmaksya', and the honey formed in the flowers by the bees feeding

contained in the plumule (13 g per plumule) and cotyledons (164 g per cotyledon) of N.nucifera; the amount of total plumule increases gradually in the maturing seed. The reduced form of glutathione is dominant in the early stages, while the amount of oxidised form exceeds that of the reduced form at the end of maturation. The amount of the reduced form of glutathione in the unripe fruit decreases markedly upon storage for 1 year. In general, the rate of germination of the stored seeds seems to be closely related to the content of reduced glutathione[21,22]. Normally, lotus seeds are rich in protein, amino acids, unsaturated fatty acids and minerals[23]. Nelumbo seeds have also been found to contain a variety of minerals such as chromium (0.0042%), sodium (1.00%), potassium (28.5%), calcium (22.10%), magnesium (9.20%), copper (0.0463%), zinc (0.0840%), manganese (0.356%) and iron (0.1990%). Other relevant nutritional elements include total ash (4.50%), moisture (10.50%), crude carbohydrate (1.93%), crude fibre (10.60%), fat (72.17%), and protein (2.70%); its energy value is 348.45 cal per 100 g.^[24] The major secondary metabolites present in the seeds (Figure 1) are alkaloids such as dauricine (1), lotusine (2), nuci-ferine (3), pronuciferine (4), liensinine (5), isoliensinine (6), roemerine (7), neferine (8) and armepavine (9).^[25,26,27,28,29,20,30,31] Procyanidin (10) was isolated from the seedpod of N. nucifera.^[19] Seeds also gallic acid (11), D(-)-3 0- bromo-O-methylcontain D-1,2,3,4-tetrahydro-6-methoxy-1-(p-methox armepavine(12) -2-methyl-7-isoquino- linol (13), saponins benzly) and carbohydrates[34]. The seed polysaccharides have also been isolated and characterized. Acid hydrolysis and methylation showed that seed polysaccharides are mainly composed of four types of monosaccharide: D-galactose, L arabinose, D-mannose and D-glucose[32]. 13C-NMR and insource pyrolysis-mass spectrometry analysis showed that the fruit wall and seed coat of N. nucifera are composed of a complex of polysaccharides, based primarily on galactose and mannose units and insoluble tannins. Curie-point pyrolysis-gas chromatography-mass spectrometry analysis of the fruit walland seed coat of Nelumbo produced some pyrolysis polysaccharide products, including 2-furaldehyde, 2hydroxy methyl furan ,(SH)- furan-2-one, 2,3-dihydro-5methylfuran-2-one, 2-hydroxy-3- methyl-2-cyclo penten-l-one, 5hydroxymethyl-2-furaldehyde, anhydrosugar(levogalactosan), 1,2benzenediol 4-methyl-1, 2-benzenediol,1,6-anhydro-a -Dglucopyranose, 2,6-dimethoxy 4- ethnylphenol and 4-carboxy-2methoxyphenol[33].

II.Leaves

Combined gas/liquid chromatography–mass spectroscopy has shown that the leaves are rich in a number of alkaloids. In the analysis of non-phenolic fractions of the leaf extract (Figure 2), the major components had retention data and mass spectra identical to those of nuciferine, roemerine, anonaine (14), pronuciferine and N-nornuciferine (15). Two benzylisoquinoline alkaloids, (+)-1(R)-coclaurine (16) and (-)-1(S)-norcoclaurine (17), were also found in leaf extract of N. nucifera[21]. Six nonphenolic bases were identified: roemerine, nuciferine, anonaine,pronuciferine, N-nornuciferine and liriodenine(18) and two

phenolic bases, armepavine and N-methyl-coclaurine (19), were also found in N. nucifera leaf extract.^[36] Dehydro- emerine (20), dehydronuciferine (21),dehydroanonaine (22),Nmethylisococlaurine (23),anonaine, pronuciferine. Nnornuciferine, O-nornuciferine (24), nuciferine, remerine (25), roemerine, armepavine, liensinine, isoliensinine, negferine, asimilobine (26) and lirinidine (27) were isolated from leaves and petioles[38,35,37,39,40]. The leaves also contain a glycoside, nelumboside (28), and flavonoids such as quercetin (29) and leuco-anthocyanidin which were identified as leucocyanidin (30) and leucodelphinidin (31)[37,42]. The presence of some other the leaves such as quercetin flavonoids in 3-O-aarabinopyranosyl-(1!2)-\beta-galactopyranoside, quercetin-3-O-β-Dglucuronide (32), rutin (33),(+)-catechin (34), hyperoside (35), isoquer-citri (36) and astragalin (37) has also been reported[38,41]. Scanning electron microscopy and chemical analysis of the chloroform extract of leaves showed that the wax was composed of a mixture of aliphatic compounds, principally nonacosanol and nonacosanediols. Analysis of gas chromatography spectra of lotus leaves waxes showed a much lower proportion of the secondary alcohol nonacosan-10-ol (16.2%by weight) compared with nonacosanediols (64.7%). Gas chromatographic analysis of the extracted leaf waxes revealed nonacosan-10-ol (16.2 \pm 1.1%), triacontan-7-ol (2.4 \pm 0.4%), nonacosane-4, 10-diol ($18.6 \pm 0.5\%$), nonacosine -5, 10-diol (34.1 \pm 1.9%), nonacosane-10, 13-diol (12.0 \pm 0.7%), hentriacontane-12, 15-diol (1.8 \pm 0.0%), tritriacontane-9, 10-diol (0.7 \pm 0.0%) and octadecanoic acid (0.7 ± 0.0) [43].

III. Flower

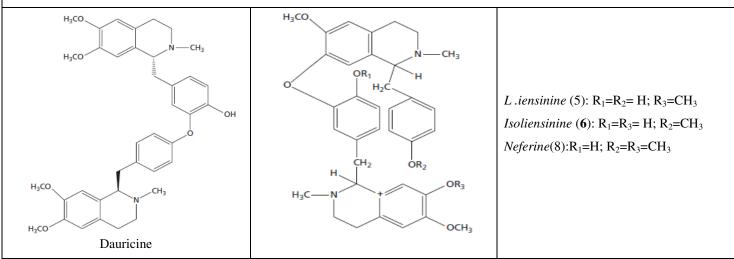
Several flavonoids have been identified in the stamens of *N.nucifera* (Figure 3). These include kaempferol (38) and seven of its glycosides: kaempferol 3-O- β -D-galactopyranoside (39), kaempferol 3-O- β -D-glucopyranoside (40), kaempferol 7-O- β -D-

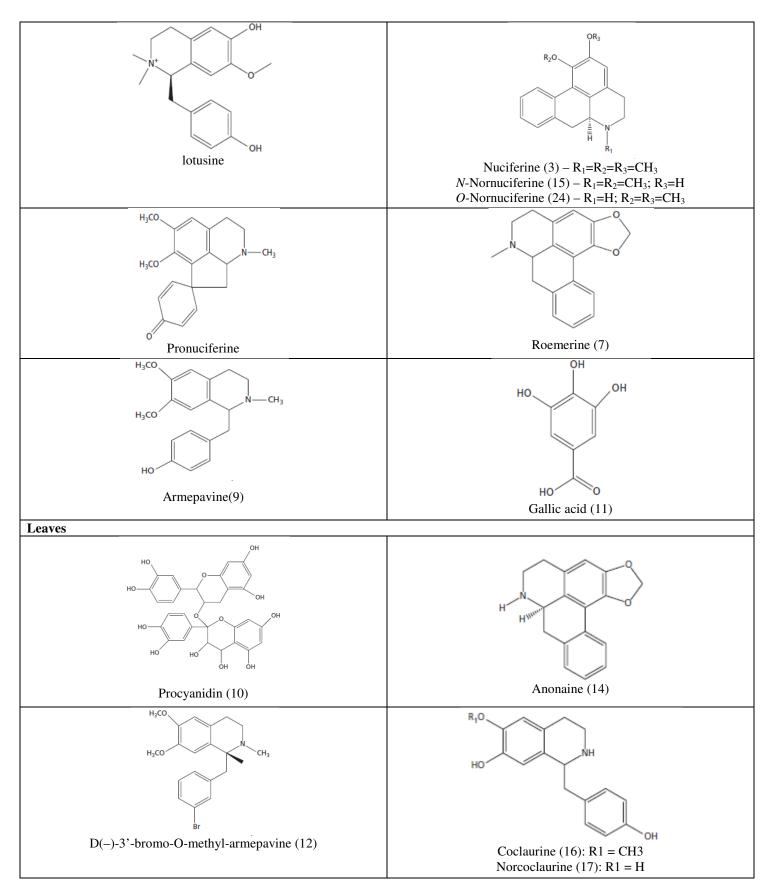
glucopyranoside (41), kaempferol 3-O-a-L-rhamnopyranosyl-(1-6)-β -D-glucopyranoside (42). kaempferol 3-O-a-Lrhamnopyranosyl-(1-2)- β -D-glucopyranoside (43), kaempferol 3-Oa-L-rhamnopyranosyl -(1-2)- β- D-glucurono-pyranoside (44), kaempferol-3- O- β- D-glucurono-pyranoside (45), kaempferol 3-O-β-D-glucuronopyranosyl methylester (46), myricetin 3 0 ,5 0 dimethylether 3-O- β -D-glucopyranoside (47), quercetin 3-O- β -D-glucopyranoside (48), nelumboroside А (49) and nelumboroside B (50). It also contains two isorhamnetin glycosides: isorhamnetin 3-O-β-D-glucopyranoside (51) and isorhamnetin 3-O-a-L-rhamnopyranosyl- $(1\rightarrow 6)$ - β -D-glucopyranoside (52)[44,45,46]. Some non-flavonoid compounds, including adenine, myo-inositol, arbutin (53) and β-sitosterol glucopyranoside (54), have also been identified in stamen extract[46].

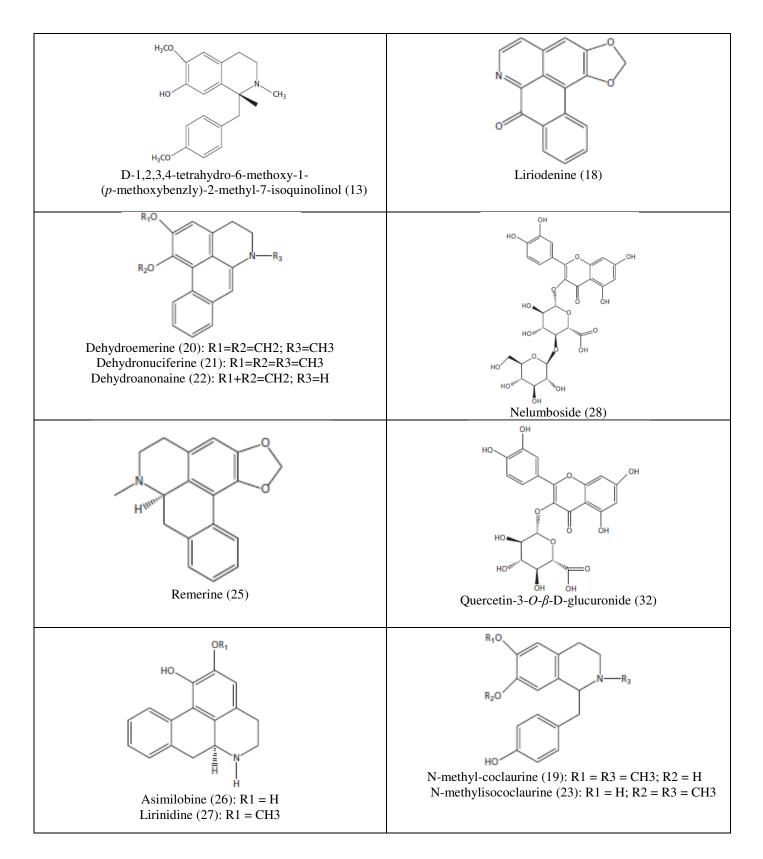
IV.*Rhizomes*

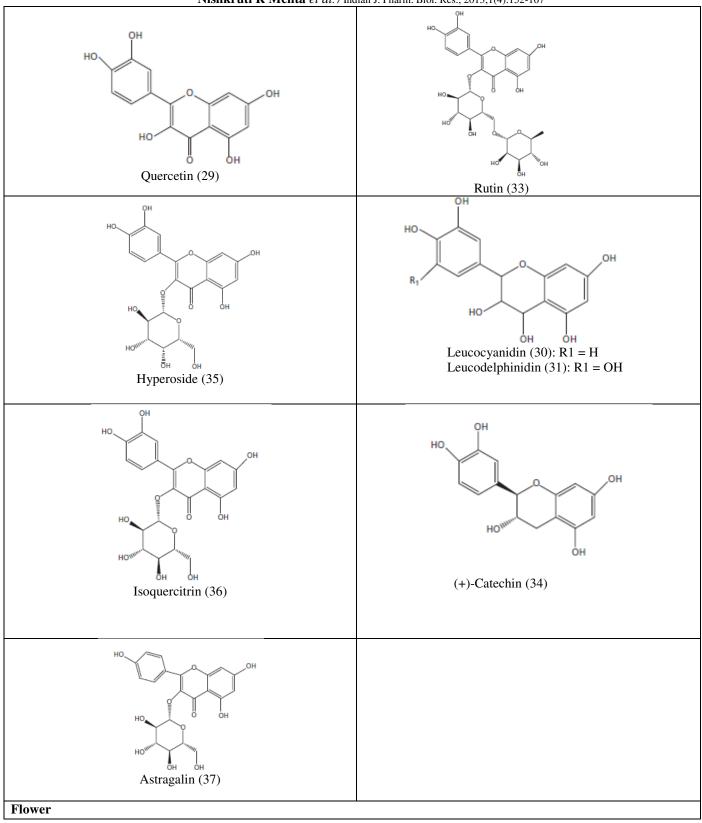
The rhizomes of lotus are consumed as a vegetable in Asian countries. They are used as health foods because of their mineral content. Abundant starch grains are present throughout the tissue. Fresh rhizome contains 31.2% starch, which shows no characteristic taste or odour. The binding and disintegration properties of isolated Nelumbo starch have been compared with maize and potato starch; Nelumbo starch was found to be superior as an adjuvant in the preparation of tablets. It has been reported that 50% (v/v) alcohol is required for maximum extraction of the constituents[48]. The methanol extract of the rhizome has been found to possess a steroidal triterpenoid – betulinic acid [49]. Fresh rhizome contains 83.80% water, 0.11% fat, 1.56% reducing sugar, 0.41% sucrose, 2.70% crude protein, 9.25% starch, 0.80% fibre, 1.10% ash and 0.06% calcium. The vitamins thiamine (0.22 mg/100 g), riboflavin (0.6 mg/100 g), niacin (2.10 mg/100 g) and ascorbic acid (1.5 mg/100 g) and an asparagine-like amino acid (2%) are also present in the rhizomes. The oxalate content of rhizome was found to be 84.3 mg/100 g[47].

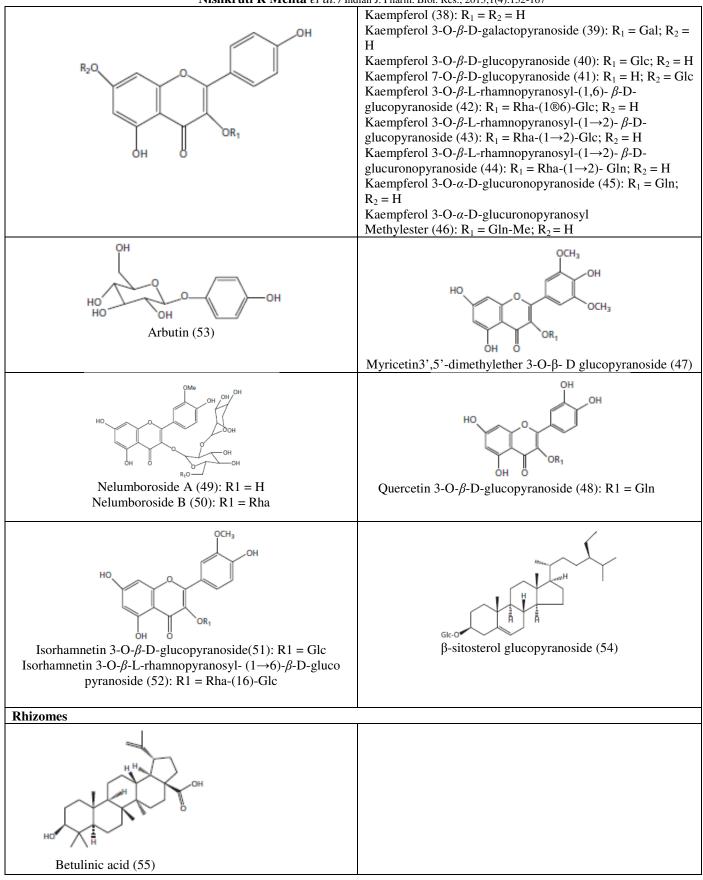












2. Pharmacological activities

N.nucifera has been screened scientifically for various pharmacological activities like anti-ischaemic activity, antioxidant activity, hepatoprotective activity, anti-inflammatory activity, anti-fertility activity, anti-arrhythmic activity, anti-fibrosis activity, antiviral activity, antiproliferative activity, antidiarrhoeal activity, psychopharmacological activity, diuretic activity, antioxidant activity, antipyretic activity, immunomodulatory activity, hypoglycaemic activity, aldose reductase inhibitory activity, antibacterial, aphrodisiac activity, antiplatellet activity, cardiovascular activity, anti-obesity activity, lipolytic activity, hypocholesterolaemic activity, hepatoprotective activity, anticancer activity.

2.1Seeds

I. Anti-ischaemic activity

The seed of *N. nucifera* shows potent anti-ischaemic effects in the isolated rat heart. The effective amount of seed extract against ischaemia induced in the isolated rat heart was assessed by measuring cardiac output, blood pressure, aortic flow and coronary flow; doses of 0.1-30 mg/ml were tested. Maximal recovery was seen at a dose of 10 mg/ml, although cardiac output was similar after treatment with 3 or 10 mg/ml doses (63.5 ± 3.2 and 65.8 ± 4.0 ml/min, respectively). Thus, the 3 mg/ml dose was determined to be the optimum dose for anti-ischaemic effects in the rat. *N.nucifera* extract has distinct anti-ischemic effects through calcium antagonism[50].

II. Antioxidant activity

The ethanol extract of the seed has been evaluated for its antioxidant activity using the 2,2-diphenyl-1picrylhydrazyl (DPPH) free radical assay. Potent free radical scavenging effects were seen, with a median inhibition concentration (IC50) of 6.49 mg/ml[51]. Procyanidin and condensed tannin isolated from the seed pod of N. nucifera have several pharmacological activities, including lipid auto-oxidation, lipoxygenase inhibition and free radical scavenging comparable to butylated hydroxytoluene (0.1%). At a concentration of 62.5 mg/ml, procyanidin inhibited lipoxygenase activity by more than 90%, with an IC50 value of 21.6 mg/ml[19]. Furthermore, the antioxidant activity of the hydroalcoholic extract of seed has been reported using the DPPH and nitric oxide methods[34]. The hydroalcoholic extract exhibited strong free radical scavenging activity, with IC50 values of 6.12 ± 0.41 mg/ml in the DPPH assay and 84.86 ± 3.56 mg/ml in the nitric oxide assay. These values were lower than those of rutin, a standard free radical scavenger. Administration of the hydroalcoholic extract of seed to Wistar rats at 100 and 200 mg/kg for 4 days before carbon tetrachloride treatment caused significant dose-dependent increases in the levels of superoxide dismutase (SOD) and catalase, and a significant decrease in the level of thiobarbituric acid reactive substances. These changes observed at 100 mg/kg were comparable to those observed with vitamin E at 50 mg/kg[34].

III. Hepatoprotective activity

An ethanolic extract of the seed of *N.nucifera* was studied for hepatoprotective effects in carbon tetrachloride and aflatoxin B1-induced hepatotoxicity models. Cell death caused by carbon tetrachloride was significantly inhibited in a dose-dependent manner by the ethanolic extract at concentrations between 10 and 500 mg/ml. The same extract reduced the genotoxicity of aflatoxin B1, showing complete inhibition at a concentration of 250 mg per plate[51].

IV. Anti-inflammatory activity

The seed extract of *N. Nucifera*, at a dose of 10 mg/kg, inhibited the production of pro-inflammatory cytokine tumour necrosis factor-a (TNF-a) and increased anti-inflammatory cytokine IL-10 in female BALB/c mice with systemic inflammation induced by an intraperitoneal injection of lipopolysaccharide (LPS)[52]. Studies in LPS-challenged mice showed that a high dose of 20 mg/day of seed extract significantly decreased TNF-a levels in the serum and significantly increased the levels of IL-10 produced by peritoneal macrophages. This result demonstrated that administration of the *N.nucifera* seed extract before systemic inflammation attenuates acute inflammation *in vivo*[52].

V. Anti-fertility activity

Chauhan et al evaluated the effect of Nelumbo nucifera Gaertn. (Nymphaeaceae) on male reproductive function and fertility, 50% ethanolic extract of its seeds was administered orally to male rats at the dose levels of 50, 100 and 200 mg/rat per day for 60 days. The body weights were not affected, whereas the weights of reproductive organs decreased significantly after this treatment. Significant suppression of cauda epididymal sperm count and motility was observed. Fertility was decreased in this treatment by 100% in Nelumbo nucifera-treated rats. The testosterone level of serum was declined significantly. Thus the ethanolic extract of N.nucifera seed was antispermatogenic effect in male rats.^[53] The 50% ethanol extract of N.nucifera seed has been reported to possess anti-fertility activity in inbred Wistar strain cyclic female albino rats- at a dose of 800 mg/kg, oral administration of N.nucifera extract brought about a significant decline in the weight of Ovary; Control (43±4.75mg), N.nucifera extract treated (25±3.86mg), Uterus; Control (236±0.004mg), N.nucifera extract treated (214±0.007mg) and Vagina; Control (221±0.002mg), N.nucifera extract treated (178±0.003mg). In addition, the diestrous phase of the estrous cycle was found to be prolonged; Control (1.81±0.21) days, *N.nucifera* extract treated (3.62±0.42) days. N.nucifera extract has the anti-estrogenic nature without altering the general physiology of the female rats[54].

VI. Anti-arrhythmic activity

Neferine, an alkaloid isolated from the seed embryo of *N*. *nucifera*, has been reported to have anti-arrhythmic effects on rabbit sinoatrial nodes and clusters of cultured cardiac myocytes

from neonatal rats[55,56]. Neferine inhibits the slow transmembrane Na⁺ and/or Ca²⁺ current of the myocardium, which leads to its anti-arrhythmic action[55,56]. Neferine causes non-specific inhibition of the Na⁺, Ca²⁺ and K+ cardiac transmembrane currents in guinea-pig papillary muscles and atria, which relates to its anti-arrhythmic activity[27]. Experiments in anaesthetised cats showed that neferine, when administered intravenously, at concentrations of 1-10 mg/kg dose-dependently decreased the amplitude and prolonged the duration of the monophasic action potential, decreased left ventricular pressure and prolonged the sinus cycle length. These effects demonstrated that neferine has similar electromechanical properties in the heart as quinidine[57]. Liensinine is another alkaloid isolated from the seed of the lotus which has been reported to have anti-arrhythmic effect; its mechanism may be related to blockade of Ca²⁺ and Na⁺ influx. Intravenous liensinine at dose 3 mg/kg temporarily inhibited all parameters of haemodynamics in anaesthetised and pithed rats. Its effects were slightly stronger than those of quinidine (3 mg/kg); the inhibitory effects of liensinine (12 mg/kg) on all haemodynamic parameters were comparable to those of verapamil (1 mg/kg). The haemodynamic effects of liensinine may be similar to verapamil but different from quinidine.^[58] Liensinine at 10-100 mM was shown to concentration-dependently decrease the amplitude of the action potential. The effects of liensinine on slow action potentials and slow inward currents have also have been studied and suggest that liensinine possesses calcium antagonistic effects[59].

VII. Anti-fibrosis activity

The inhibitory effect of isoliensinine isolated from the seeds of *N.nucifera* was studied on bleomycin-induced pulmonary fibrosis in mice.^[60] Administration of isoliensinine remarkably suppressed the increase in hydroxyproline content and abated the lung tissue injury induced by bleomycin. It enhanced SOD activity and decreased the malondialdehyde level in a concentration-dependent manner. Moreover, isoliensinine significantly inhibited the over-expression of TNF- α and transforming growth factor- β (TGF- β) induced by bleomycin. These results indicated that isoliensinine possesses significant inhibitory activity against bleomycin -induced pulmonary fibrosis, probably due to its antioxidant and/or anti-inflammatory activities and inhibitory effect on TNF- α and TGF-b induced by bleomycin.^[60]

VIII. Antiviral activity

Ethanol extract of the *N.nucifera* seed (100 mg/ml) significantly suppressed replication of herpes simplex virus-1 (HSV-1), with an IC50 of 50 mg/ml. Furthermore, a sub-fraction of *N. Nucifera* (NNFR) has an inhibitory effect on HSV-1. NNFR at a concentration of 50 mg/ml inhibited HSV-1 replication in HeLa cells by up to 85.9%, attenuating aciclovir-resistant HSV-1 propagation.^[61] In a bioassay-guided fractionation, NNFR significantly blocked HSV-1 multiplication in HeLa cells without apparent cytotoxicity. The production and mRNA transcription of infected cell protein was found to be decreased in NNFR-treated

HeLa cells. The antiviral actions of NNFR is therefore likely to be mediated through inhibition of immediate early transcripts, such as infected cell protein (ICP) 0 and ICP4 mRNA and then blocking the downstream accumulation of all viral products[61].

IX. Antiproliferative activity

The ethanolic extract of N. nucifera seed suppressed cell cycle progression, cytokine gene expression and cell proliferation in human peripheral blood mononuclear cells (PBMC). To study the effects on PBMC proliferation, resting cells or cells activated with phytohaemaglutinin (PHA) were treated with 100 mg/ml of an ethanolic extract of N. nucifera seed[13]. Cell proliferation was determined on the basis of uptake of tritiated thymidine. PBMC proliferation was not affected by DMSO treatment. Ciclosporin blocked PHA-activated PBMC proliferation. Ethanolic extract of N. nucifera seed (100 mg/ml) significantly suppressed PBMC proliferation stimulated with PHA. The ethanol extract of N. Nucifera suppressed proliferation in PHA-activated PBMC. The stimulated cell cycle progression in PHA-activated PBMC was significantly arrested at G0/G1 stage, and gene expression and production of interleukin(IL)-2, IL-4, IL-10, interferon gamma (IFN-g) and cyclin-dependent kinase 4 in activated PBMC were also decreased by N. nucifera extract[13]. Liu and co-workers have isolated (S)-armepavine ($C_{19}H_{23}O_3N$; molecular weight 313) from N. nucifera seed extract. (S)-Armepavine inhibited the proliferation of human PBMCs activated with PHA and gene expression of IL-2 and IFN-g without direct cytotoxicity, which leads to the improvement of autoimmune diseases in MRL/MpJlpr/lpr mice[29]. The mechanism involved in these inhibitions is blockade of membrane-proximal effectors such as IL-2- inducible T cell kinase and phospholipase C g in a phosphatidylinositol 3kinase-dependent manner[63]. An isoliensinine alkaloid isolated from the seed embryo had inhibitory effects on the proliferation of porcine coronary arterial smooth muscle cells induced by angiotensin II. Its mechanisms were investigated by counting cultured cell number, the MTT assay, immunohistochemistry and Western blotting. Angiotensin II (0.1 mM) significantly evoked cell proliferation by 42%, which could be dosedependently inhibited by 0.01-3 mM isoliensinine; the percentage of inhibition of isoliensinine was 25% at 0.01 mM. These results suggest that isoliensinine possesses antiproliferative effect, which is related to a decrease in the over-expression of platelet-derived growth factor, basic fibroblast growth factor and proto-oncogenes c-fos, c-myc and hsp70[63]. The effect of neferine on platelet aggregation, thromboxane A2/prostaglandin (PG) I2 and cAMP/cGMP balance were studied using turbidimetry and radioimmunoassay. It significantly inhibits rabbit platelet aggregation induced by ADP, collagen, arachidonic acid and platelet-activating factor with IC50 values of 16, 22, 193 and 103 mM, respectively. Neferine was found to increase vascular 6keto-PGF1a and platelet cAMP levels in a dose-dependent manner, but inhibited arachidonic acid-stimulated thromboxane A2 release from platelets[64].

X. Immunomodulatory

The immunomodulatory activity of N.nucifera seed extract was evaluated using various in vivo models including the total and differential leukocyte count (TLC and DLC), nitrobluetetrazolium reduction (NBT) test, neutrophil adhesion test, phagocytic response and delayed type hypersensitivity (DTH) reaction. Sheep red blood cells (SRBC, 5×109 cells/ml) were used to immunize the animals. N.nucifera seed extract at the doses of 100 and 300 mg/kg was administrated. A dose-dependent potentiation of DTH reaction induced by SRBC was observed from the extracts. The percentage of neutrophil adhesion to the nylon fiber was increased in rhizome extract treated groups (54.86 and 54.23%). The extract of seeds of N. nucifera altered the total and differential WBCs count, potentiated the effect on DTH response and phygocytosis. Thus extract of seed of N. nucifera stimulate defense system by modulating several immunological parameters[65].

2.2 Rhizomes

I. Antidiarrhoeal activity

The antidiarrhoeal potential of *N. nucifera* rhizome extract has been reported. A study was undertaken to evaluate the effects of methanolic extract of rhizomes of *N.nucifera* Gaertn for its antidiarrhoeal potential against several experimental models of diarrhoea in rats. The extract produced significant inhibitory effects against castor-oil-induced diarrhoea and PGE2-induced enteropooling; the propulsive movements of a charcoal meal were also reduced significantly[66].

II. Hypoglycaemic activity

The oral hypoglycaemic effect of N. nucifera was demonstrated using an methanolic extract of the rhizome, which markedly reduced the blood sugar level of normal, glucose-fed hyperglycaemic and streptozotocin-induced diabetic rats, when compared with control animals. The extract (300 mg/kg and 600 mg/kg, orally) caused a reduction of blood glucose levels in streptozotocin-induced diabetic rats by 53% (p<0.001) and 55% (p < 0.001) respectively at the end of 12 h. The results of this study indicate that the methanol extract of the rhizome possesses favourable hypoglycaemic activity in hyperglycaemic animals taking chlorpropamide as a standard[67]. An anti-diabetic constituent (tryptophan) has been isolated from the nodes of lotus rhizome by the analysis of spectroscopic evidence.[68] In glucosefed hypoglycaemic mice, the methanolic extract of nodes at a dose of 400 mg/kg and 100 mg/kg of isolated tryptophan showed potential anti-diabetic activities[68].

III. Psychopharmacological activity

The methanol extract of the rhizome of *N. nucifera* produced significant psychopharmacological actions in rats and mice. Reduction in spontaneous activity and a decrease in exploratory behaviour in the head dip and Y-maze tests were reported. Thus, the extract possesses most of the pharmacological characteristics of a minor tranquilizer[69].

Review Article

IV. Diuretic activity

The diuretic activity of *N. nucifera* rhizome was reported. The methanol extract of the rhizome induced significant diuresis in rats at doses of 300, 400 and 500 mg/kg. There was a dose-dependent increase in the volume of urine, with Na⁺ and Cl⁻ excretion, accompanied by a significant excretion of K⁺. The increase in volume of urine was less than with the standard diuretic Furosemide (20 mg/kg). There was a significant increase in natriuretic and chloruretic activity but kaliuresis was less than natriuresis[70].

V. Anti-inflammatory activity

The anti-inflammatory activity of the methanol extract of *N.nucifera* rhizome as well as of betulinic acid, a steroidal triterpenoid isolated from it, were evaluated on carrageenin and serotonin induced rat paw oedema[49]. The rhizome extract at doses of 200 and 400 mg/kg, and betulinic acid at doses of 50 and 100 mg/kg (administered orally) showed significant antiinflammatory activity; the effect was comparable to that of the standard drugs phenylbutazone and dexamethasone[49].

VI. Antioxidant activity

Yang and coworkers have performed in-vitro studies of the antioxidant activity of methanol and acetone extracts of the *N. nucifera* rhizome using the DPPH assay.^[71] The methanol and acetone extract showed highest DPPH scavenging activity, at 66.7 and 133.3 mg/l, respectively; the methanol extract exhibited a higher antioxidant activity coefficient than ascorbic acid. The rhizome knot also exhibited radical scavenging activity, measured spectrophotometrically and by electron spin resonance[72].

VII. Antipyretic activity

The methanolic extract of *N. nucifera* rhizome showed antipyretic activity in rats with yeast-induced pyrexia. Yeast suspension (10 ml/kg, s.c.) increased rectal temperature after 19 hr of administration. Oral doses of the extract of 200, 300 and 400 mg/kg produced significant dose-dependent lowering of normal body temperature and yeast-provoked elevation of body temperature in rats. The result was comparable to that of the standard antipyretic drug paracetamol (150 mg/kg intraperitoneally)[47].

VIII. Immunomodulatory activity

The immunomodulatory activity of *N.nucifera* rhizome extract was evaluated using various *in vivo* models including the total and differential leukocyte count (TLC and DLC), nitroblue-tetrazolium reduction (NBT) test, neutrophil adhesion test, phagocytic response and delayed type hypersensitivity (DTH) reaction. Sheep red blood cells (SRBC, 5×109 cells/ml) were used to immunize the animals. Rhizome extract at the doses of 100 and 300 mg/kg was administrated. The TLC and lymphocyte

count increased significantly but the neutrophil count was decreased for rhizome extract treated groups compared to the control. A dose-dependent potentiation of DTH reaction induced by SRBC was observed from the extracts. The percentage of neutrophil adhesion to the nylon fiber was increased in rhizome extract treated groups (63.22 and 62.91%). This finding suggests that the extract of rhizome of *N. nucifera* stimulate defense system by modulating several immunological parameters[65].

2.3 Flower

I. Hypoglycaemic activity

Sun-dried flower powder of *N.nucifera*, as well as the aqueous and alcoholic extract of the flower, produced significant hypoglycaemia in fasting normal albino rabbits. There was no significant difference in the activities of 1000 mg/kg of the test drug (sun-dried powder of the flower) and equivalent amounts of the extracts. Glucose tolerance studies with normal rabbits showed that oral doses of both extracts, equivalent to 1000 mg/kg of the test drug, produced significant depression of the peak rise in fasting blood sugar after glucose load; the effects of both extracts were 50% to that produced by 250 mg/kg of tolbutamide. A study of glucose tolerance curves shows that the duration of hyperglycaemia was also notably reduced compared with the controls. In normal rabbits, the extract at a dose of 1000 mg/kg significantly lowered hyperglycaemia induced by subcutaneous injection of 0.5 mg/kg adrenaline hydrochloride[73].

II. Antioxidant activity

The potential of *N. nucifera* stamens to scavenge 1,1-diphenyl-2picrylhydrazyl (DPPH) free radicals and peroxynitrites (ONOO-), and the inhibition of total ROS generation by kidney homogenates using 2v,7'-dichlorodihydrofluorescein diacetate (DCHF-DA) was examined[44]. The methanol extract showed strong antioxidant activity in the ONOO- system and marginal activity in the DPPH and total ROS systems. Similarly, seven known flavonoids were isolated from lotus stamens, most of which also showed potent antioxidant activity[44]. The glycosides nelumboroside A, nelumboroside B, isorhamnetin glycoside and isorhamnetin rutinoside isolated from N. nucifera stamens showed potent antioxidant activity in DPPH and ONOO- assays.^[45] 'Yunyupju', a liquor made from the blossoms and leaves of lotus, has been reported to have antioxidant activity. The maximum scavenging activity on hydroxyl radicals (40%) could be achieved when lotus liquor was more than 500 μ g. Lotus liquor also has a potent superoxide radical scavenging activity with value of 0.93 unit mg⁻¹ as superoxide dismutase equivalents with an IC50 value of $1.07 \pm 0.04 \text{ mg}[74]$.

III. Antipyretic activity

The ethanol extract of stalks of *N. nucifera* was evaluated for its antipyretic potential on normal body temperature and yeast induced pyrexia in rats. In the model of yeast provoked elevation of body temperature, the stalk extract showed significant activity

in both models at oral doses of 200 and 400 mg/kg. The stalk extracts showed dose-dependent lowering of body temperature up to 4 h; the results were comparable to those with paracetamol[75].

IV. Aldose reductase inhibitory activity

Two glycosides, namely kaempferol 3-O-a-L-rhamnopyranosyl-(1,6)-_-D-glucopyranoside and isorhamnetin 3-O-a-Lrhamnopyranosyl-(1!6)-_-D-glucopyranoside, isolated from the methanol extract of stamens of *N. nucifera* exhibited a high degree of inhibitory activity against rat lens aldose reductase *in vitro*, with IC50 values of 5.6 and 9.0 mM, respectively[46].

V. Antibacterial Activity

The hydroethanolic extract of flowers of N.nucifera Gaertn in vitro was reported to possess antibacterial activity. The antibacterial activity was screened against different bacterial strains like Escherichia coli Klebsiella pneumonia Pseudomonas aeruginosa Bacillus Subtilis Staphylococcus aureus by detecting zone of inhibition and minimum inhibitory concentration (MIC). The maximum zone of inhibition was exhibited by N.nucifera flowers against Escherichia coli (14mm), Bacillus Subtilis (13mm) and Staphylococcus aureus (11mm). The moderate zone of inhibition was found against Klebsiella pneumonia (10mm) and Pseudomonas aeruginosa (8mm). Gram-negative bacteria were more susceptible to the N.nucifera flower extracts than gram-positive bacteria which contradict the previous reports that plant extracts are more active against gram-positive bacteria than gram-negative bacteria. These results were compared with the standard antibiotic chloramphenicol (30µg/ml)[76].

VI. Aphrodisiac activity

Adult wister albino rats were used for aphrodisiac activity protocol. Sexual behavioural parameters were observed on wister albino rats. Blood samples were collected from control and experimental rats to measure hormone testosterone. Testosterone levels showed significant increase in experimental animal compared with control. The test drug may be effective as aphrodisiac through mechanisms such as vasodilation, generation of nitric oxide, elevation of androgens and gonadotropins. Stamens of *N. nucifera* white variety uniformly suspended in 2% Carboxy Methyl Cellulose (CMC) in water (Test drug) to obtain 100mg/ml concentration as stock solution has definite positive effect on male sexual behaviour and increased in hormone profile. The test drug at 500mg/kg body weight, both Mount frequency (MF) and Intromission frequency (IF) were increased (P<0.01) compared to the 2% CMC in saline-administered control and body weight also significantly increased. Sildenafil citrate was used as standard. The MF of the test drug treated animals was remarkably altered and it was statistically significant. Administration of single dose of test drug at 500mg/kg body weight the EF increased significantly (P<0.01). Test drug at the dose of 500mg/kg body weight could be used as a stimulator of sexual behaviour in male rats and also indicates the profound

increase in improvement of sperm health and possesses anti-obesity effect using mice with obesity induced by a high-fat diet. The extract showed a concentration- dependent inhibition of

VII. Antiplatellet activity

The antiplatelet activity of hydroethanolic extract of N.Nucifera flowers using platelet-rich plasma in different concentrations (100 500 μ g/ ml) was reported. N.nucifera flower extracts showed dose-dependent effective antiplatelet activity with maximum activity at 500 μ g/ml concentration; prevention of platelet aggregation was 50% of that achieved with standard aspirin[78].

2.4 Leaves

I. Cardiovascular activity

Two alkaloids that act as serotonin antagonists, namely asimilobine and lirinidine, were isolated from the leaves of N.nucifera. Both alkaloids inhibited serotonin-induced contractions in isolated rabbit aorta (10 -6)[40].

II. Antioxidant activity

Hydrogen peroxide-mediated cytotoxicity in Caco-2 cells was used to investigate the potential antioxidant activity of the methanol extract from the N.nucifera leaf[79]. A dose-dependent protective effect against reactive oxygen species (ROS)- induced cytotoxicity was observed when Caco-2 cells were treated with 10 mM hydrogen peroxide in combination with the methanol extract of the N.nucifera leaf (0.1–0.3 mg/ml). The N.nucifera extract also exhibited concentration-dependent antioxidant activities against haemoglobin-induced linoleic acid peroxidation and Fenton reaction-mediated plasmid DNA oxidation[79].

III. Antiviral activity

The 95% ethanol extract of N.nucifera has been reported to show anti-HIV activity (EC50 < 20 mg/ml). Some anti-HIV principles, including (+)-1(R)-coclaurine, (-)-1(S)-norcoclaurine and quercetin 3-O__-D-glucuronide, were found in N. nucifera leaves.[38] Both (+)-1(R)-coclaurine and (-)-1(S)-norcoclaurine showed potent anti-HIV activity, with EC50 values of 0.8 and < 0.8 mg/ml, respectively, and therapeutic index values above 125 and 25, respectively, whereas quercetin 3-O__-D-glucuronide was less potent (EC50 2 mg/ml). Other potent anti-HIV bisbenzylisoquinoline alkaloids such as nuciferine, liensinine, negferine and isoliensinine have also been isolated from the leaves of N. nucifera, with EC50 values below 0.8 mg/ml and therapeutic index values of 36, > 9.9, > 8.6 and > 6.5, respectively[38].

IV. Anti-obesity activity

Ono *et al* reported the effects of leaf extract on digestive enzymes, lipid metabolism and theromogenesis, together with the

anti-obesity effect using mice with obesity induced by a high-fat diet. The extract showed a concentration- dependent inhibition of the activities of a-amylase and lipase, and up-regulated lipid metabolism and expression of uncoupling protein-3 mRNA in C2C12 (mouse myoblast cell line) myotubes. It also prevented increases in body weight, parametrical adipose tissue weight and liver triacylglycerol levels[80].

V. Lipolytic activity

A 50% ethanol extract of N. nucifera leaves was reported to stimulate lipolysis in the white adipose tissue of mice. Chromatographic analysis of the extract showed that the phytomolecules responsible for lipolytic activity included quercetin-3-O-a-arabinopyranosyl- $(1\rightarrow 2)$ - β -galactopyranoside, catechin, hyperoside, isoquercitrin and astragalin[41].

VI. Hypocholesterolaemic activity

The aqueous extract of N.nucifera leaves was studied for its effects on serum lipids in a rat model. The rats were fed a high-fat diet containing 1.5% cholesterol and 1% cholic acid. Subsequent oral treatment with a crude aqueous extract of lotus leaves resulted in sharp decreases in serum total cholesterol, free cholesterol and phospholipids compared with the highfat- loaded control group[16]. The effect of N.nucifera leaf extract for the improvement of lipid metabolisms and the alleviation of liver damage in high fat diet treatment was studied in hamster model. The effects of flavonoid-enriched N. nucifera leaf extract supplement and two lipid-lowing drugs; silymarin and simvastatin, on the disorders induced by high fat diet were investigated. Flavonoid-enriched N.nucifera leaf extract supplement may significantly improve the high fat diet-induced abnormal blood lipids and liver damage as significantly as the common drugs[81].

VII. Hepatoprotective Activity

An ethanolic extract of the leaves of N. nucifera was studied for its hepatoprotective activity against CCl4-induced liver toxicity in rat. It was reported that the hepatoprotective activity of N.nucifera leaf extract (LLE) at doses of 300 and 500 mg/kg was comparable with that of a standard treatment comprising 100 mg/kg of silymarin[82].

VIII. Anticancer Activity

Methanol and acetone leaf extracts were used for anticancer activity by MTT assay. About 6.25 μ g/mL to 100 μ g/mL of sample was used for MTT assay. Methanol leaf extract showed 27% and acetone leaf extract showed 7% in 100 μ g/mL of MCF-7 breast cancer cell line. Both extracts showed less anticancer activity against breast cancer. According to Weng *et al.* (2009), armepavine (Arm, C₁₉H₂₃O₃N), an active compound from N. nucifera, has been shown to exert immunosuppressive effects in

in vitro. Arm (1-10 μ M) concentration dependently attenuated al., 2009). Arm also suppressed TNF- α -induced collagen TNF- α - and LPSstimulated α -SMA protein expression and AP-1 deposition, NF κ B activation and MAPK (p38, ERK1/2 and JNK) activation by HSC-T6 cells without adverse cytotoxicity (Weng et phosphorylation[83].

Activity	Part of plant used	Reference (s)
Aldose reductase inhibitory	Flower	[46]
Anti-arrhythmic	Seed	[55-57], [58, 59]
Anti- bacterial	Flower	[76]
Anticancer	Leaves	[83]
Anti-diarrhoeal	Rhizome	[66]
Anti-fertility	Seed	[54]
Anti-fibrosis	Seed	[60]
Anti-ischaemic	Seed	[50]
Anti-inflammatory	Seed, Rhizome	[52, 49]
Anti-obesity	Leaves	[80]
Antioxidant	Leaves, Flower, Rhizome	[79, 44, 45, 74,
		71,72]
Antiplatellet	Flower	[78]
Anti-proliferative	Seed	[63,64]
Antipyretic activity	Flower, Rhizome	[75, 47]
Antiviral	Seed, Leaves	[61, 38]
Aphrodisiac	Flower	[77]
Cardiovascular activity	Leaves	[40]
Diuretic activity	Rhizome	[70]
Hepatoprotective	Seed, Leaves	[82]
Hypocholesterolaemic	Leaves	[81]
Hypoglycaemic	Flowers, Rhizome	[73, 68]
Immunomodulatory	Seed, Rhizome	[65]
Lipolytic	Leaves	[41]
Psychopharmacological	Rhizome	[69]

3. Conclusion

The pharmacological investigations carried on N.nucifera have demonstrated that it's various organic and aqueous extracts possess an array of multidimensional pharmacological activities such as anti-ischaemic, antioxidant, hepatoprotective, antianti-fertility, anti-arrhythmic, inflammatory, anti-fibrosis, antiviral, antiproliferative, antidiarrhoeal, hypoglycaemic, psychopharmacological, diuretic, antipyretic, immunomodulatory, aldose reductase inhibitory, antibacterial, aphrodisiac, anti-obesity, antiplatellet. cardiovascular, lipolytic, hypocholesterolaemic, anticancer activities. The plant is also reported to contain a wide range of chemical constituents. These compounds could serve as leads in the search for novel medicinial agents. With the availability of primary investigations, further

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studies on N.nucifera should be designed to investigate the molecular mechanism(s) of action of isolated phytoprinciples using specific biological screening models and clinical trials, and also to discover novel leads from them. Also studies should be extended to standardize the various extracts of N.nucifera for the purpose of their use in specific herbal formulations. The data presented here, emphasize the potential of tradition medicine Nelumbo nucifera.

Declaration of interest

The authors report no conflict of interest. The authors, alone are responsible for the content and writing of the paper.

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