Chemical constituents, nutritional, pharmcological and therapeutic importance of *Juglans regia*- A review

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Abstract: The phytochemical analysis of the bark of *Juglans regia* showed that it contained reducing sugars, alkaloid, tannins, phenols and saponins. Preliminary phytochemical test of the leaves of *Juglans regia* showed the presence of alkaloids, carbohydrates, cardiac glycosides, flavonoids, saponins, steroids and tannins. Nutritional analysis of the kernels of *Juglans regia,* revealed that it contained carbohydrates, starch, sugars, fiber, fat (saturated, monounsaturated and polyunsaturated), protein, vitamins (folates, niacin, pantothenic acid, pyridoxine, riboflavin, thiamin, vitamin A, vitamin C, vitamin E and vitamin K) and minerals (potassium, phosphorus, calcium, magnesium, sodium, iron, copper, manganese, zinc and aluminum). However, the nutritional contents differs from a cultivar to another which can be influenced by genotype, cultivator, different ecology and different soil. The previous pharmacological studies showed that different parts of *Juglans regia* possessed nutritional, cardiovascular, antioxidant, anticancer, antidiabetic, antimicrobial, antiparasitic, immunological, antiinflammatory, analgesic, protective, gastrointestinal, endocrine and many other pharmacological effects. The current review highlighted the chemical constituents, nutritional, pharmacological and therapeutic characteristics of *Juglans regia.*

Keywords: *Juglans regia*, chemical constituents, nutrition, pharmcology, therapeutic

I. INTRODUCTION:

Herbal medicine is the oldest form of healthcare known to mankind. Herbs had been used by all cultures throughout history and still provide some of our most valuable medicines. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours and biopesticides.

The previous reviews showed that medicinal plants possessed wide range of pharmacological activities included: gastrointestinal [1-3], respiratory[4-5], antibacterial antiviral and antifungal [6-10], antiparasitic, antiprotozoal and molluscicidal [11-13], dermatological [14-17], anticancer [18-21], detoxification [22-24], anti-inflammatory[25-27], analgesic and antipyretic [25, 28], antiurolithiatic and diuretic effects [29-30], hypolipidemic, hemostatic, fibrinolytic, anticoagulant and cardiovascular [31-34], central nervous [35-36], immunological [37-38], antioxidant and free radical scavenging [39-40], smooth muscle [41], antidiabetic[42-43], reproductive [44-49], and mammary gland stimulating effects [50-52].

In addition, each medicinal plant species has its own nutrient composition besides having pharmacologically important phytochemicals. These nutrients such as carbohydrates, fats, proteins, vitamines and minerals are essential for the physiological functions of human body. The current review will highlight the chemical constituents, nutritional, pharmacological and therapeutic characteristics of *Juglans regia*.

Plant Profile:
Synonyms:
Juglans duclouxiana Dode, *Juglans fallax* Dode, *Juglans kamaonia* C. DC. Dode, *Juglans orientis* Dode, *Juglans regia* subsp. *fallax* Popov, *Juglans regia* var. *kamaonia* C. DC,. *Juglans regia* var. *sinensis* C. DC., *Juglans sinensis* C. DC. Dode and *Regia maxima* Loudon ex C. DC [53].
Taxonomic classification:
Kingdom: Plantae, **Subkingdom**: Viridiplantae, **Infrakingdom**: Streptophyta, **Superdivision**: Embryophyta, **Division**: Tracheophyta, **Subdivision**: Spermatophytina, **Class**: Magnoliopsida, **Superorder**: Rosanae, **Order**: Fagales, **Family**: Juglandaceae, **Genus***: Juglans*, **Species:** *Juglans regia* [54].
Common names:
Arabic: Joz; **Chinese**: Hu tao; **English**: Walnut, Carpathian walnut, English walnut, Madeira walnut, Persian walnut; **French**: Noyer commun; **German**: Echte Walnuß; **India**: Akhort; **Portuguese**: Nogueira-comum,

Nogueira-européia; **Spanish**: Nogal común, Nogal europeo, Nogal inglés; **Swedish**: Valnöt [55-57].
Distribution:
It was native in Asia (Azerbaijan, Tajikistan, Turkmenistan, Afghanistan, Iran, Iraq, Turkey, Pakistan) and in Europe (Czech Republic, Slovakia, Bosnia and Herzegovina, Bulgaria, Croatia, Greece, Macedonia, Montenegro, Serbia, Slovenia). However, it was widely naturalized elsewhere in temperate regions, and it was widely cultivated [55].

Traditional Uses:
Archaeological evidence suggested gathering and consumption of walnuts by humans occurring c.a. 7300 yr B.P in proximity to the Mediterranean [58].

Historically, several parts of plant including seeds, bark, leaf, and seeds green husks were used as natural remedies in folk medicine**.** The edible part of the fruit (the seed or kernel) was consumed, fresh or toasted, alone or with other edible products. It was globally popular and valued for its nutritional and health promoting properties [59].

Walnut leaves were widely used in traditional medicine for the treatment of skin inflammation, venous insufficiency, hyperhidrosis haemorrhoidal symptoms, ulcers, for diarrheic, as antihelmintic, depurative, antioxidants, antiseptic, antibacterial, astringent and chemopreventive Purposes [60].

The root and stem bark were used as anti-helmentic, astringent and detergent. The stem bark was dried and used as a tooth cleaner and whitener. The decoction of leaves and bark was used with alum for staining wool brown [56, 61].

In Kashmir Himalaya, the leaves were used as mosquito replant, lice killer, for the treatment of itching, chronic dysentery and frost bite; fruits were used as brain tonic, aphrodisiac, in constipation and for the treatment of rheumatism; the oil was used as dandruffs, in muscular pain, to improve eye sight and as memory enhancer; while roots were used in hair fall, tooth decay, as antiseptic and to heal the wounds [62].

In Turkish folk medicine, fresh leaves applied on the naked body or forehead to reduce fever or on swelled joint to alleviate the rheumatic pain. The kernel of *Juglans regia* has been used for the treatment of inflammatory bowel disease and diabetes in Iranian traditional medicine. The bark, branches and exocarp of the immature green fruit were used to treat gastric, liver and lung cancer a long time in China. *Juglans regia* was used by traditional healer in northeastern region of Mexico to protect against liver damage. In Nepal the bark paste was used in arthritis, skin diseases and toothache. The shell of *Juglans regia* was used in Calabria folk medicine to heal malaria [63-64].
The wood is of very high quality, and was used to make furniture, and gunstocks. The dye was used as a coloring and tonic for hair [65].

Part used:
Oil, seeds, bark, leaf, and seeds green husks [64].

Physicochemial characteristics:
Physicochemial properties of the *Juglans regia* bark (% w/w): total ash 9.51%, acid insoluble ash 0.125%, water soluble ash 1.035%, alcohol soluble extractive 6.03% and water soluble extractive 4.02% [56]. Physicochemical characteristics of walnut oil separated by cold pressing and solvent extraction method were: refraction index 20 oC: 1.475 and 1.476, saponification number: 188.5 and188.0, iodine number 145.1 and150.1, FFA (% oleic acid) 0.18 and 0.20 respectively, and peroxide number ($mmolO_2/mg$): 0 0.1[66].

Chemical constituents:
Preliminary phytochemical test for hot and cold methanolic extract of the bark of *Juglans regia* showed that the bark contained reducing sugars, alkaloid, tannins, phenols and saponins. Hot and cold methanolic extract of *Juglans regia* bark showed 1.4% and 1.08% of gallic acid respectively [56].

Preliminary phytochemical test for extract of the leaves of *Juglans regia* showed the presence of alkaloids, carbohydrates, cardiac glycosides, flavonoids, saponins, steroids and tannins [67].

The content of juglone in the methanolic extract of the leaves was 9.9 ± 0.2 mg/100 g; small amounts (1.3 ± 0.02 mg/100 g) were recorded in the infusion, whereas in the decoction it was not detected [68].

The constituents of 12 different cultivars of *Juglans regia* kernels grown in a replicated trial in an experimental orchard at Lincoln University were evaluated. The total oil content ranged from 62.6 to 70.3% while the crude protein ranged from 13.6 to 18.1%. Dietary fiber ranged from 4.2 to 5.2%, while the starch content made up no more than 2.8% of the remaining portion of the kernel. The amino acid content of the walnuts was similar between cultivars and included: aspartic acid, threonine, serine, glutamic acid, proline, glycine, alanine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, histidine, lysine and arginine [69].

Nutritional analysis of the kernels of *Juglans regia,* revealed that per 100 g, it contained energy: 2,738 kJ (654 kcal), carbohydrates: 13.71, starch: 0.06, sugars: 2.61, dietary fiber: 6.7, total fat: 65.21, saturated fat: 6.126, monounsaturated fat: 8.933, polyunsaturated fat: 47.174, protein: 15.23; it also contained vitamins: folates: 98 mcg, niacin: 1.125 mg, pantothenic acid: 0.570 mg, pyridoxine: 0.537mg, riboflavin: 0.150 mg, thiamin: 0.541 mg, vitamin A : 20 IU, vitamin C : 1.3 mg, vitamin E : 20.83 mg and vitamin K : 207 mcg; and minerals: potassium: 441 mg, phosphorus: 346 mg, calcium: 98 mg, magnesium: 158 mg, sodium: 2 mg, iron: 2.9 mg, copper: 1.5 mg, manganese: 3.8 mg, zinc: 3.09 mg and aluminum: 0.58 mg; Unsaturated fatty acids%: palmitoleic acid: 0.77, oleic acid: 25.26, gadoleic acid: 0.05, linoliec acid: 57.10, lineliec acid: 10.34; saturated fatty acid %: myristic acid 0.24, palmitic acid: 4.28, stearci acid: 1.85 and archidic acid: 0.19. However, the nutritional contents differs from a cultivar to another which can be influenced by genotype, cultivator, different ecology and different soil [63, 70-72].

Phenolic compounds were extracted from green walnut fruits, cultivars (Elit) and (Franquette). In ethanolic extract, the total phenolic content ranged from 126.2 mg GAE per g in cultivar Elit to 135.3 mg GAE per g in cultivar Franquette. In methanol extract, more phenolic compounds were extracted in both cultivars respectively (161.07 ± 7.28 and 148.98 ± 4.74mg GAE per g) [73].

Phenolic compounds identified in walnut seeds were included phenolic acids, namely gallic, ellagic, syringic, 5-Ocaffeoylquinic, caffeic, p-coumaric, ferulic and sinapic acids, and tannins, such as glansrins A, B and C, casuarinin and stenophyllarin [74-75].

However, nine phenolic compounds were identified in the walnut leaves collected from eleven cultivars (Mayette, Fernor, Mellanaise, Elit, Orientis, Lara, Hartley, Franquette, Parisienne, Arco, Marbot) grown in Iran: (3-caffeoylquinic, 3-p-coumaroylquinic and 4-pcoumaroylquinic acids, quercetin 3-galactoside, quercetin 3-arabinoside, quercetin 3-xyloside, quercetin 3-rhamnoside, quercetin 3-pentoside and kaempferol 3-pentoside) [76].

Four cyclic diarylheptanoids (rhoiptelol, juglanin A, juglanin B and juglanin C) and an alpha-tetralone derivative (sclerone) were identified in the extract of *Juglans regia* husks [77-78].

The analysis of hydrolysable tannin constituents of seed of *Juglans regia* revealed identification of 1, 2, 3, 4, 6-penta-O-galloyl-3-D-glucose, rugosin C, 1, 2, 3, 6-tetra-O-galloyl-3-D-glugose, tellimagrandin II, casuarictin and 1-degalloylrugosin F [79].

Walnut leaves also contained many phenolic compounds included three hydroxycinnamic acid derivatives, the 3-O-caffeoylquinic, 3-O-p-coumaroylquinic and 4-O-p-coumaroylquinic acids, and six flavonol heterosides, the quercetin 3-O-galactoside, a quercetin 3-O-pentoside derivative, quercetin 3-O-arabinoside, quercetin 3-O-xyloside, quercetin 3-O-ramnoside and a kaempferol 3-O-pentoside; and hydroxycinnamic acid derivatives, the 5-O-caffeoylquinic and p-coumaric acids [80-81].

Bioassay-guided fractionation of chloroform extract of *Juglans regia* leaves afforded isolation of 5-hydroxy-3,7,4'-trimethoxyflavone, lupeol, daucosterol, 4-hydroxy-α-tetralone, β-sitosterol, 5,7- dihydroxy-3,4'-dimethoxyflavone and regiolone [82].

The total phenolic content in the methanolic extract of *Juglans regia* flowers was 71.7±3.2 mg gallic acid equivalent/ g of extract, while, the total flavonoid contents was 61.7±2.7 mg quercetin equivalent/g of extract [83].

However, ten compounds were identified in methanol and petroleum ether walnut extracts: 3- and 5-caffeoylquinic acids, 3- and 4-pcoumaroylquinic acids, p-coumaric acid, quercetin 3-galactoside, quercetin 3-pentoside derivative, quercetin 3-arabinoside, quercetin 3-xyloside and quercetin 3-rhamnoside [84].

The principle polyphenolic constituents and their respective distribution in walnut (%) were: pedunculagin: 16.0, ellagic acid: 15.8, tellimagrandin I: 6.6, casuarictin: 4.1, tellimagranin II: 1.2, rugosin C: 1.8 and casuarinin: 1.0 [85].

The total oil content of *Juglans regia* kernel from Turkey, ranged from 61.97 to 70.92%, while the crude protein ranged from 15.17 to 19.24%. Ash ranged from 1.26 to 2.06%, while the moisture was found between 3.25-3.91% of the kernel. The total carbohydrate was calculated as between 8.05-13.23%. The oleic acid content of the oils ranged from 21.18 to 40.20% of the total fatty acids, while the linoleic acid content ranged from 43.94 to 60.12% and the linolenic contents from 6.91 to11.52%. It was found that palmitic acid was between 5.24 and 7.62%, while stearic acid ranged from 2.56 to 3.67% [86].

The fatty acid composition of two US commercial cultivars (Tehama and Vina), three European commercial cultivars (Esterhazy, 139,G120) and five New Zealand selections (Rex, Dublin's Glory, Meyric, McKinster, Stanley) was evaluated. The total oil content of the nuts ranged from 62.4 to 68.7%, the oleic acid content of the oils ranged from 14.3 to 26.1% of the total fatty acids, while the linoleic acid content ranged from 49.3 to 62.3% and the linolenic contents from 8.0 to 13.8%. Furthermore, it appeared that *Juglans regia* was a rich source of n-3 and n-6 polyunsaturated fatty acids [87].

Palmitic acid, n-octadecane, 9-E-hexadecanoic acid, tetra-tetracontane, 4,8,12,16-olide, n-heptadecanoic acid, 1-iodohexadecane, stearic acid, oleic acid, erucic acid and Di-n-octyl phthalate were isolated from the bark material of *Juglans regia* from Pune, India [88].

The fatty acid composition (as methyl esters %) of walnut oil from Greek were: tetradecanoic: 0.1, pentadecanoic: 0.1, 9-hexadecenoic: 0.4, hexadecanoic: 10.4, heptadecanoic: 0.1, 9,12-octadecadienoic: 74.0, 9,12,15-octadecatrienoic: 10.0, octadecenoic: trace, octadecanoic: 3.9, 11,14-eicosadienoic: trace, nonadecanoic: trace, 11-eicosenoic: 0.6, eicosanoic: 0.3, heneicosanoic: trace, docosanoic: 0.1, total saturated: 15.0, total unsaturated 85.0, unsaturated/saturated ratio: 5.7, mono unsaturated fatty acids: 1.0, poly unsaturated fatty acids: 84.0 and PUFA/MUFA: 84.0 [89].

Pharmacological effects:
Cardiovascular effects:

Diet supplemented with walnuts possessed beneficial effect on blood lipids, lowering blood cholesterol and lowering the ratio of serum concentrations of low density lipoprotein:high density lipoprotein by 12% [90].

In cross-sectional surveys, it appeared that high levels of HDL cholesterol and apo A1 were associated with a high amount of walnut consumption (oil and kernel) in the regular diet [91].

A randomized, double blind case-control study was conducted to evaluate the lipid-lowering effect of Persian walnut oil (encapsulated in 500 mg capsules, 3 g/day, for 45 days) in the population of southern Iran. Lipid profiles were checked before; on days 15, 30, and 45 after the beginning; and 15 days after termination of the study. Plasma TG concentrations decreased by 19% to 33% of baseline (P<0.05). No statistically significant change was observed in other measured parameters [92].

In a randomized, double-blind, placebo-controlled clinical trial, consumption of walnut oil by type 2 hyperlipidemic diabetic patients (15 ml Persian walnut oil) resulted in a significant decrease in total cholesterol levels (treatment difference (TD)= -30.04, P<0.001), triglyceride level (TD= -15.04, P=0.021), low-density lipoprotein level (TD= -30.44, P<0.001) and total cholesterol to high-density lipoprotein ratio (TD= -0.72, P<0.001) compared to the control group. There was an increase in the HDL level with consumption of walnut oil (TD=2.28, P=0.06). Frequency of patients reaching a LDL level below 100 was higher in the treated group (20 vs 0%) [93].

The polyphenol of walnut (WP) was evaluated for its hypolipidemic effect in high fat diet fed mice. Oral administration of WP (100 and 200 mg/kg) significantly reduced liver weight and liver and serum triglycerides (TG). Hepatic beta-oxidation in cytosol, including peroxisome, was enhanced by WP (50-200 mg/kg). mRNA expressions of hepatic peroxisome proliferator-activated receptor (PPAR) alpha and acyl coenzyme A oxidase (ACOX) 1 were enhanced by WP (50-200 mg/kg). The mRNA expressions of PPARalpha, ACOX1, and carnitine palmitoyltransferase (CPT) 1A in HepG2 cells were significantly enhanced by addition of WP (100 microg/ml). Tellimagrandin I, a polyphenolic constituent in WP, enhanced ACOX1 expression at 1-100 microg/ml [94].

The walnut diet improved endothelium-dependent vasodilation and reduced levels of vascular cell adhesion molecule-1 (P<0.05). The walnut diet significantly reduced total cholesterol (-4.4±7.4%) and LDL cholesterol (-6.4±10.0%) (P<0.05) [95].

Regular consumption of nuts has been associated with a reduced risk of both fatal coronary heart disease and non-fatal myocardial infarction. The epidemiological studies showed that people who consumed nuts five or more times a week had a 50% reduced risk of coronary heart disease relative to those who never consumed nuts. A reduction in cardiovascular risk was also recorded in a cohort of women from the nurses health study [96-98].

The effect of methanol extract of *Juglans regia* kernel extract 100 and 200 mg/ kg/day, orally on dexamethasone-induced hypertension was studied in rats. Dexamethasone increased the diastolic BP and MDA/GPX ratio in comparison with control group (128 ± 7 vs. 105 ± 3 mmHg, P< 0.05 and 0.2 ± 0.046 vs. 0.08 ± 0.02, P< 0.05). Combination of dexamethasone and walnut (200 mg/kg) prevented the dexamethasone-induced diastolic hypertension (109 ± 3 vs. 128 ± 7 mmHg; P< 0.05), increased the GPX level (14.8 ± 1.46 vs. 5.1 ± 0.64 unit/mg, p < 0.05), reduced the MDA/GPX ratio (0.16 ± 0.015 vs. 0.2 ± 0.046) and improved serum NO level [99].

The potential anti-hypertensive effects of walnut was investigated clinically on 130 hypertensive subjects. The result showed that it normalized high blood pressure, high cholesterol and serum electrolytes if short term meal of walnut is taken. Walnut meal has no effect on haemoglobin concentration, white blood cell count, Packed cell volume and platelet counts compared with their corresponding controls [100].

The effect of walnut methanolic extract and ellagic acid (one of its major polyphenolic components) was studied on the expression of vascular cell adhesion molecule (VCAM)-1 and intracellular adhesion molecule (ICAM)-1 in human aortic endothelial cells. After incubating the cells with TNF-alpha (1 ng/ml) in the

absence and in the presence of walnut extract (10-200 microg/ml) or ellagic acid, the VCAM-1 and ICAM-1 expression was quantified by cell-ELISA. Walnut extract and ellagic acid decreased significantly the TNF-alpha-induced endothelial expression of both VCAM-1 and ICAM-1 (P<0.01; P<0.001). Both walnut extract (at 10-25 microg/ml) and ellagic acid induced nodule formation in KS483 osteoblasts. These results suggested that the walnut extract has a high anti-atherogenic potential and a remarkable osteoblastic activity, an effect mediated, at least in part, by its major component, ellagic acid [101].

The antihemolytic activities of the methanolic extract of *Juglans regia* flowers were evaluated by various *in vitro* assays. The extract showed good antihemolytic activity against H_2O_2 and CuOH induced hemolysis in comparison with control [102].

CNS effects:

The potential anticonvulsant effect of walnut kernel extract (WKE) was evaluated in pentylenetetrazole (PTZ; 2 mg/ml/min) induced seizures in rats. WKE administration significantly increased the PTZ dose needed to induce the first myoclonic jerk (13.09 ± 1.29 vs. 49.71 ± 12.03 mg/kg; P<0.001), decreased the severity of seizure grades and reduced the mortality rate to 0%. Flumazenil (FMZ; 5 mg/kg ip), did not significantly reduce the anticonvulsant effect of WKE. The combination of diazepam (DPZ; 0.5 mg/kg ip) and WKE showed a synergic anticonvulsant effect, whereas ethosuximide (ESM) had no significant influence (P>0.05) on the WKE effects. It seemed that the anticonvulsant effect attributed to signaling pathways other than benzodiazepine mediated γ-aminobutyric acid receptors [103].

The antidepressant effect of *Juglans regia* fruit extract (100 and 150 mg/kg bw) was studied in animal models of depression (forced swimming test and tail suspension test). Both doses significantly decreased duration of immobility in both models of depression. The effect of extract was less significant than standard drug fluoxetine. The antidepressant activity could be attributed to the presence of omega 3 fatty acid in the extract [104].

In forced swimming test, methanol leaf extract at doses of 1000 and 1500 mg/kg significantly and dose dependently reduced the immobility period to 110.1±4.1 and 90.2±6.6 s, respectively as compared to control mice 164.2±11.3 s (P<0.001). Extract at 1500 mg/kg showed the same activity as imipramine. In tail suspension testmodel, extract (500 and 1000 mg/kg) decreased significantly and dose dependently the immobility time to 114.3±15.1 and 79.9±3.4s, respectively, as compared to control mice 157.8±12s (P<0.001). Extract at 1000 mg/kg showed the same activity as imipramine (P>0.05) [83].

The anxiolytic effect of hydroalcoholic extract of *Juglans regia* fruit (200 and 400 mg/kg bw) was studied on the basis of effect on exploration behaviour and anxiety in elevated plus maze, zero maze, and light-dark model. *Juglans regia* extract produced significant effect on exploration and time spent in open area of elevated plus maze and zero maze. Extract also increased time spent in lighten area in light and dark model. Increase in number of head twitches was also observed at selected doses [105].

The molecular effects of walnut supplementation (6% walnut diet) on the hippocampal expressions of NMDARs involved in cognitive functions and lipid peroxidation levels were studied in rats. The expression of NR2A and NR2B was elevated in the walnut-supplemented rats compared with the control group (P < 0.05) and the levels of lipid peroxidation in the walnut-supplemented group were significantly decreased compared with the control group [106].

Extracts of *Juglans regia* fruits and leaves exhibited low inhibition of butyryl cholinesterase, and it possessed no significant effect on acetyl cholinesterase [107].

The effects of walnuts on learning and memory was studied in male rats. Walnut was given orally to rats for a period of 28 days. Memory function in rats was assessed by elevated plus maze (EPM) and radial arm maze (RAM). A significant improvement in learning and memory of walnut treated rats compared to controls was observed. Analysis of brain monoamines exhibited enhanced serotonergic levels in rat brain following oral intake of walnuts [108].

The effects of walnut supplementation on motor and cognitive ability were investigated in aged rats. The motor testing showed that the 2% walnut diet improved performance on rod walking, while the 6% walnut diet improved performance on the medium plank walk; the higher dose of the 9% walnut diet did not improve psychomotor performance and on the large plank actually impaired performance. All of the walnut diets improved working memory in the Morris water maze, but the 9% diet showed impaired reference memory [109].

The effects of walnut consumption by mothers during pregnancy and lactation on learning and memory in adult offsprings were studied in rats. The results showed that there was a significant difference in learning and memory of rat offsprings between experimental and control groups [110].

Studying the effect of walnut to maintain the brain health with age, revealed that polyphenolic compounds found in walnuts not only reduced the oxidant and inflammatory load on brain cells but also

improved interneuronal signaling, increased neurogenesis, and enhanced sequestration of insoluble toxic protein aggregates[111].

The neuro-protective effect of dietary walnut (6%) against cisplatin-induced neurotoxicity was investigated through studying the alteration in performance of hippocampus- and cerebellum-related behaviors following chronic cisplatin treatment (5 mg/kg/week for 5 consecutive weeks) in male rats. The exposure of rats to cisplatin resulted in significant decrease in explorative behaviors and memory retention. Walnut consumption improved memory and motor abilities in cisplatin treated rats, while walnut alone did not show any significant changes in these abilities compared to saline. Cisplatin increased latency of response to nociception, and walnut reversed this effect of cisplatin [112].

The neuro protective efficacy of dietary supplementation of walnut (6 %) for 28 days was examined in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (20 mg/kg bw/day, ip) for last four consecutive days. MPTP injection diminished the levels of GSH, dopamine and metabolites along with decreased activities of GPx and mitochondrial complex I. The levels of TBARS and enzymatic antioxidants such as SOD and catalase, MAO-B activities were enhanced by MPTP treatment. Behavioral deficits and lowered TH expression were also proved in MPTP induced neurotoxicity. Dietary supplementation of walnut attenuated MPTP-induced impairment in PD mice, which could be attributed to its MAO-B inhibitory, antioxidant and mitochondrial protective actions [113].

Walnuts, rich in polyphenols, antioxidants, and omega fatty acids such as alpha-linolenic acid and linoleic acid, improved the age-associated declines in cognition and neural function in rats. Possible mechanisms of action of these effects include enhancing protective signaling, altering membrane microstructures, decreasing inflammation, and preventing accumulation of polyubiquitinated protein aggregates in critical regions of the brain. The serum collected from aged animals fed with walnut diets (0, 6, and 9%, w/w) enhanced protection on stressed BV-2 microglia *in vitro*. Walnut significant reduced pro-inflammatory tumor necrosis factor-alpha, cyclooxygenase-2, and inducible nitric oxide synthase. These results suggested antioxidant and anti-inflammatory protection or enhancement of membrane-associated functions in brain cells [114].

Anticancer effect:

The anticancer properties of walnut special mixture, walnut milk (WM), as a potential anticancer treatment were studied in DU145, MCF7 and TG/HAVSMC cells. The results indicated that WM dramatically reduced cell viability and selectively induced caspase-dependent apoptosis in DU145 and MCF7 cells without affecting TG/HA-VSMC noncancerous cells by triggering intrinsic apoptotic signalling and increases in ROS production [115].

The anticancer activity of *Juglans regia* leaf hexane extract and its effect on cell cycle analysis, apoptosis and cancer cell morphology was studied against human prostate cancer (PC3) cells. The extract of *Juglans regia* exhibited a potent and dose-dependent anti-proliferative activity against human prostate cancer cells *in vitro*. The extract also induced significant apoptosis in PC3 cancer cells as revealed by annexin V binding assay as well as inverted phase contrast microscopy. It triggered a significant formation of apoptotic bodies after treatment with varying concentrations of the extract. Within 48 h of incubation, approximately 9.5, 15.5 and 26.3 % of the cells underwent early apoptosis after treatment with 5, 50 and 100 μg/ml of the extract, respectively. Similarly, 5.2, 11.2 and 18.9 % of the cells underwent late apoptosis after treatment with 5, 50 and 100 μg/ml of the extract, respectively. Treatment with different concentrations of the extract for 48 h induced an increase in the population of cells in the sub-G1 phase and a slight decrease in the G2/M phase [116].

The cytotoxic effects of *Juglans regia* extracts and juglone, a napthoquinone isolated from the chloroform extract of the root part of *Juglans regia* and its novel series of triazolyl analogs, were studied against various human cancer cell lines. The different extracts of *Juglans regia* and the isolated compound (juglone) exhibited satisfactory cytotoxic activity against a panel of eight different human cancer cell lines [prostate colon (Colo-205 and HCT-116), breast (T47D), prostate (PC-3 and DU-145), skin (A-431) and lung (NCI-H322 and A549)]. Furthermore, all the synthesised analogs displayed enhanced and selective cytotoxic activity against lung cancer cell lines only. Of the synthesized derivatives, 15a and 16a displayed the best activity with IC_{50} of 4.72 and 4.67 μM against A549 cells. Both these derivatives exhibited superior potency to BEZ-235 against both the lung cancer cell lines [117].

The anticancer effect of a methanol extract of walnuts was evaluated on human MDA-MB-231, MCF7 and HeLa cells. The extract was cytotoxic to all cancer cells. Walnut extract decreased the intracellular pH, depolarized the mitochondrial membrane with release of cytochrome c and phosphatidylserine flipping. The antimitogenic effects of walnut extract were associated with a twofold reduction of mitochondria respiration. The results suggested impairment of mitochondrial function and apoptosis as relevant mechanism of anticancer effects of the walnut extract. The predominant compounds in the methanol extract were Tellimagrandin I and Tellimagrandin II, the members of the ellagitannin family [118].

The anti-proliferative and apoptotic activities of compounds identified in chloroform extract of *Juglans regia* leaves were evaluated in human breast and oral cancer cell lines (MCF-7 and BHY). Bioassay-guided fractionation of chloroform extract of *Juglans regia* leaves afforded isolation of 5-hydroxy-3,7,4'-trimethoxyflavone, lupeol, daucosterol, 4-hydroxy-α-tetralone, β-sitosterol, 5,7- dihydroxy-3,4'-dimethoxy flavone and regiolone. All compounds inhibited proliferation of MCF-7 (human breast adenocarcinoma) and BHY (human oral squamous carcinoma) cells in a concentration-dependent manner. Compounds (5,7-dihydroxy-3,4'-dimethoxyflavone and regiolone) had potent cytotoxic effects on both MCF-7 and BHY cells (IC$_{50}$ 21-51 μm), this concentration was not toxic to normal cells. MCF-7 growth inhibition was attributed to apoptosis; population of apoptotic cells increased from 1.12% in controls to 5.64 and 8.1% after 48-h treatment with compounds (5,7- dihydroxy-3,4'-dimethoxyflavone and regiolone), indicated their potential at inducing early and late apoptosis. This effect wasn't mediated by caspase-3 pathway [82].

The antiproliferative activity of total extract and several fractions from the leaves of *Juglans regia* was evaluated against human oral cancer, breast adenocarcinoma and colon adenocarcinoma cell lines. Chloroform fraction showed the lowest IC$_{50}$ values (0.36-0.81 mg/ml) and also induced cell cycle arrest (G0/G1 phase) after a 24 h treatment [119].

The effect of walnut green husk extracts on cell proliferation was evaluated on PC-3 human prostate cancer cells. Green husk extracts suppressed proliferation and induced apoptosis in a dose- and time-dependent manner by modulating expression of apoptosis-related genes. This involved DNA fragmentation and significant changes in levels of mRNA and the expression of corresponding proteins. An increase in expressions of Bax, caspase-3, and tp53 genes and their corresponding proteins was detected using real-time PCR and western blot analysis in PC-3 cells treated with the green husk organic extracts. In contrast, Bcl2 expression was downregulated after exposure to the extracts [120].

The various fractions of walnut extract were screened for antiproliferative activity against human cancer cell lines. Chloroform and ethyl acetate fractions exhibited a high level of antiproliferation against HepG-2 liver cancer cell line (IC$_{50}$ = 9 and 15 μg/ml, respectively) [121].

The antiproliferative effect of root bark of *Juglans regia* (RBJR) organic extracts was studied in cell proliferation on MDA-MB-231 human breast cancer cells. The results demonstrate that walnut root bark suppressed proliferation and induced apoptosis in a dose and time dependent manner by modulating expression of key genes. This involved characteristic changes in cytoplasmic and nuclear morphology, DNA fragmentation, levels of mRNA and expression of corresponding proteins. The expression of Bax, caspases, tp53, and TNF-alpha was markedly increased in MBA-MB-231 cells treated with the root bark extract. In contrast Bcl2 and mdm-2 expression was down regulated after exposure [122].

The anti- cancer stem cells (CSCs) potential of walnut phenolic extract (WPE) and its bioactive compounds, including (+)-catechin, chlorogenic acid, ellagic acid, and gallic acid were studied. CD133^{+}CD44^{+} cells were isolated from HCT116 cells using fluorescence-activated cell sorting (FACS) and then treated with WPE. The survival of the CD133^{+}CD44^{+} cells was inhibited and cell differentiation was induced by WPE. Furthermore, WPE down-regulated the CSC markers, CD133, CD44, DLK1, and Notch1, as well as the β-catenin/p-GSK3β signaling pathway. WPE suppressed the self-renewal capacity of CSCs and exhibited stronger anti-CSC effects than its individual bioactive compounds. WPE inhibited specific CSC markers in primary colon cancer cells isolated from primary colon tumor which indicated that WPE can suppress colon cancer by regulating the characteristics of colon CSCs [123].

Walnut methanolic extracts were assayed for their antiproliferative effectiveness using human renal cancer cell lines A-498 and 769-P and the colon cancer cell line Caco-2. All extracts showed concentration-dependent growth inhibition toward human kidney and colon cancer cells. Concerning A-498 renal cancer cells, all extracts exhibited similar growth inhibition activity (IC$_{50}$ values between 0.226 and 0.291 mg/ml), while for both 769-P renal and Caco-2 colon cancer cells, walnut leaf extract showed a higher antiproliferative efficiency (IC$_{50}$ values of 0.352 and 0.229 mg/ml, respectively) than green husk or seed extracts [84].

Two diarylheptanoids, juglanin A and B, were isolated from the extract of the seed husks of *Juglans regia*. They possessed cytotoxic activities against human hepatoma (Hep G2) cells [124].

The antimutagenic and antiproliferative activities of water and acetone extract of *Juglans regia* were studied *in vitro*. The water and acetone extracts were more effective than the benzene and chloroform extracts in inhibiting the revertants induced by 2-aminoflourene (2AF) in TA100 tester strains of *Salmonella*. The most effective extracts in the Ames assay were further evaluated using the Lucifer luciferase assay and in time course studies for antiproliferative activities using the Hoechst staining to observe apoptotic cell deaths. The acetone extract showed a correlation of antimutagenic activities in the Ames assay with its antiproliferative effect in different cell lines, while the water extract exerted its effect distinctly in each cell line [125].

Antidiabetic effect:

The antidiabetic effect of *Juglans regia* leaves in type 1 diabetes was evaluated in streptozotocin induced diabetes in rats. Treatment with the *Juglans regia* extracts resulted in a significant decrease in blood glucose, glycosylated hemoglobin, LDL, triglyceride, and total cholesterol, and a significant increase in insulin and HDL level [126-127].

The effect of a 30-day oral administration of aqueous extract of walnut leaf (10, 50, 150, 300, and 500 mg/day) was studied in comparison with glibenclamide in normal and diabetic rats. Administration of all doses over 10 mg/kg significantly lowered the blood glucose level in normal rat and diabetic rats, compared with control groups. This effect was higher for doses of 50 and 150 mg/kg in normal rats and for doses of 300 and 500 mg/kg in diabetic rats, which was similar to glibenclamide (4 mg/kg) [128].

The mechanism of hypoglycemic action of *Julans regia* leaves methanolic extract (JRLME) was studied in rats. After three weeks of treatment, the plant extract had a significant hypoglycemic action in both short and long term models. There was also permanent blood glucose reduction in treated groups, the *in vitro* assay of α-glucosidase activity displayed inhibitory action of JRLME, like Acarbose, but less effectively [129].

The antidiabetic effect of ethanolic walnut leaf extract (200 mg/kg) was evaluated in nondiabetic, alloxan-induced diabetic rats. Fasting blood sugar decreased meaningfully in diabetic rats treated with *Juglans regia*. Insulin level increased and glycosylated hemoglobin decreased significantly in diabetic groups receiving *Juglans regia* compared with the diabetic group without treatment. Size of islets of Langerhans enlarged consequentially in *Juglans regia* treated rats [130].

The hypoglycemic effect of oral methanolic extracts of leaf and fruit peel (200 mg/kg for both) of walnut was evaluated in alloxan induced diabetic rats. Four weeks later, blood was collected for biochemical analysis and pancreases were removed for β-cells counts in histological sections. Diabetes increased fast blood sugar (FBS) and HbA1c, and decrease β-cell number and insulin. FBS decreased only in leaf extract group. HbA1c decreased in leaf extract and insulin groups. The β-cells number increased in leaf and peel extract groups. Insulin increased moderately in all treatment groups [131].

The antihyperglycemic properties of the *Juglans regia* leaf extract was investigated in streptozotocin-nicotinamide induced diabetic rats. One week after induction of diabetes, oral treatment started with extract of *Juglans regia* and metformin and continued for 4 weeks. Fasting blood sugar, body weight, serum lipids and insulin level were measured in different groups. A significant reduction of glucose, HbA1c, total cholesterol and serum triglycerides were detected after 4 weeks in rats treated with *Juglans regia* leaves compared to the control groups. *Juglans regia* extract treatment showed potential hypoglycemic and hypolipidemic effects in type 2 diabetic rats [132].

The effects of the *Juglans regia* leaf extract on hyperglycemia lipid profiles in type II diabetic patients were investigated clinically using 61 patients, suffering from type II diabetes with fasting blood glucose (FBG) between 150 and 200mg/dl, glycated hemoglobin (HbA1c) between 7% and 9%. First group received 100mg *Juglans regia* leaf extract in capsules form two times a day for 3 months and other group received 100mg placebo capsule with the same dosage. The standard anti-diabetic therapy (metformin and glibenclamide, and nutritional regimen) was continued in both groups. The results indicated that FBG, HbA1c, total cholesterol and triglyceride levels in *Juglans regia* treated patients significantly decreased after 3 months compared with the baseline and with placebo group. Patients in *Juglans regia* group were significantly satisfied with *Juglans regia* treatment compared with the placebo group. No liver, kidney and other side effects were observed in the groups, except more gastrointestinal events (specially a mild diarrhea) associated with extract treatment at the beginning of the study [64].

Fifty eight Iranian male and female patients with type 2 diabetes were enrolled in a clinical trial, received *Juglans regia* leaves extract for two months for determination of HbA1c and blood glucose level as a main outcome and insulin, SGOT, SGPT, and ALP level as secondary outcome. The results revealed that serum fasting HbA1C and blood glucose levels were significantly decreased and the insulin level was increased in patients in the *Juglans regia* group [133].

A pilot study was carried out to determine the efficacy and safety of walnut hydrosol (WH) in patients with type 1 diabetes. Eight patients with diabetes mellitus (DM) type 1 were enrolled in the study. They were advised to drink 250 ml WH after meals twice a day for four weeks. WH can control the glycemic level in people with diabetes, but it may be associated with minor and major side effects. The average daily blood sugar level, and insulin dose decreased in seven subjects. Two subjects developed generalized pruritic erythematous skin rash. One patient presented hypoglycemic coma [134].

The effect of *Juglans regia* ethanolic leaf extract on lumbo-sacral spinal cord was evaluated in 18 and 20 days old fetus of diabetic mother rats. Female rats became diabetic by intraperitoneal injection of streptozotocin (50 mg/kg). In their first day of pregnancy, they received walnut leaf extract at a dose of 250 mg/ kg. After formation of the nervous system, two fetuses were obtained after anesthezing animals on 18th and 20th gestational days. The animals were euthanized, their birth weight were recorded and the lumbo-sacral spinal

cord samples were taken and fixed. Significant decrease in the transverse diameter, vertical diameter, and the number of neurons in the spinal cord gray matter of the spinal cord at days 18 and 20 of pregnancy in the diabetic group compared to other groups was observed (P≤0.05) and a significant difference in the number of neurons in the spinal cord white matter was observed on day 18 of pregnancy (P≤0.05). The result confirmed the ameliorative effects of ethanolic extract of walnut leaves in controlling the metabolic disorders in diabetic pregnancy on the fetus's central nervous system [135].

Antioxidant activity:

The *in vitro* effects of walnut husk hydroalcoholic extract was studied on serum LDL oxidation caused by copper sulfate. The results indicated that walnut husk hydroalcoholic extract reduces serum LDL oxidation, with lag times equal to 87%, 178% and 202% for concentrations of 0.2, 2 and 20 μg/ml, respectively [136].

The antioxidant activity and protective effects in stabilizing sunflower oil of methanolic extract of *Juglans regia* green husk were studied. Total flavonoids and phenolics were 144.65±2.1 mg quercetin and 3428.11±135.80 mg gallic acid equivalent per 100 gram of dry sample respectively. EC_{50} values of extract in reducing power and DPPH assays were 0.19 and 0.18 mg/ml respectively. The 400 ppm extract was as effective as 200 ppm BHA in retarding sunflower oil deterioration at 600C [137].

The methanol extract of *Juglans regia* leaves showed strong antioxidant activity with the using of DPPH radical scavenging and reductive power tests. The antioxidant effects were concentration dependent [138]. The methanolic extract of *Juglans regia* flowers was capable of scavenging H_2O_2 in a concentration dependent manner. IC_{50} for H_2O_2 scavenging activity was 311±12.8 μg/ml [139].

Different extracts (hot water, hydroalcoholic, chloroform and petroleum ether) of *Juglans regia* bark were studied for antioxidant activity using different models (DPPH radical scavenging, ABTS radical scavenging, FRAP assay and superoxide radical scavenging assay). The results showed that the hot water and hydroalcoholic extracts of *Juglans regia* possessed potent antioxidant activity than the chloroform and petroleum ether extracts. In all the testing, a significant correlation existed between concentrations of the extract and percentage inhibition of free radicals [140].

The optimal solvent for antioxidant extraction from walnut leaves is 70:30%, from walnut green husks is 50:50% and from walnut membrane septum is 30:70% mixture of water and ethanol, respectively. Walnut leaves, green husk and membrane septum extracts obtained by soxhlete extraction possessed considerable amounts of phenols compounds and a significant radical scavenging activity towards stable DPPH free radical [59].

The effect of the solvent (water, chloroform, methanol, ethanol, ethyl acetate and N-butanol) on the extraction, total flavonoids content and antioxidant properties was analyzed. Antioxidant activity was measured by hydroxyl, 2,2-diphenyl-1-picrylhydrazyl (DPPH) and superoxide anion radical scavenging capacity and the total antioxidant capacity and reducing power assay. The greatest total flavonoids content was shown by the samples extracted with ethyl acetate. The highest ability to scavenging DPPH, hydroxyl and superoxide radicals was ethyl acetate extract (EC_{50}=81.03μg/ml), methanol extract (EC_{50}=131.35 μg/ml) and chloroform extract (EC_{50}=176.35μg/ml) respectively at the concentration of 500 μg/ml. The methanol extract showed the greatest total antioxidant activity and reducing power [141].

Walnut polyphenols had superoxide dismutase-like activity (EC_{50}: 21.4-190 microM) and a remarkable radical scavenging effect against 1,1-diphenyl-2-picrylhydrazyl (DPPH) (EC_{50}: 0.34-4.72 microM) [75].

Juglans regia kernel ethanolic extract showed a protective effect on the DNA strand breaks induced by thiol/Fe^{3+}/O_2 mixed function oxidase, tert-butyl hydroperoxide or UVC radiations in acellular and cellular models [142].

Antimicrobial effects:

The antibacterial effect of *Juglans regia* leaf extract was studied against the pathogens caused acne lesions, *Propionibacterium acnes*, and other organisms that were isolated from acne lesions. The zones of inhibition due to *Juglans regia* leaf extract (15%) were *Providencia stearti*: 20mm, *Providencia rettgeri*: 15mm, *Streptococcus* group C: 15mm, *Streptococcus faecalis*: 17mm, *Staphylococcus aureus*: 10 and *Candida albicans* 20mm [143].

The influence of a walnut (*Juglans regia*) extract was evaluated on the growth of Escherichia coli AB1157, on the plasmid DNA topology and on the labeling of blood constituents. The extract possessed an inhibitory action of the growth of the E. coli AB1157 culture, no protective action of the walnut extract in plasmid DNA treated with SnCl2. Moreover, walnut was also not capable to induce modifications in the DNA mobility in agarose gel but walnut was capable to decrease the distribution of 99mTc on the blood cell compartment [144].

The effects of hydroalcoholic extract of *Juglans regia* stem bark were studied on 6 pathogens (*Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Streptococcus* spp., *Pasteurella multocida*

and *Mannheimia haemolytica*). Hydroalcoholic extract did not possess antibacterial effects on *E. coli* and *K. pneumoniae*. Minimum inhibitory concentration against *S. aureus, P. multocida, M. haemolytica* and *Streptococcus* spp. was 62.5mg/ml. There was not any significant response with concentrations below 100mg/disc on *S. aureus, Streptococcus species, P. multocida and M. haemolytica*. The minimum bactericidal concentration of the extract was 100mg/ml against all isolates [145].

The antibacterial activity of *Juglans regia* aqueous bark extract was studied against methicillin-resistant strains of *Staphylococcus epidermidis* and *Staphylococcus hemolyticus*. *Juglans regia* extract was more effective against *S. epidermidis* at an average MIC of 312.5 ug/ml than against *S. hemolyticus* with an average MIC of 2500 ug/ml [146].

Acetone, methanol and ethanol extracts of the leaves of *Juglans regia* were tested for antimicrobial activity against *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli* and *Klebsella pneumonia*. Antimicrobial activity was done by disc diffusion method at concentrations of 50 and 100μg/ ml/ disc of the extracts. All extracts showed varying degrees of inhibitory activity against all bacterial species. Ethanolic and acetone extract showed significant activity against *E.coli* and *Klebsella* [67].

The effect of hydroalcoholic extract of the stem bark of *Juglans regia* was studied against 50 methicillin-resistant *Staphylococcus aureus*. All of 50 MRSA strains were multi-drug resistant, resisted penicillin, ampicillin and methicillin. A low resistance was observed toward erythromycin (48%) and then ciprofloxacin, gentamycin and clindamycin (34%). All strains except one were sensitive to vancomycin. All strains except one were *mec*A carrier in PCR. The hydroalcoholic extract of the stem bark of *Juglans regia* showed low MICs (15.62 mg/ ml) against the standard *S. aureus* strain (PTCC: 33591) and 7.81 mg/ml against MRSA isolates. Minimum bactericidal concentrations of the extract were 15.62 mg/ml and 31.25 mg/ml against *S. aureus* isolates and the standard strain, respectively [147].

The ethanol extract of walnut leaves was examined for antibacterial activities against *Streptococcus mutans, Streptococcus salivarius, Streptococcus sanguinis,* and *Actinomyces viscosus* using the microdilution method. The minimum inhibitory concentrations for ethanolic extract ranged between 15.6 and 187.5 mg/ml and minimum bactericidal concentrations ranged between 31.25 and 250 mg/ml [148].

The antibacterial activities of methanol extracts of stem bark of *Juglans regia* were investigated against two Gram positive bacteria (*Staphylococcus aureus, Streptococcus mutans*). Methanolic bark extract of *Juglans regia* possessed antibacterial activity, it showed zone of inhibition of 7.2 and 8.7mm against *S. mutans, S. aureus* respectively, while the inhibition zones of ciprofloxacin were 15.52mm and 15.1mm against *S. mutans* and *S. aureus* respectively [149].

Juglone potently inhibited the three key enzymes of *Helicobacter pylori,* cystathionine γ-synthase (HpCGS), malonyl-CoAacyl carrier protein transacylase (HpFabD), and β-hydroxyacyl-ACP dehydratase (HpFabZ) with IC_{50} values of 7.0±0.7, 20±1 and 30±4 μmol/l, respectively [150].

Over 45% of clinical isolates of *Helicobacter pylori* strain were inhibited by *Juglans regia* aqueous and equal mixture of methanol, diethyl ether and petroleum benzene extract [151].

The antifungal effects of an extract of the leaves of a walnut and several fractions obtained during the separation by column chromatography, were studied against *Ascosphaera apis*. The antifungal activity was attributed mainly to juglonu and eugenol [152].

The antifungal potential of four extract fractions (methanolic, ethyl acetate, alkaloid, and hydrolyzed methanolic) of *Juglans regia* leaves was evaluated against 140 pathogenic *Candida albicans* isolate. Methanolic extract from walnut leaves characterized by the highest anticandidal activity, the alkaloid fraction possessed a slightly lower antifungal efficacy, while ethyl acetate and hydrolyzed methanolic preparates inhibited the growth rate of the examined fungal pathogens in the lowest degree [153].

95% ethanol and ethyl acetate leaves extract of *Juglans regia*, inhibited tobacco mosaic virus, while, the methanol extract inhibited Sindbis virus at a concentration of 1.5 μg/ml [154-155].

Effect on oral health:

2% and 3% concentration of petroleum-ether and ether fractions in propylene glycol and 2% water soluble extract of the bark of *Juglans regia* were tested against developing plaque. All the preparations were applied twice a day on 20 subjects for 3 days. *Juglans regia* exhibited antiplaque activity in all the preparations tried. Ether extracts and aqueous extracts showed promising results as compared to petroleum extracts. 2% and 3% ether fraction of *Juglans regia* showed the antiplaque activity of 32.12% and 31.56% respectively. 2% aqueous solution of *Juglans regia* inhibited 30.32% plaque; 2% and 3% petroleum ether fraction showed 17.62% and 19.45% of plaque inhibitions respectively [156].

The effect of acetone and aqueous extracts of *Juglans regia* was studied by testing on salivary samples of patients suffering from dental carries. Antimicrobial assay was carried out using disc diffusion method. Acetone extract was found to be effective as anti-cariogenic medicine [157].

The antimicrobial effects of ethanolic and aqueous extracts of *Juglans regia* bark were studied against different oral bacteria, *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus sanguis*, and *Staphylococcus aureus*. The results showed that *S. sanguis* was the most sensitive and *S. mutans* was the most resistant bacteria for the ethanolic and aqueous extracts. Ethanolic extract possessed significant antibacterial effect against all the tested bacteria. While, aqueous extract did not show antibacterial effect against *S. mutans*, in contrast to ethanolic extract. Aqueous extract had significantly antibacterial effect against *Staphylococcus aureus*, *S. salivarius*, and *S. sanguis* compared to control (P<0.0001), but it did not show effect on *S. mutans* when compared with erythromycin [158].

The *in vitro* antimicrobial activities of hot and cold bark extracts of two varieties of *Juglans regia*, were tested against four microorganisms related to dental caries (*Streptococcus mutans, Streptococcus sobrinus, Actinomyces viscosus*). Both varieties of *Juglans regia* possessed antibacterial activity, chloroform extracts was the more potent antibacterial. Accordingly, both varieties of *Juglans regia* extracts exerted good anti plaque activity [159].

The antibacterial effects of ethanolic walnut leaf extract were compared with chlorhexidine mouth rinse against *Streptococcus mutans* and *Streptococcus sanguinis* using agar-diffusion and microdilution methods. The results showed that MIC of ethanolic extract of walnut leaf was 125 and 15.6 mg/ml against *Streptococcus mutans* and *Streptococcus sanguinis*, respectively. There was significant different between ethanolic extract and chlorhexidine in the inhibition zone against *Streptococcus mutans* (P=0.000) but no significant difference between them against *Streptococcus sanguinis* (P=0.058) [160].

Juglans regia bark extract showed a broad spectrum antimicrobial activity in a dose dependent manner. It inhibited the growth of several species of pathogenic microorganisms representing Gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus mutans*), Gram-negative bacteria (*Esherichia coli* and *Pseudomonas aeruginosa*) and a pathogenic yeast (*Candida albicans*). The extract has either synergistic or additive action when tested with a wide range of antibacterial drugs. It also increased the pH of saliva. Thus, brushing the teeth with this bark may improve oral hygiene, prevent plaque and caries formation, and reduce the incidence of gingival and periodontal infections [161].

Antiparasitic effect:

The extracts of *Juglans regia* stem bark were investigated for anthelmintic activity on adult Indian earthworm, *Pheretima posthuma*. The stem bark of *Juglans regia* was extracted with different solvents (petroleum ether, benzene, chloroform, acetone, methanol, ethanol and distilled water). Benzene, methanol and ethanol extracts exhibited significant anthelmintic activity as comparable to that of standard drug piperazine citrate [162].

The anthelmintic activity of different extracts of *Juglans regia* leaf were tested against adult Indian earthworms *Pheretima posthuma.* The methanolic leaf extract of *Juglans regia* L demonstrated paralysis as well as death of worms in a less time as compared to piperazine citrate especially at concentration of 50 mg/ml. Water extract showed significant activity, while, petroleum ether extract being the least active among all the extracts [163].

Petroleum ether, chloroform, ethyl acetate, and methanol leaf extracts of the walnut, *Juglans regia* were evaluated under laboratory conditions for their acaricidal activity on the mites, *Tetranychus cinnabarinus* (Boisduval) and *Tetranychus viennensis* Zacher (Acari: Tetranychidae). Extracts had both contact and systemic toxicity to these mites. The crude extracts with petroleum ether resulted in the highest mite mortality (79.04-0.52%) in a slide dip bioassay. Mites mortalities of the chloroform, ethyl acetate, methanol, or distilled water extracts were significantly lower than petroleum ether. The mean lethal concentrations (LC_{50}) of the petroleum ether, chloroform, ethyl acetate, methanol, and distilled water extracts to the two mite species were 0.73-0.04, 1.66-0.28, 4.96-0.35, 7.45-0.67, and 9.91-0.32 mg/ml, respectively [164].

The antileishmanial activity of *Juglans regia* hydroalcoholic extract was tested on the growth of the promastigotes of *Leishmania major*. The results showed that both *Juglans regia* and *L. inermis* extracts reduced the promastigotes number significantly (P<0.01) [165].

The effects of topical application of the ointment-based extract (2 and 4% of 50% ethanol extract) of *Juglans regia* was studied on *Leishmania major* (MRHO/ IR/75/ ER) induced infection in mice. The results showed significant post-treatment decrease in the lesion size and parasite count in infected animals, compared to control groups [166].

Immunological effect:

The immunocorrective properties of the aqueous extract of walnut septa were studied in experimental model of leukopenia caused by a single injection of cyclophosphamide in white mice. The results revealed that walnut septa extract had corrected the suppressed myelopoiesis in white mice caused by injection of cyclophosphamide. The blood formula normalization process by the mentioned extract was provided by the fast

increasing in number of immature (band neutrophil) and mature neutrophils in the peripheral blood. Walnut septa extract stimulated the division, differentiation and maturation of blast forms of myeloid as well as lymphoid line in the bone marrow of mice with leukopenia [167].

The effects of walnut polyphenol extract (WPE) on immunotoxicity induced by PP and PNMC were studied in murine splenic lymphocytes. Treatment with WPE significantly enhanced the proliferation of splenocytes exposed to PP or PNMC, characterized by increases in the percentages of splenic T lymphocytes (CD3+ T cells) and T cell subsets (CD4+ and CD8+ T cells), as well as the production of T cell-related cytokines and granzymes (interleukin-2, interleukin-4, and granzyme-B) in cells exposed to PP or PNMC. These effects were associated with a decrease in oxidative stress, as evidenced by changes in OH, SOD, GSH-Px, and MDA levels [168].

Antiinflammatory and analgesic effects:

Methanol leaf extract produced statistically significant inhibition of edema induced by carrageenan at nearly all doses (250-1000 mg/kg ip) when compared to the control groups. The effect was dose-dependent. The highest activity showed at 1000 mg/kg ip, that inhibited 77% of inflammation. The same activity was found for diclofenac at 100 mg /kg ip (73%) (P>0.05) [83].

The ethanolic extracts of *Juglans regia* leaves exhibited potent anti-inflammatory activity (as potent as indomethacin) against carrageenan-induced hind paw edema model in mice without inducing any gastric damage [169].

When BV-2 microglial cells were treated with walnut methanolic extract prior to LPS stimulation, the production of nitric oxide and expression of inducible nitric oxide synthase were attenuated. Walnut extract also decreased tumor necrosis-alpha (TNFalpha) production. Walnut extract induced internalization of the LPS receptor, toll-like receptor 4, and that the anti-inflammatory effects of walnut were dependent on functional activation of phospholipase D2 [170].

The nociceptive effect of alcohol extract of *Juglans regia* leave (0.5, 1 and 1.5 mg/kg) alone and in combination with morphine was tested in rats. Alcohol extract of walnut leave in dose of 1.5 mg/kg caused a significant nociception decrease in acute phase of formalin test and this effect was dose dependent. Moreover, rats received a combination of morphine and alcohol extract showed more nociception especially in acute phase of formalin test, in comparison to the groups that received each separately [171].

The protective effects:

The protective effect of *Juglans regia* extract was studied in a rat model of bleomycin (BLM)-induced pulmonary toxicopathy. Methanolic extract 150mg/kg bw was given per os to Wistar rats for 14days prior to BLM exposure. A single intratracheal injection of BLM (10U/kg bw) was administered on the eleventh day of the treatment. BLM caused marked increase in the hydroxyproline level, lipid peroxidation, nitric oxide production, and in the activities of xanthine oxidase and myeloperoxidase in the lung tissue compared to control animals. BLM also decreased the activities of antioxidant enzymes such as glutathione reductase and catalase and increased the lung inflammation and apoptosis by upregulating the NF-κB signaling pathway and caspase-3 expression. Treatment with walnut extract attenuated these changes in a significant manner, it significantly modulated the lung injury as measured by markers of cellular injury such as lactate dehydrogenase and alkaline phosphatase, total cell count, total protein and reduced glutathione in bronchoalveolar lavage fluid. Histological findings supported the protective effects of walnut extract against BLM-induced lung injury [172].

The polyphenol-rich fraction (WP, 45% polyphenol) prepared from the kernel pellicles of walnuts was assessed for its hepatoprotective effect in mice. A single oral administration of WP (200 mg/kg) significantly suppressed serum glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) elevation in liver injury induced by carbontetrachloride, while it did not suppress d-galactosamine (GalN)-induced liver injury. However, of the isolated constituents, only ellagitannins with a galloylated glucopyranose core, such as tellimagrandins I, II, and rugosin C, suppressed CCl_4-induced hepatocyte damage significantly [173].

The protective effects of *Juglans regia* kernel extract against cigarette smoke extract (CSE)- induced lung toxicities was studied in Wistar rats. Prophylactic treatment of methanolic extract of *Juglans regia* kernel at the doses of 50 mg/kg bw and 100 mg/kg bw was given by gavage to Wistar rats for 1 week prior to CSE exposure. *Juglans regia* extract significantly decreased the levels of LDH, total cell count, total protein and increased the GSH level, it also significantly restored the levels of GR, catalase and reduced the XO activity in lung tissue [174].

The modulatory effects of walnut extract on the toxicity of an anticancer drug, cyclophosphamide (CP) was evaluated in mice. Plant extract + CP showed restoration in the level of cytochrome P450 (CYP) content and in the activities of glutathione S-transferase (GST), glutathione peroxidase (GP) and catalase (CAT) in both liver and kidneys. But plant extract restored the activity of superoxide dismutase (SOD) and the level of reduced

glutathione (GSH) in the kidneys only when compared with CP-treated animals. Plant extract treatment alone caused significant reduction in the content of CYP in the kidneys mainly. The extract showed a significant increase in the level of GSH and in the activities of GP in both the tissues and CAT in liver only, whereas no significant change was observed in the activities of GST and SOD. The extract+CP showed a significant decrease in the LPO in liver and kidneys when compared with the CP-treated group [175].

The antioxidant effect of aqueous extractof walnut bark and its modulatory effect on cyclophosphamide (CP)-induced urotoxicity were studied in Swiss albino male mice. Walnut bark extract treatment (150 mg/kg po for 10 days) resulted in protective restoration of decreased antioxidants in CP-treated animals. CP treatment caused decreases in the activities of catalase (CAT), glutathione peroxidase (GP), glutathione reductase (GR) and glutathione S-transferase (GST) and in the glutathione (GSH) content in urinary bladder and a significant concomitant increase in lipid peroxidation (LPO). Administration of extract restored all the antioxidants significantly and lowered the elevated LPO in the bladder [176].

Thirty minutes after ip administration of extract 62.5, 125 and 250 mg/kg to mice, NaF (150 mg/kg) was applied ip to each mouse and the antihypoxic activity was estimated in minutes as the latent time of evidence of hypoxia. A statistically significant antihypoxic activity of the extract was established in the experimental model of haemic and circulatory hypoxia in mice. The effects were found to be dose-dependent [83].

Effect on gastric ulcer and colitis system:

The gastro protective effect of aqueous extract of *Juglans regia* leaves was studied in albino rats. The aqueous leaf extract of *Juglans regia* was investigated for its anti- ulcer activity against pylorus ligation, aspirin induced and ethanol induced gastric ulcer in rats at 500mg/kg bw po. A significant reduction ($P<0.01$) in ulcer index was seen in leaf extracts of *Juglans regia* treated rats of pylorus ligation, aspirin induced and ethanol induced gastric ulcer models. The gastro protective effect was further confirmed by histopathological examination of rat stomach [177].

Juglans regia (walnut) extract was evaluated in acute and chronic murine colitis. In the acute colitis model, mice were given 4% dextran sulfate sodium (DSS) for 5 days. Walnut extract (5 mg/kg/day and 20 mg/kg/day) was dissolved in PBS and administered once daily by oral gavage, beginning 2 days before DSS administration. Severe colitis was induced by DSS administration for 5 days. In contrast, administration of walnut extract significantly reduced the severity of DSS-induced murine colitis, as assessed by the disease activity index and colon length. In the histopathological analysis, histological grading showed that walnut extract significantly reduced overall colitis score in comparison to the scores of the PBS-treated controls. Immunohistochemical analysis showed that the DSS-induced phospho-IKK activation in intestinal epithelial cells was significantly decreased in walnut extract–treated mice. Immunoreactivity for occludin was significantly inhibited by the treatments with walnut extract. Walnut extract was also significantly reduced the severity of chronic colitis in mice [178].

Endocrine effect:

The effects of alcoholic extract of walnut (10 - 20 and 50 mg/ kg/ ip) on FSH, LH and testosterone concentration were studied in adult male rats. In comparison with control group, only in group treated by 50 mg/kg of walnut extract, FSH and LH concentration increased significantly ($P<0.05$). Concentration of testosterone in experimental groups (20 mg/kg and 50mg/kg dose of extract) showed significant statistical difference compared with other groups ($P<0.05$) [179].

α-amylase inhibitory effect:

Juglans regia was tested for α-amylase inhibition. Different concentrations of leaf aqueous extracts were incubated with enzyme substrate solution and the activity of enzyme was measured. Extract showed time and concentration dependent inhibition of α-amylase. 60% inhibition was seen with 0.4 mg/ml of *Juglans regia* aqueous extract. Dixon plots revealed the type of α-amylase inhibition was competitive inhibition [180].

Toxicity and side effects:

Juglone found in *Juglans regia* can cause irritation and skin hyper pigmentation in experimental animals but, contact allergy was considered a very rare event in man [181-182].

Methanol leaf extract exhibited no toxicity up to 4 g/kg bw when injected ip in mice [83].

Mice were given orally 2000 mg/kg walnut polyphenols and maintained for observation for 14 days. No fatal event occured nor abnormal changes observed upon comparison with control group. No evident abnormalities detected in organs upon autopsy. Oral LD_{50} of walnut polyphenols was deduced to be >2.000mg/kg for both male and female mice [85].

No liver, kidney and other side effects were observed with the using of 100 mg leaves extract capsules for 3 months in patients, except more GI events (specially a mild diarrhea) associated with extract treatment at the beginning of the study [64].

Acute and subchronic toxicity study of the median septum of *Juglans regia* were carried out in Wistar rats. In the acute toxicity study, female Wistar rats were treated with doses of 10, 100, 1000, 1600, 2900 and 5000 mg/ kg of the *Juglans regia* septum methanol extract (JRSME), and were monitored for 14 days. In subchronic study, JRSME was administered by gavage at dose of 1000 mg/kg daily in Wistar rats for 28 days. The extract did not produce any toxic signs or deaths; the medium lethal dose was higher than 5000 mg/kg. In subchronic study, No significant morphological and histopathological changes were recorded. There was a significant increase in serum malondialdehyde (MDA) level in treated group compared to control after 4 weeks of JRSME intake. The treatment of rats resulted in a significant reduction of serum urea level (P<0.05), kidney's xanthine dehydrogenase (XDH) activity (P<0.001) and elevation of aldehyde oxidase (AO) activity (P<0.05) in kidney. The mean diameter of glomerulus and proximal urine tube epithelium stature was slightly greater in the treated group than control group [183].

II. CONCLUSION:

The current review discussed the chemical constituents, nutritional, pharmacological and therapeutic characteristics of *Juglans regia* as a promising medicinal plant with wide range of pharmacological activities which could be utilized in several medical applications because of its effectiveness and safety.

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