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A REVIEW ON PHARMACOLOGICAL ACTIVITY OF *JUGLANS REGIA*

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ABSTRACT: From ancient times, various natural products are used as food and as medicine for the treatment of diseases. In the last few decades, herbal medicine has been used in the field of medicine because of its natural origin and lesser side effects. One such medicinal plant is *Juglans regia* (Family: Juglandaceae). The plant is also known as Persian walnut, English walnut, white walnut, or in common known as walnut. All parts of this plant *viz*. bark, kernel, leaves, *etc*. are extensively useful. Traditionally the kernels of walnut are used for the treatment of diabetes, asthma, gastric cancer, prostate cancer, liver damage, malaria, arthritis, toothache, dermal inflammation, *etc*. by the folk of different countries. Whereas researchers worldwide also proved that different parts of *Juglans regia* (JR) also possess beneficial effects such as anti-oxidant, anthelmintic, insecticidal, hepatoprotective, anti-inflammatory, anti-diabetic, wound healing, anti-depressant, fungicidal, anti-microbial, anti-nociceptive, anti-cancer, analgesic, immunomodulatory, lipolytic, neuroprotective and many other medicinal properties. Chemical analysis indicates that presence of various phytochemicals like alkaloids, flavonoids, carotenoids, glycosides, saponins, polyphenols, omega 3 and 6 fatty acids, steroids and other compounds are responsible for the pharmacological effects of *J. regia*. The objective of this review article is to summarize the traditional, phytochemical, and various pharmacological activities of *J. regia* for future research work.

INTRODUCTION: Our nature has blessed us with an immense treasure of natural products that have proved to become a vital component to mankind. These basically include the number of fruits, nuts, vegetables, *etc.* Plants not only fulfill the need for food, but now these natural products and their rich phytochemistry are extensively scrutinized for establishing means of therapeutic treatment in many diseases and disorders.

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Walnut tree is known to human being back to 7000 BC. Romans call walnut *Juglans regia*, "Jupiter's royal acorn." At least 30 types of walnuts are grown all over the world, but only 3 varieties are grown for commercial purposes that are *J. regia, J nigra*, and *J. Cinerea* (Family: Juglandaceae). English walnut started from ancient Persia, where they reserved for royalty and due to this also known as "Persian walnut" [1].

Presently being native to Central Asia, western Himalayas, and Kyrgyzstan, the Walnuts are now even cultivated for commercial purposes throughout Southern Europe, eastern Asia, northern Africa, and few parts of South America [2]. The California walnuts are considered to be of most superior quality world-wide. On the commercial

scale, the walnuts are traded extensively for its kernels. The genetic diversity is extreme in the areas of forestry, productivity, chemical, and physical characteristics of NUTS [3]. Walnut provides great commercial interest for the food industries as its kernels are edible that are consumed fresh, dried, and toasted. It is internationally considered for its nutritional, fitness, and sensory attributes. Walnuts have already proved to be immensely beneficial in the treatment of cancer, hypertriglyceridemia, diabetes, obesity, *etc*. Walnuts are evaluated pharmacologically for ample of activities like antioxidant, antimicrobial, antiatherogenic, anti-inflammatory, anti-tumor, anti-mutagenic, anthelmintic and anti-diabetic and hepatoprotective potentials. Most importantly, the kernels of walnuts are consumed for memory enhancing and neuroprotective functions world-wide. These activities occur in *Juglans regia* due to its extreme richness in phytoconstituents. The walnut is very rich in vitamins, protein, minerals and is a good source of a variety of flavonoids, phenolic acid and related polyphenols [4, 6].

2. Morphology: *Juglans regia* is a deciduous tree with a height measuring from 25-35 m in length, and the diameter of a tree trunk measured variably up to 2 m. It requires full-fleshed sunlight for proper growth as it belongs to a species that demands sufficient light. The surface of the bark of the tree is smooth when the tree is young; the color of the bark is olive-brown, but as the tree becomes older, the color of the bark of the tree transforms to silvery-grey with more broad fissures and rough texture. The pith of the twigs of walnuts contains air spaces, having a brown color. The leaves on the tree are arranged alternately termed as phyllotaxic arrangement.

The leaf measured from 25-40 cm in length, with 5-9 oddly pinnate leaflets that are paired throughout except at the tip. The leaflet is largest at the apex present in triplet, which measures 10-18 cm along its length, and 6-8 cm along its width, with entire margin [7, 8]. As the tree is unisexual, the female flowers are located at terminals in a set of 2-5, while the male flowers are 5-10 cm in length arranged on the central stems that are drooping. During the autumn season ripening of the entire edible fruit occurs, which is green in color that possesses a semi-fleshy husk with a ridged brown nut within [9]. These walnuts are edible when it gets dry, and the color of the hull turns brown and opens slightly to expose light brown colored shell from inside that further encloses edible bilobed kernels within a hard shell. The shape of the nut is spherical as that of lemon, with a weight of around 10-15 gm. Structurally, the kernel of walnut seeds resembles that of the brain that is enclosed inside a hard skull, and similar to it the walnut kernels are composed of corrugated lobes that are uneven and off-white in color. These kernels are further enveloped by a thin, light brown papery sheet loosely joined from the center part [3].

3. Taxonomical Classification:

Kingdom	:	Plantae
Subkingdom	:	Tracheobionta
Superdivision	:	Spermatophyta
Division	:	Magnoliophyta
Class	:	Magnolionpsida
Subclass	:	Hamamelididae
Order	:	Juglandales
Family	:	Juglandaceae
Genus	:	Juglans
Species	:	*J. regia*

4. Nutrient Composition: In the entire world, the walnuts are known to be highly rich in its phytochemistry that makes it nutritively more beneficial from the ancient period as a result of which it has even been include in the list of priority plants. The kernels of *Juglans regia* L. contain high content of proteins, oils (fatty acids), vitamins, and minerals; hence they can be consumed fresh or toasted. The content of phytochemicals varies as per the geographical location, climatic conditions, soil composition, and genotypic features of the tree. Fat is the most abundant component of the kernels of walnuts with a percentage of 67.4%, which is further followed by proteins with a percentage of 15.7% [10].

The major element of oil obtained from walnuts is triacylglycerol with a concentration of 980 g/kg of oil that are composed of polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs). Among 9 TAGs identified in walnut, oil trilinolein is the predominant of all with concentration of 37.7%.

Other TAGs include dilinoleoyl-oleoyl-glycerol and dilinoleoyl – linolenoyl - glycerol with a percentage of 18.5 and 18.4%, respectively [11]. The oil of *Juglans regia* contains various amounts of linoleic acid and oleic acid. Stearic and palmitic acid are the saturated component present in all species of walnut.

Some other compounds like ascorbic acid, Ca, K, P, Mn, Mg, and Na are present in various amounts in kernels of *Juglans regia* [12]. The total phenolic compounds present in walnuts are usually extracted in methanolic and petroleum ether extracts of its seeds, green husk, and leaves. But maximum phenolic compounds are obtained from petroleum ether extract of seeds of walnuts.

These mainly involve phenolic acids like ellagic acids, gallic acid, syringic, caffeic, p-coumaric, 5-o-caffeoylquinic, ferulic and sinapic acids and tannins like casuarinin, glansrins A, B and C, stenophyllarin and others [13, 14].

Hydroxycinnamic acid derivatives were also identified in certain varities of walnuts, 3-o-caffeo-ylquinic, 3-o-coumaroylquinic and 4-o-p-coumaroy lquinic acids and some flavanol heterosides were also identified in which the major component was quercetin 3-o-galactoside. Other flavonoids that were present in certain walnut species are quercetin 3-o-ramnoside, quercetin 3-o-arabinoside, quercetin 3-o-galactoside, quercetin 3-o-oxyloside and kaempferol 3-o-pentoside [15, 16].

Flavonoids like catechin, epicatechin, gallo-catechin, procyanidin B2, epigallocatechin and epicatechingallate are also present in kernels of *Juglans regia* [17]. The steroids present in the *Juglans regia* are mainly lupeol, betullinic acids, daucosterol and beta sitosterol. Apart from above mentioned phytochemicals the plant is even rich in essential oils composition that mainly involves juglone A, B, reglolone, 4-hydroxy-a-tetralone, alfa-pinene, beta-pinene, germacrene-D, beta-caryophylline, limonene, camphene, Sabininene, myrcene and eugenol [6, 18]. *Juglans regia* also contain vitamin E, folate, melatonin and a significant amount of omega 3 and omega 6 fatty acids [4].

5. Traditional uses: Traditionally, the plant of walnut is used for dermal inflammation and excessive hand or feet perspiration. It is also a common remedy for the treatment of scrofula and eczema.

The leaves of this plant are used to treat scalp dandruff and itching, superficial and sunburn [19, 20]. Fresh leaves are applied to the body or forehead to reduce fever and even applied on swollen joints to relieve rheumatic pain [21]. In China, the bark, branches, and exocarp of immature green fruit are used in the treatment of gastric, lung, and liver cancer [22, 23]. Kernels of *J. regia* are used to treat inflammatory bowel disease in Iran. It is also used for the treatment of diabetes, asthma, vascular, and prostate disturbances in Palestine [24].

In Mexico, it is used for healing against liver damage [25]. In Calabria, shells of the fruit are used to heal malaria [26]. In Nepal, bark paste is used for the treatment of arthritis, toothache, skin disease, and growth of hairs. The bark is used as a tooth-cleaning twig [1, 27]. In the traditional Indian system, the bark and roots of walnut are used to treat toothache, cleaning of teeth and fruit peel is used to treat ringworm infestation [28, 29]. The tribes of Nagaland use the bark and unripe fruits of *J. regia* for pesticidal activity and leaves as astringent, anthelmintics as well as to treat eczema and herpes [30]. The kernels of *Juglans regia* also have high anti-atherogenic activity and osteoblastic activity due to this fact it is used as cardioprotective and to prevent bone loss [31].

6. Pharmacological uses:

6.1 Antidepressant Activity: In the year 2009, Rath B. P. Pradhan D evaluated the effect of *J. regia* fruit on depression. This activity was carried out by the forced swim test and tail suspension test performed on rats, and the results of the above study concluded that the hexane extract of fruits has antidepressant activity at 100 mg/kg or 150 mg/kg doses due to omega-3 fatty acid [32].

In another study different extracts *viz.* petroleum ether, ethanol, chloroform and aqueous of almond and walnut were used to evaluate antidepressant activity in mice using elevated plus maze (EPM) and forced swim test (FST), the result concluded that the ethanolic extract of *Juglans regia* showed significant antidepressant activity at 200 mg/kg and 400 mg/kg [33].

6.2 Anxiolytic: The anxiolytic effect of hydro-alcoholic extract of kernels of *Juglans regia* was evaluated in rats and mice, and the results concluded that the extract of kernels possesses anxiolytic activity and it may be due to the presence of Omega-3 fatty acids which are found in walnut [34]. In another study the different extracts *viz*. petroleum ether, ethanol, chloroform and aqueous of almond and walnut were used to evaluate anxiolytic activity in mice using elevated plus maze and forced swim test, the result concluded that the ethanolic extract of *Juglans regia* showed significant anxiolytic activity at 200 mg/kg and 400 mg/kg [33].

6.3 Antioxidant Activity: As mentioned earlier, fruits are a great source of antioxidants that prevent aging and other apoptotic pathways. Similar to other fruits and nuts, walnut is also found to be extremely rich in its antioxidant phytochemistry, which prevents oxidation in one's body. Hence, the walnut tree has been entirely screened for antioxidant activity and involves various instances. In 2008, the husk of walnut was evaluated for antioxidant activity using the *in-vitro* DPPH oxidation method, and the results of this study showed that total phenolic contents present in the walnut husk reduce scavenging property of DPPH [35]. In the same year, the hydroethanolic extract of leaves of *Juglans regia* was evaluated for its *in-vitro* scavenging effect on reactive oxygen species and reactive nitrogen species, and the results concluded that the extract of leaf used as a natural source of antioxidants [36].

Similar to this zhang zinjiain in 2009 tried to extract the antioxidant phenolic compound from the kernels of walnuts and successfully concluded that seven antioxidant compounds isolated from kernels were found to possess significant DPPH scavenging activity [37].

In another study, Carvalho Marcia and his coworkers screened the antioxidant activity of methanol and petroleum ether extracts of walnut leaves, seeds as well as a husk. The methanolic and petroleum ether extracts of all the parts were reported to have DPPH free radical and AAPH induced oxidative hemolysis scavenging property [10]. In the same year, Bullo *et al.,* reported that the consumption of whole walnut or walnut skin decreases the antioxidant burden in an enzymatic and non-enzymatic antioxidant system in C57BL/6 mice [38].

The methanolic extract of the green husk of *Juglans regia* was screened for antioxidant activity by DPPH scavenging method, and the results concluded that *Juglans regia* is a natural source of antioxidant compounds [39]. In the year 2012, an exactly similar study was carried out by akbari vali in which he analyzed the antioxidant activity of different parts of *Juglans regia* whose studies concluded that the phenolic extracts of fruits contain maximum considerable antioxidant activity among all the extracts [40]. In 2015, another study by Flores-Almonte Carolina Dulce and his co-workers evaluated Pharmacological and genotoxic property of phenolic extract of *Juglans regia* bark, while the results of the study concluded that roots have high antioxidant activity [41].

6.4 Antimicrobial Activity: The antimicrobial effects of methanolic, chloroform, and aqueous extract of *Juglans regia* on airborne microorganism concluded that the chloroform and aqueous extracts had the microbicidal effect [42]. The antibacterial activity of *Juglans regia* leaves extract against propionibacterium acne, and other acne developing organisms by disk diffusion method revealed that *Juglans regia* leaf extract might be beneficial to treat acne [43].

The antimicrobial effect of leave of *Juglans regia* was evaluated against gram-positive (*Bacillus cereus*, *B. subtilis*, *Staphylococcus aureus*) and gram-negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*) and fungi (*Candida albicans*, *Cryptococcus neoformans*) and the results concluded that the leaves selectively inhibited the growth of gram-positive bacteria, being *B. cereus* the most susceptible one (MIC 0.1 mg/ml). Gram-negative bacteria and fungi were resistant to the extracts at 100 mg/ml [44, 45]. In the year 2008, Oliveira Ivo and his coworkers evaluated the antimicrobial action of the green husk of walnuts.

The antimicrobial action was estimated against enormous strains of bacteria of which aqueous extract of green husk inhibited the growth of *B. cereus*, *B. subtilis*, *S. aureus*, *E. coli*, *P.*

aeruginosa, *K. pneumoniae*, *C. albicans* and *C. neoformans*, while the acetone extract of bark was able to inhibit the growth of microflora [35]. The *in-vitro* antimycobacterial activity of various extract of *Juglans regia* bark and leaf extract showed that the hexanoic bark extract of *Juglans regia* is most active with minimum inhibitory concentration against M. tuberculosis [46]. In 2008 Kong YH *et al.,* investigated the effect of juglone on helicobacter pylori three keys enzyme (cystathionine gamma-synthase HPCGs, malonyl-co-A:acyl carrier protein transacylase Hpfab and beta-hydroxyacyl-ACP dehydratase HpfabZ and the result concluded the juglons shown potently inhibit three key enzymes of *H. pylori* [47]. A similar study was carried out by Deshpande R. Rahul in 2011, in which different extracts of *J. regia* were screened for antimicrobial effect on oral microflora, and the result of the above study implies that the acetonic extract of the bark was able to inhibit the growth of microflora [48].

The methanolic, ethanolic, and aqueous solution of the green husk of walnut was screened, and the results concluded that the aqueous extract of the husk of walnut has the ability to inhibit the growth of gram-positive bacteria [49]. The antifungal activity of methanolic, ethyl acetate, alkaloid, and hydrolyzed methanolic extract of leaves of *Juglans regia* against pathogenic *Candida albicans* strains and the study concluded that the methanolic extract of *Juglans regia* leaves exerts highest anticandidal activity [50].

6.5 Antiviral Activity: The antiviral activities of methanolic extract of 75 Moroccan plants used traditionally to treat diseases that could be caused by viruses and microbes (herpes simplex virus, Sindbis virus and poliovirus) was conducted and the extracts of *Juglans regia* inhibited Sindbis virus at a minimum concentration of 1.5 mg/ml [51]. The antiviral activity of different extract of leaves of *Juglans regia* shows that the main antiviral constituents are present in 95% ethanol and ethyl acetate leaf extract of *Juglans regia,* which inhibits Tobacco mosaic virus (TMV) infecting nicotiana glutinosa [52]. In molegro virtual docker, the antiviral activity of juglone were evaluated in silico and concluded that juglone is the potential drug against viruses due to its protein-ligand binding affinity [53].

6.6 Anthelmintic Activity: Upadhyay V *et al.,* screened various extracts according to the polarity of stem bark of *Juglans regia* for anthelmintic activity against Indian earthworm, *Pheretima posthuma* and concluded that the benzene, methanol and ethanol extracts of stem bark exert anthelmintic activity [54].

In 2011, the anthelmintic activity of various extracts of stem bark of *Juglans regia* was also evaluated against eicinia foetida and concluded that the acetone and methanolic extract exert a significant anthelmintic activity and the ethanolic extract shows quite weak anthelmintic activity [55].

In the year 2011, an *in-vitro* anthelmintic effect of leaves of walnut was determined using Pheretima Posthuma. The leaves of walnuts confirmed the anthelmintic activity as its extract took very less time to paralyze the worm and result in its death [56].

6.7 Immunostimulant Activity: In the year 2015, Ruijun Wang screened the immature fruits of *J. mandchurica* for the immune regulative activity. The results of the study had concluded that the extract of immature fruits of *J. mandchurica* improved lymphocytes proliferation and phagocytic activity of macrophages [57].

6.8 Anticancer Activity: Various studies are carried out to identify the anticancer potential of walnuts. Juglone, the chemical constituent present in walnut has been reported to inhibit intestinal carcenogenesis in rats induced by azoxymethane could be the promising chemoprotective agent to treat intestinal neoplasia [58]. The light petroleum ether extract of *Juglans regia* kernels evaluated for anticancer activity in Swiss albino mice with the help of 7, 12- dimethylbenz(a)anthracene (DMBA) and croton oil and the result showed the extract was reducing the cancer cells [59]. In the same year, an anti-proliferative activity of *Juglans regia* was evaluated using human cancer cells. The results showed that the methanolic extract of walnut seeds, leaves, and green husk inhibited the growth of human colon and renal cancer cell lines in a dose dependent manner [10].

Another study to investigate the effect of juglone on apoptosis of human gastric cancer SGC-7901 cells tested by sulforhodamine B (SRB) assay concluded that juglone induces apoptosis in SGC-7901 cells mediated by the generation of reactive oxygen species and a reduction in the Bcl-2/bax

protein ratio [60]. The study of leaves of *Juglans regia* on Hela cells by MTT assay was concluded that the juglone inhibits the proliferation of HeLa cell by induction of apoptosis by the activation of caspase-9, 8, 3 and PARP cleavage in a dose-dependent manner and prevent cervical cancer [61]. In the same year, the human cancer cell lines were used to evaluate the cytotoxic effects of various leaf extracts of *Juglans regia*. Results concluded that the chloroformic leaves extract of walnut possess human oral and breast cancer antiproliferative activity [62]. Antitumor effects of an extract obtained from immature fruits of *Juglans regia* were evaluated in 2015 whose results indicate that the epicarp of immature fruits of *J. mandchurica* inhibited the growth of S180 cells 57. In the same year, the anticancer activity of hexanic extract of leaf of *Juglans regia* against human prostate cancer cell by MTT assay shows that the extract exhibited a potent and dose-dependent anti-proliferative activity in human prostate cancer cell [63].

6.9 Hepatoprotective Activity: In 2002, the study of the effect of Walnut extract on acute renal failure in rabbit by the subcutaneous injection of mercuric chloride concluded that walnut exerts beneficial effect against mercuric chloride-induced acute renal failure and could be effective against in-vivo and in-vitro regeneration of nephron cells [64]. In 2008, the hepatoprotective effects of walnuts were established against carbon tetrachloride and d-galactosamine.

In this study, an oral administration of 200mg/kg, dose of a walnut pellicle in mice reduced the risk of liver damage that was induced by carbon tetrachloride (CCl4) [65]. In another study held in 2013, the effects of *J. regia* against carbon tetrachloride induced oxidative damage in rats was analysed and the results of the study stated that extract obtained from leaves reduced carbon tetrachloride induced liver damage by decreasing the level of AST, ALP and AST [66].

6.10 Memory Enhancing Activity: In 2009, Willis Lauren M and his co-workers evaluated the effects of walnut on the motor and cognitive functions in old aged rats in a dose-dependent manner. Results of the given study concluded that walnut has the ability to reverses age-related motor and cognitive functions [67]. The *Juglans regia* was further evaluated for memory and learning functions in 2011. The results of the study concluded that walnut enhances the serotonin level in the brain leading to advancements in learning and memory functions and even helps in reducing obesity [68]. In 2013, Majid AS and his co-worker evaluated the effects of walnut consumption by pregnant and lactated rats on learning and memory in rat's offsprings and concluded that walnut significantly improves the learning and memory of rat's offspring [69].

In another study, the effect of polyphenol extracts of walnut testa on learning and memory functions in hypercholesterolemia mice based on obesity, hypercholesterolemia, and oxidative stress shows that the polyphenolic extract of walnut improves learning and memory function by decreasing cholesterol, triglyceride and malondialdehyde level in serum and increased superoxide dismutase activity in brain tissues [70].

6.11 Anti-diabetic Activity: Jelodar and Nazifi-Habibabadi study on the effect of pomegranate and walnut leave extract on biochemical parameters on diabetic rats concluded that the extract of walnut leaves on alloxan-induced diabetic rats to decrease the blood glucose level [71]. In 2006, the effect of hydroalcoholic extract of walnut leaves was studied on diabetic rats, and the result shows that the dose-dependent consumption of extract decrease blood glucose level in diabetic rats [72].

The study on the effect of ethanolic extract of *Juglans regia* on blood sugar in alloxan-induced diabetic rats shows that the ethanolic extract of walnut leaves decreases fasting blood sugar level in diabetic rats and increase insulin level and glycosylated hemoglobin [73].

In other study effects of hydroalcoholic extract of walnut on streptozotocin-nicotinamide induced diabetes in rats was evaluated whose results concluded that alcoholic extract of leaves of walnut prevents chances of type II diabetes induced by streptozotocin-nicotinamide [74]. Later in the same year, the screening of methanolic extract of leaf and fruit peel of *Juglans regia* on diabetic rats concluded that the methanolic extract of leaf decrease fasting blood sugar, HbA1c and β-cell

number increased in both leaf and peel extract [75]. In another study, the effect of ether, ethanol and cyclohexane extract of leaves of *Juglans regia* in alloxan-induced diabetic rats showed the dose and duration dependent antihyperglycemic effect on diabetic rats, with few side effects [76]. In another study, the effect of alcoholic extract of *Juglans regia* leaves on allaxon induced diabetic rats was evaluated whose results concluded that the alcoholic extract of leaves might decrease the level of blood glucose and urea level and increases cholesterol and triglyceride level [77].

In the same year, a study on the pharmacological and genotoxic property of polyphenolic extract of bark of *Juglans regia* against diabetic rats indicated that it exerts a hypoglycemic effect [41].

6.12 Anti-hypercholesterolemic Activity: The study of anti-hypercholestremic activity of *Juglans regia* oils in human being concluded that the oil of walnut lower the plasma triglyceride and increases the level of HDL in blood [78]. In 2015 a study indulged in the screening of Pharmacological and genotoxic property of phenolic extracts of bark of *Juglans regia.* The study ended on a conclusion that the methanolic extract of bark of walnut reduces cholesterol level in mice [41].

6.13 Anti-neurodegenerative Activity: An *in-vitro* neuroprotective activity of leaves and fruits of walnut were evaluated in 2011, whose results mainly concluded that leaves and fruits of walnut exerted neuroprotective effect by inhibition of cholinesterase activity [79]. Later in the same year, the protective effects of walnut extract against β-amyloid peptide were evaluated, whose results suggested that walnut extract offers protection against amyloid β mediated cell death and hence prevent neuronal loss [80].

In 2012 Mohammad Shabani and his coworker evaluated the effect of walnut diet against cisplatin-induced neurotoxicity in rats and concluded that walnut alters the performance of the hippocampus and cerebellum and improve motor and cognitive functions in male rats [81]. In another study, the effects of walnut diet in the brain of aged rats were studied and the studies concluded that walnut diet reduces inflammation and accumulation of polyubiquitinated proteins in brains of aged rats as result of its antiradical activity [82]. The neuroprotective activity of walnut consumption on scopolamine-induced memory impairment in rats shows that the walnut diet prevents scopolamine neurotoxicity by decreasing ACHE activity in the whole brain and useful for the management of Alzheimer's disease [83]. In 2019 Ming chuan Liu and his coworker evaluate the memory-enhancing and neuroprotective effects of the antioxidant peptide from walnut protein hydrolysates and found that the walnut peptide able to inhibit the H_2O_2-induced PC12 cell death and in zebrafish model exert neuroprotective effect by inhibiting the activity of caspases 3/7 and 8, mRNA expression of Bax and glial cell line and improve mRNA expression of brain and also improve learning and memory in male and female mice due to this ameliorating effects of walnut protein may be useful for the Alzheimer's and its related disease [84].

6.14 Anti-hypertriglyceridemic Activity: The polyphenolic extract of walnut was evaluated for diet-induced hypertriglyceridemia in mice through fatty acid oxidation in the liver. The study concluded that walnut pellicle reduces the triglycerides level from serum and liver [85].

6.15 Thyroid Hormone: In 1994, ozturk Y evaluate the effect of kernels of *Juglans regia* on thyroid hormone in mice, and the study concluded that the unripe fruit extract of walnut enhances the level of thyroid hormone in mice [86].

6.16 Other Activity: The ethanolic extract of leaves of *Juglans regia* was evaluated against carrageenan-induced hind paw edema in mice without inducing gastric damage and concluded that leaves extract exhibited a potent anti-inflammatory activity as potent as indomethacin [87]. In 2008, the anti-nociceptive effects of walnut leaves extract were evaluated on male rats to increase analgesic effect of morphine in the minimum dose, and the result concluded that the alcoholic extract of walnut leaves at 1.5 mg/kg dose cause significant nociception decrease in the acute phase of formalin test and when to combine with morphine increase in the anti-nociceptive effect of morphine in acute phase [88].

The methanolic extract of kernels of *Juglans regia* was evaluated against cigarette smoke extract

(CSE)-induced lung toxicities in Wistar rats and the result concluded that the extract decreased the level of LDH, total cell count, total protein and increased the GSH level in Bronchoalveolar lavage fluid and restore the level of Glutathione reductase, catalase and decrease the activity of xanthine oxidase in lung tissues [89]. Another study on the anti-nociceptive activity using hot-plate and writhing tests, anti-Inflammatory activity using xylene induced ear edema and cotton pellet test of aqueous and ethanolic extract of *Juglans regia* leaves in male and female albino mice showed that the aqueous (2.87 and 1.64 g/kg) and ethanolic (2.044 and 1.17 g/kg) extracts showed anti-nociceptive activity in hot-plate test and both extracts showed anti-inflammatory activity in some doses [90].

7. Clinical Study: A study conducted on the daily intake of kernels of *Juglans regia* for 4 weeks on 40 healthy Japanese males and females showed that the walnut diet decreased total cholesterol level and modifies lipoprotein profile, especially in females [91]. A daily intake of walnut in the diet for 4 weeks improves endothelium-dependent vasodilation and decrease the level of vascular cell adhesion molecule-1 of 21 hypercholesterolemic men and women by reducing total cholesterol and LDL cholesterol this finding explains the cardioprotective effect of walnut [92].

The hypoglycemic effect was even established in the aqueous extract of walnut leaves on 61 type-II diabetic patients given 100 mg extract twice a day for three months concluded that the extract of leaves of walnut prevents type II diabetes and lipid profile without exerting any adverse effects on liver and kidney [93]. In a double-blind study, 20 diabetic patients out of 50 patients receive capsules containing 100 mg *Juglans regia* leaf extract (hydroalcoholic) twice daily for 8 weeks showed that *Juglans regia* leaf extracts effective in decreasing body weight and blood pressure and had no significant effect on glucose level and HOMA-IR score in type-II diabetic patient [94].

8. Toxicity Study: The modulatory effects of aqueous extract of *Juglans regia* was studied on the toxicity of an anticancer drug, cyclophosphamide with special reference to protection against disruption of drug-metabolizing and antioxidant enzymes during chemotherapy. The extract reduced cytochrome P450 in the kidney and significantly enhanced the activity of glutathione peroxidase and level of reduced glutathione in both liver and kidney tissue and catalase in liver tissues.

The plant extract with cyclophosphamide showed a significant decrease in the level of lipid peroxidation in liver and kidney tissues [95]. The aqueous extract of *Juglans regia* leaves reduced 3-(4, 5- dimethyl thiazol-2yl)-2, 5-diphenyl tetrazolium bromide formation at a concentration of 500 µl/ml on Hep G2 cell and the co-culture of Hep G2 with THP1 revealed no negative effect at all concentration of the extract. The investigator also reported no changes in the level of LDH and albumin on the culture medium after 24 h of exposure to the extract [96].

Hosseinzadeh H and his co-worker studied the anti-inflammatory, anti-nociceptive, and acute toxicity effects of aqueous and ethanolic extract of *Juglans regia* and concluded that the LD_{50} values were 5.5 and 3.3 g/kg, respectively [90]. The oral acute toxicity study of methanolic extract of the septum of *Juglans regia* in female Wistar rats was treated with doses of 10, 100, 1000, 1600, 2900 and 5000 mg/kg for 14 days and In a subchronic study, the extract was given at a dose of 1000 mg/kg daily in Wistar rats for 28 days, and the results showed that the extract did not produce any toxic signs or deaths; the medium lethal dose must be higher than 5000 mg/kg and extract has no acute or subacute adverse effects with a dose of 1000 mg/kg [97].

CONCLUSION: The review article documents the publication of *Juglans regia* (walnut) and its constituents in recent and last few years. The paper focused on the review of traditional as well as pharmacological use of the plant and claimed many *in-vivo* and *in-vitro* biological activities of this plant. The different extracts of the different parts of walnut have been used and found to be significantly effective in improving the various pathological conditions in rats as well as human beings due to the presence of a variety of photochemical in it. The review even concludes that the toxicity level of the kernels of *Juglans regia* is about 3.3 and 5.5 g/kg so that the consumption of walnut doesn't have toxicity to the patient. Furthermore, clinical trials in humans are required to analyze the long term and prophylactic

efficacy of walnut extracts or one or more of its phytoconstituents and also to observe the detailed toxicological studies on the consumption of walnut.

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