Review Article

Insights of Pharmacological Activities, Patents and Clinical Applications of Polyphenolic Compounds Enriched Nuts of *Juglans regia*: A Review

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***Juglans regia* L. is a exotic nut widely used as functional food owing to its multi-nutritional qualities. It is generally found in Southeast Europe extending towards the Himalayas and Southwest China. This historical plant is extensively used ethno-medicinally in the treatment of digestive, respiratory, cardiovascular and skin diseases. Its seeds are highly proteinaceous and polyphenolic containing triacylglycerol-rich oil especially mono and polyunsaturated fatty acids. The diverse lipid profile of the walnut has attracted the researchers of the decade towards scientific validation of its traditional aspects and isolation of important chemical compounds for improving human health. The present review comprehends the ameliorative effect of *Juglans regia* on various chronic diseases including cancer, gut dysbiosis, cardiovascular and neurodegeneration concerning its specific chemical profile.**

Key words: *Juglans regia*, walnut, α-linolenic acid, juglone, sankrutin, polyphenolic, cardiovascular

Nuts, the enveloped kernels and seeds, are wonderful gifts from earth to mankind. They are considered complete meals as they come packed with energy, proteins, antioxidants, vitamins, and minerals. They contain heart-friendly Monounsaturated Fatty Acids (MUFA), omega-3 essential fatty acids, and polyphenols such as carotenes, resveratrol, and lutein. There are various types of nuts available in markets worldwide, including almonds, cashews, hazelnuts, peanuts, chestnuts, walnuts, and pine nuts, each with its unique importance.

Various types of nuts are available in markets worldwide, including almonds, cashews, hazelnuts, peanuts, chestnuts, walnuts, and pine nuts, each possessing its unique importance. Several varieties of walnuts are available in the market, including black walnut (*Juglans nigra*), English walnut (*Juglans regia* (*J. regia*) L.), and butter or white walnut (*Juglans cinerea*). *J. regia* L. of the family Juglandaceae, is most commonly referred to as walnut. It is native to Kyrgyzstan but is widely distributed across parts of Southern Europe, the United States of America (USA), Turkey, Tajikistan, Australia, New Zealand, China, and India[1]. China leads in walnut production, followed by the USA, Iran, Turkey, Ukraine, Romania, France, and India. In recent years, countries like Chile and Argentina have also seen increased production rates[2]. The Juglandaceae family comprises 60 species in the Northern Hemisphere. *Juglans* is a plant genus whose seeds are known as walnuts[3]. Walnuts are an integral part of Mediterranean diets and come from deciduous trees found in Europe, Asia, and the Eastern and Southern USA[4].

Walnuts, whether Persian or black varieties, possess a thicker shell with an intense flavor. As deciduous trees, they are easy to cultivate, with harvesting beginning from early September to November. When 85 % of the hull is removed, the shells are ready for harvest, and proper irrigation is crucial during cultivation and harvesting. Delayed harvesting can result in shell blackening and give the kernels a bitter, rancid flavor[5]. The nut is the powerhouse

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of vitamin E, MUFA, omega-3 fatty acids, and arachidonic acids[6]. Due to its nutrient-rich oil and high protein content, the walnut is listed on the Food and Agriculture Organization's (FAO) priority plants list and is classified as a strategic species[7]. Beyond the nut, other parts of the plant such as the leaves, bark, husk, shell, and fruit also hold pharmacological importance[8]. Walnut protein has been reported to contain minimal allergenic levels, with an Eliciting Dose 01 (ED01) among 14 food allergens, according to a study using the stacked model averaging statistical method. Walnuts are versatile, being used across the cosmetic, food, and pharmaceutical industries[9,10]. They contain a variety of flavonoids, phenolic acids, and related polyphenols, making them powerful antioxidants with anti-atherogenic, anti-inflammatory, and antimutagenic properties[11,12]. Several studies have revealed that regular consumption of walnuts decreases cardiovascular risk by lowering Low-Density Lipoprotein (LDL) cholesterol, reducing inflammation, and improving arterial function[13-15]. The remarkable properties of the walnut plant have been discussed in various complementary and folk medicines. The leaves have been used ethnomedicinally in Turkey to relieve fever and swelling, while the kernels have been used in Iran to treat bowel inflammation. In Palestine, walnuts are used to treat diabetes and asthma, and in Calabria's folk medicine, the shells are used as an anti-malarial remedy[16-18]. The plant is commonly used in traditional medicine for treating topical or dermal inflammations, particularly with its leaves and bark[19,20].

Numerous scientific reports suggest that walnuts, rich in fibers, Polyunsaturated Fatty Acids (PUFAs), polyphenols (such as tannins and ellagic acid), vitamins (riboflavin, tocopherols), proteins (arginine, lysine, tryptophan), non-sodium minerals (calcium, magnesium, potassium, phosphorus), and trace elements (copper, zinc, selenium), possess anti-inflammatory, antioxidant, anti-aging, and cognitive improvement properties. Walnuts, particularly rich in omega-3 and omega-6 fatty acids, have also been found to enhance memory[21]. *J. regia* L. is a crucial tree with leaves, branches, trunk, roots, flowers, and fruits that are extensively used for nutritional, medicinal, and industrial purposes. The unripened walnut consists of an epicarp, mesocarp, and endocarp (the hard shell of the nut), which encases the edible kernels. The different stages of fruit development are illustrated in fig. 1. The green husk of the walnut is traditionally used in Chinese medicine for its anti-cancer and antioxidant properties, as well as for combating inflammation and dermal infections[22]. The phenolic-rich walnuts of *J. regia* L. are oxidized by Polyphenol Oxidase (PPO), while Gallate 1-B-Glucosyltransferase (GGT) acts as a precursor molecule in the synthesis of hydrolysable tannins. The genome of *J. regia* L. contains 130 GGT genes and 2 PPO genes; however, the locations of PPO1 and PPO2 remain unidentified, which is vital for basic research and molecular breeding[23]. This review provides insights into the remarkable nut, *J. regia* L., focusing on its phytochemistry, ethnobotanical importance, and reported pharmacology.

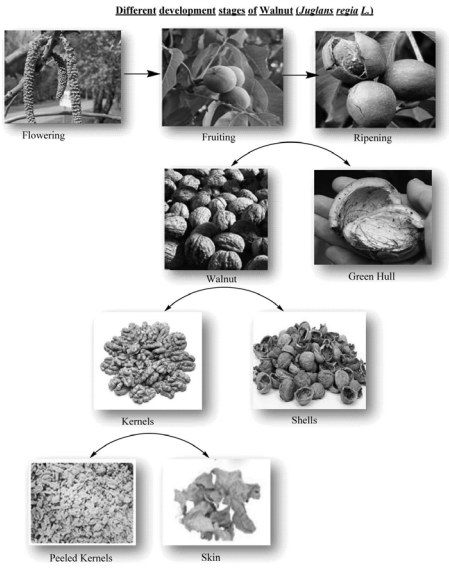
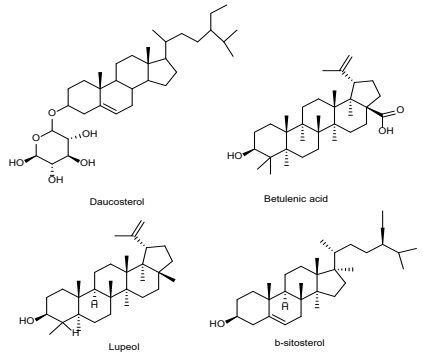
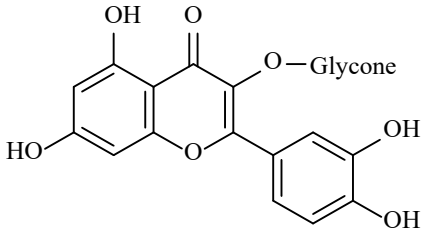
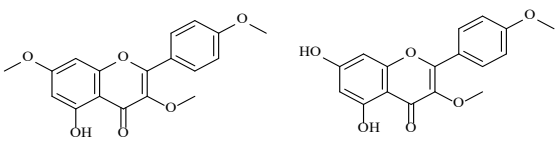


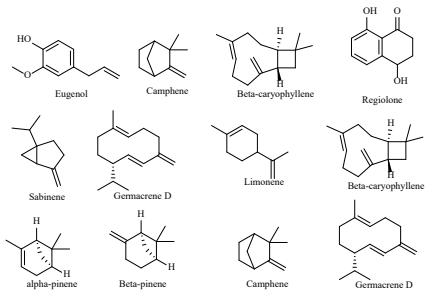
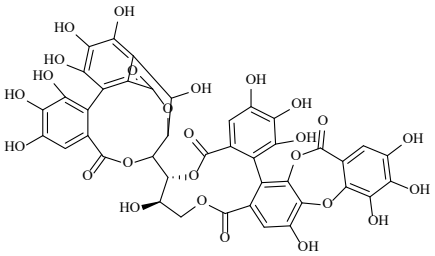
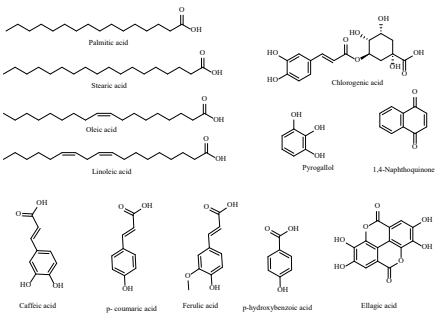
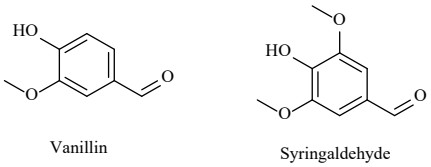
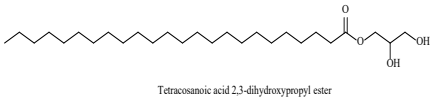
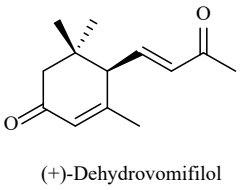
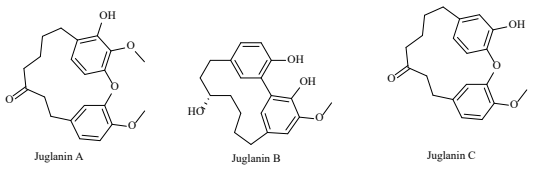
Fig. 1: Different development stages of walnut (*J. regia* L.)

BIOACTIVE CONSTITUENTS

The kernels of *J. regia* L. without shells consist of 4 % water, 15 % protein, 64 % lipids, and 14 % carbohydrates, with 7 % dietary fiber. A 100 g serving of walnuts provides 654 kcal of energy, along with minerals, including 163 % of the daily value for manganese, and vitamins A, C, and folate[24]. Walnut oil is rich in unsaturated fatty acids (both mono and poly), such as Alpha (α)-linolenic acid, linoleic acid, palmitic acid, stearic acid, and oleic acid, which make up the total fat content[25]. Walnut residue after oil extraction is commonly used as fodder, fertilizer, or low-value feed. However, through the technique of enzymolysis, bioactive peptides can be generated from this residue, which possess xanthine oxidase inhibitory properties. These peptides could serve as nutraceutical supplements for populations suffering from malnutrition and excessive junk food consumption[26]. Juglone (5-hydroxy-1,4-naphthoquinone) and pyrogallol are major phenolic compounds that exhibit anti-cancer activity by inhibiting key enzymes required for metabolism[27,28]. Sakuranetin, an aglycone derived from sakuranin found in *Juglan* species, is a 7-O-methylated flavonoid with various pharmacological activities, including antioxidant, anti-inflammatory, antimycobacterial, antiprotozoal, hypoglycemic, neuroprotective, and antineoplastic effects. Although the pharmacokinetics and toxicity of this compound have not yet been thoroughly examined, it may play a role in promoting health[29]. The structures of bioactive constituents from different categories are presented in Table 1. Walnut shells, which are rich in lignocellulosic content, are used as abrasives in industrial applications. Additionally, due to their biodegradable properties, walnut shells can be utilized for packaging and, in pharmaceutical applications, as adsorbents for heavy metals, synthetic dyes, and hazardous chemicals[29-36].

TABLE 1: THE LIST OF DIFFERENT BIOACTIVE MOIETIES REPORTED TO BE PRESENT IN *J. regia* L.

S. No.	Secondary metabolites	Structures
1	Steroid derivatives[31]	 Daucosterol; Betulenic acid; Lupeol; b-sitosterol
2	Flavonoid C-glycoside derivative[32]	 Quercetin
3	Flavones derivatives[33]	 5-Hydroxy-3,7,4'-Trimethoxyflavone; 5,7-dihydroxy-3,4'-dimethoxyflavone

4	Essential oil compounds[34]	
5	Tannins derivative	
6	Organics acid derivatives[35]	
7	Phenolic aldehyde derivatives[36]	
8	Monoglyceride derivative	
9	Sesquiterpene derivative	
10	Diarylheptanoid derivatives[36]	

PHARMACOLOGICAL ACTIVITY OF *J. regia* L.

Neuroprotective activity:

Tan *et al.*[37] concluded that a walnut-rich diet can combat chronic inflammation and the progression of neurodegenerative diseases. Diets high in *J. regia* L. significantly reduce the expression of phosphorylated Nuclear Factor kappa B (NF-κB) and oxidative stress in rodents induced by Lipopolysaccharides (LPS). Furthermore, a balanced gut microbiome contributes to a reduction in microbial-derived pro-inflammatory mediators such as Interleukin-6 (IL-6), IL-1 Beta (β), and TNF-α, aiding in the maintenance of neural health. In Persian medicine, walnuts are believed to promote brain health and alleviate fatigue, as walnut extract increases dopamine levels and LPS in treated rat hippocampal cells. The ellagic acid present in walnut leaves and fruits contributes to their anti-inflammatory activity[38].

Bleomycin-induced pulmonary toxicity protection:

A methanolic extract of *J. regia* L. (150 mg/kg) was administered 14 d prior to bleomycin exposure to evaluate its effects on bleomycin-induced pulmonary toxicity. Following the administration of bleomycin (10 μ/kg), results indicated that the *J. regia* L. treated rats showed increased expression of glutathione and catalase, along with decreased expression of lactate dehydrogenase and alkaline phosphatase, thus regulating apoptosis *via* the NF-κB pathway[39]. Therefore, the *J. regia* L. extract was reported to protect against the harmful effects caused by bleomycin in cancer individuals[40].

Improvement in male fertility:

J. regia L. has been found to exhibit the highest antioxidant activity after hazelnuts and pistachios. It contains tocopherols, essential fatty acids such as oleic, linoleic, palmitic, and stearic acids, as well as tannins, flavonoids, melatonin, fibers, and sterols[41]. The whole walnut kernel has been reported to improve semen quality, sperm morphology, and motility[42]. In a clinical study, the intake of 75 g/d of walnut kernels for 12 w as part of the routine diet of young males resulted in improved sperm count, vitality, and motility compared to the control group. The increase in omega-3 and omega-6 fatty acids was identified as a key factor responsible for enhancing sperm and hormonal balance. Another study concluded that the intake of 42 g/d of walnut kernels offered potential benefits for men with impotence and sperm quality issues[43,44]. The omega-3/omega-6 ratio in walnut kernels was found to be 4.25, the highest among superfoods such as hempseed, chia seeds, and flax seeds. This ratio, along with α-linolenic acid, is considered essential for long-term health maintenance[45].

Gut microbiome:

Walnuts, rich in polymerized polyphenols, starch, Non-Starch Polysaccharides (NSPs), and n-3 fatty acids, possess a prebiotic effect[46]. After cereals, walnuts have the second-highest fiber content per 100 g. The fiber bypasses digestion in the small intestine and is transported directly to the colon, where it is used as a substrate by microbes. This stimulates the growth of microbiota, which, in turn, leads to the production of metabolites such as Short-Chain Fatty Acids (SCFAs) like butyrate, providing health benefits to the host[47,48].

Gastroprotection *via* dual Cyclooxygenase (COX)-2/5-Lipoxygenase (LOX) inhibition:

The phenolic extract from walnuts was found to have a preventative effect on indomethacin-induced gastric ulcers. Chronic use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) can induce gastrointestinal ulcers, perforations, and bleeding[49]. In walnut extract-treated groups, there was significant upregulation of 5-Hydroxyprostaglandin Dehydrogenase (15PGDH), which subsequently increased Heme Oxygenase-1 (HO-1) expression and nuclear translocation of Nuclear factor erythroid 2-related factor 2 (Nrf2) *via* Kelch like ECH Associated Protein 1 (KEAP1) inactivation. The downstream regulation of NF-κB and AP-1 led to the modulation of COX-1 enzymes, providing mucoprotective effects. Additionally, the eradication of *Helicobacter pylori* by walnut extract was attributed either to the repression of Signal Transducer and Activator of Transcription 3 (STAT 3) or the activation of Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) receptors[50-61].

Anti-aging activity:

Walnut septum extract, rich in ellagic acid and other compounds, demonstrated significant tyrosinase inhibitory activity and has been proposed for use in cosmetic formulations to alleviate dermal hyperpigmentation and reduce wrinkles[61-69]. Table 2 summarizes the major pharmacological activities reported for various bioactive constituents, along with their mechanisms of action.

TABLE 2: LIST OF MAJOR PHARMACOLOGICAL ACTIVITY REPORTED BY DIFFERENT BIOACTIVE CONSTITUENT AND THEIR MECHANISM OF ACTION

S. No.	Pharmacological activity	Bioactive compound reported	Description	Reference
1	Anti-neoplastic activity	Hydroalcoholic extract	30 % reduction of prostate and breast cancer	[52-54]
		Juglone	Cellular apoptosis and mitotic arrest	[55]
2	Anti-oxidant	Ellagitannin derivatives	Metabolic process regulation	[56]
		Hydroalcoholic extract	Free radical scavenging activity	[57-59]
3	Neuroprotective	Omega-3	Inflamo-protective	[60]
		Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA)	Anti-inflammatory	[61]
		Walnut aqueous extracts	brain function and connectivity	[62]
		Ellagic acid, melatonin, and γ-tocopherol	Anti-oxidant in β-amyloid reign	[63]
4	Cardio-protective	Walnut kernels	Delayed onset of cardiovascular	[64]
		Walnut kernels	Boost defense system by improving good cholesterol	[65]
		Ellagic acid	Antiatherosclerotic effect	[66]
		Ellagitannin	Combat oxidative stress and inflammation	[67]
5	Diabetes mellitus	Dietary fats	Glycaemic index and insulin levels improvement	[68,69]
6	Gut microbiome	Omega-3 and omega-6 fatty acid	Regulate intestinal microbes	[70]
		Walnut polyphenol extracts	Improve LDL levels, good bacteria	[71,72]

INTERPRETIVE PATENTS

J. regia L. (Persian walnut) is a highly valued medicinal plant. Its various parts, extracts, and decoctions have been extensively used for therapeutic purposes in treating conditions such as hypertension, thrombophlebitis, hypercholesterolemia, and mood disorders[70-78]. According to patent (No: IN201921025805), the hydroalcoholic extract of the green hull of walnut fruit, rich in caffeic acid and ferulic acid, was found to be effective in the treatment of cerebral ischemia. The (No: US20190111098) patent disclosed that a powdered formulation of the fifth part of *J. regia* L. was found to be effective in improving penile erection and sperm motility. Another patent, (No: CN107913302), revealed that green dragon paste, containing juglone, oleanolic acid, vanillin, vanillic acid, quercetin, and naphthoquinone, when taken in a 2 g dose on an empty stomach, exhibited anti-inflammatory, anti-bacterial, anti-helminthic, analgesic, antioxidant, and anti-tumorigenic activities. An herbal formulation containing *J. regia* L. (fruit shell), *Acacia arabica* (bark), *Mimusops elengi* (bark), and *Mangifera indica* (leaves) has been indicated for periodontal care, specifically for preventing dental plaque and gingivitis[79-81]. A list of patents along with their associated pharmacological activities is presented in Table 3.

TABLE 3: THE LIST OF PATENTS DISCLOSING VARIOUS PHARMACOLOGICAL BENEFITED FORMULATIONS

S. No.	Patent number	Description
1	US20210093688	10 parts by weight of 70 % ethanolic extract of *J. regia* L. root along with other plant extracts were used to prepare a natural plant preparation indicated for the regulation of cardiovascular disease including hypertension, thrombophlebitis, hypercholesterolemia, and mood disorders[73].
2	IN201921025805	Hydroalcoholic extract of the green coat of *J. regia* L. fruit was used in the treatment of cerebral ischemia. Phenolic compounds comprising caffeic acid and ferulic acid are enriched in the hydroalcoholic extract[74].
3	US20190111098	A powder formulation including *J. regia* L., *Dimocarpus longan*, *Ziziphus jujube*, *Lycium barbarum*, *Rehmannia glutinosa*, and others was prepared for the enhancement of eroticism, libido, and sperm motility. The formulation increases the stability and ease of oral administration. The 400 g of *J. regia* L. in 2000 g of powder treated group was found to be effective penile erection value and a sperm motility percentage increase[75].
4	EP3441076	An extract of *Julans regia L*, *Blumea aromatica*, and *Eugenia caryophyllata*, were formulated in a weight ratio of 77:54:98 and indicated to possess anti-neoplatic activity and tumor recurrence by arresting the cellular growth in prophase stage[76].
5	CN107913302	The green dragon paste containing juglone, oleanolic acid, vanillin, vanillic acid, quercetin, and naphthoquinone was taken 2 g empty stomach and found to be inflamo-protective, bactericidal, antihelminthic, analgesic, combating oxidative stress and anti-tumorogenic activity[77].
6	EP3441078	A formulation capsule containing *J. regia* L. (1 part), *Artemisia absinthium* (0.5-2 parts), *Panax quinquefolium* Linn. (1-5 parts), and *Dendrobium nobile* (1-10 parts) was used to treat lupus erythematosus. Additionally, the formulation is also indicated for analgesic, anorectic, hepatoprotective, normoglycaemic, and blood purifier[78].
7	WO2015174808	Nutraceutical drink containing *Panax ginseng*, *Allium sativum*, *Mel*, *Laurus nobilis*, *Syzygium aromaticum*, *J. regia* L., and *Vitis vinifera* and claimed to robustness and enhance sexual functioning. This drink is organic, capable, and apposite for both males and females[79].
8	IN1102/MUM/2012	Herbal formulation containing *J. regia* L. (fruit shell), *Acacia arabica* (bark), *Mimusops elengi* (bark), and *Mangifera indica* (leaves) was indicated for the periodontal care i.e., preventing dental plaque and gingivitis. The formulation could be a mouthwash, toothpaste, and mouth rinse or applying the powder directly on the gums and teeth for 2 w daily[80].
9	WO2012033422	A mixture of herbs including *J. regia* L. fruit was mixed in 1:6 of 96 % ethanol/ glycerine and 40 % of volcanic mineral water, prepared for the treatment of skin disorders. The *J. regia* L. possess folic acid and a green coat of unripe fruit rich in ascorbic acid and iodine[81].

CLINICAL TRIALS

A meta-analysis of anthropometric parameters in obesity revealed that an intake of 35 g/d of walnuts for 50 w resulted in significant reductions in body weight, waist circumference, and body mass index; however, it did not lead to a reduction in fat mass[82].

The analysis of randomized controlled trials involving 195 subjects with type 2 diabetes mellitus and lipid profiles was conducted over duration of 8 to 12 w. Participants received a hydroalcoholic extract of *J. regia* L. leaves at doses ranging from 100 to 750 mg/d, with an initial dose of 100 mg/d for the 1st w followed by 200 mg/d for the subsequent 7 w. No significant results were found in lipid-lowering effects; however, glycosylated Hemoglobin (HbA1c) levels were shown to decline after 8 w of treatment[83]. Another study examining walnut consumption in individuals with type 2 diabetes mellitus assessed Fasting Blood Glucose (FBG) levels, HbA1c, and insulin resistance. The researchers concluded that there was no significant reduction in blood glucose or insulin levels, and no association was found between walnut intake and alleviation of type 2 diabetes. However, including walnuts in the daily diet may help delay the progression of chronic disease[84].

The effect of walnut consumption in the routine diet has been evaluated for metabolic syndrome in

adults. In this analysis, 549 individuals from eight randomized controlled trials were studied concerning blood glucose levels, lipid profiles, C-reactive protein concentrations, and anthropometric indices. The results showed a significant decline in triglyceride levels, while other cardiovascular parameters and glucose levels remained unchanged[85]. Furthermore, another study investigated the association between cognitive improvement and walnut intake, concluding that there was no significant cognitive improvement in individuals who consumed walnuts[86].

A clinical trial involving 99 obese women was conducted to study the effects of a combined marine and plant omega-3-rich diet over 12 w. The participants were divided into 3 groups: One received fish alone (300 g/w), another received walnuts alone (18 walnuts/w), and the 3rd group consumed both fish and walnuts (150 g of fish plus 9 walnuts/w). The results revealed that the combined group, which included both marine and plant sources, showed a significant reduction in anthropometric measurements, blood pressure, glycemic indices, and fibrinogen levels[87].

In a clinical trial, 236 adults with borderline blood pressure were supplemented with walnut kernels, comprising approximately 15 % of their daily energy intake, over a duration of 2 y. The study concluded that walnut supplementation resulted in a reduction of systolic blood pressure compared to controls on a normal diet. Walnuts contain n-3 PUFAs, particularly α-linolenic acid, which has potent vasodilatory and anti-inflammatory properties. They are also rich in γ-tocopherols, powerful antioxidants, and non-sodium minerals (potassium, calcium, magnesium) that help lower blood pressure. Additionally, the amino acid arginine, a precursor to nitric oxide release, suggests that walnut intake positively affects endothelial function in blood vessels[88]. In another study, the authors concluded that a walnut-supplemented diet did not significantly contribute to the reduction of hypertension. Although walnuts are rich in zinc, magnesium, and fiber, tocopherols may serve as a complementary component in a healthy dietary plan[89].

A meta-analysis of 14 clinical trials involving 883 individuals was conducted to evaluate the effects of walnut consumption (dosing of 15-57 g/d) on glycemic biomarkers, including FBG levels, insulin, HbA1c, adiponectin, and leptin, over intervention periods ranging from 5 w to 1 y. The results suggested that regular dietary intake of walnuts did not significantly alter FBG, insulin, or HbA1c levels; however, adiponectin and leptin levels increased significantly. Pharmacologically, leptin transmits signals from hypothalamic neurons and mediates the activity of Neuropeptide Y (NPY), Agouti-Related Protein (AgRP), and Pro-Opiomelanocortin (POMC). NPY and AgRP levels stimulate orexigenic (appetite-stimulating) effects, while POMC signals induce anorexic (appetite-suppressing) behavior. Furthermore, leptin-modulated immune cell proliferation may be associated with an individual's nutritional status and immune function. Thus, the studies concluded that adiponectin and leptin levels contribute to immune function and nutritional status, while showing no significant association with improvements in blood glucose level biomarkers in acute or chronic metabolic diseases[90].

A clinical trial involving the intake of various nuts (almonds, pistachios, walnuts, peanuts, and others) examined their influence on gut microflora and gut function in adults. The microbiota, including *Dialister*, *Lachnospira*, and *Parabacteroides*, showed no significant changes in excretion in both walnut intake and control groups. In contrast, *Roseburia* and *Clostridium* levels in feces were found to significantly increase in individuals consuming walnuts. The dose and duration of nut intake played a crucial role in these outcomes. Walnuts, rich in omega-3 fatty acids, were identified as the bioactive compounds responsible for maintaining gut microbiota[91].

An extract of walnut tree leaves, combined with extracts from other medicinal plants, was administered to a pediatric population (aged 6-18 y) and found to be effective in treating acute non-bacterial tonsillitis. In Romanian ethnomedicine, *J. regia* L. has been recognized since prehistoric times for its activity against dermal infections such as eczema, scrofulosis, and atopic dermatitis. It demonstrates ethnopediatric therapeutic versatility, with a reported effectiveness of 71.42 %[92].

Regular dietary intake of walnuts, consumed every 6 mo, has been shown to delay the progression of chronic diseases and downregulate the expression of cancer metabolic biomarkers due to their richness in juglanin, juglone, and ellagitannin metabolites (urolithins)[93]. A study involving 56 g of walnuts in the daily diet for 8 w indicated a significant increase in endothelial function, characterized by enhanced membrane fluidity, increased nitric oxide release, and decreased levels of Vascular Cell Adhesion Molecule-1 (VCAM-1), along with a reduction in endothelin-1. Walnuts are abundant in

polyphenolic compounds, dietary fiber, healthy fatty acids, selenium, and magnesium, all of which have beneficial effects on cardiovascular risk, particularly regarding atherosclerosis and arrhythmia[94]. Additionally, walnuts, rich in the bioactive fatty acid A-Linolenic Acid (ALA) and non-sodium minerals, help lower the risk of myocardial infarction[95].

DISCUSSION

Nuts are of prime importance worldwide due to their multifactorial health benefits, attributed to their highly nutritious profiles. The genus *Juglans* encompasses 7 subgenera and 59 species distributed globally. The kernels of *J. regia* L. contain 4 % water, 15 % protein, 64 % lipids, and 14 % carbohydrates, along with 7 % dietary fiber. A 100 g serving of walnuts provides 654 kcal of energy, along with minerals (163 % of the daily value for manganese) and vitamins A, C, and folate. Numerous scientific reports indicate that nuts, rich in fiber, PUFAs, polyphenols (such as tannins and ellagic acid), vitamins (including riboflavin and tocopherols), proteins (such as arginine, lysine, and tryptophan), minerals (like calcium, magnesium, potassium, and phosphorus), and trace elements (such as copper, zinc, and selenium), exhibit anti-inflammatory, antioxidant, anti-aging, and cognitive enhancement properties.

J. regia L. is a highly valued medicinal plant. Various parts of the plant, including extracts and decoctions, have been extensively used for their therapeutic properties in treating conditions such as hypertension, thrombophlebitis, hypercholesterolemia, and mood disorders. An herbal formulation containing *J. regia* L. (fruit shell), *Acacia arabica* (bark), *Mimusops elengi* (bark), and *Mangifera indica* (leaves) has been indicated for periodontal care, specifically in preventing dental plaque and gingivitis.

Walnuts contain omega-3 PUFAs, specifically α-linolenic acid, which serves as a potent vasodilator and exhibits anti-inflammatory activity. They are also rich in γ-tocopherols, powerful antioxidants, and non-sodium minerals (such as potassium, calcium, and magnesium) that help lower blood pressure. Additionally, walnuts provide the amino acid arginine, a precursor for nitric oxide release, thus enhancing endothelial function in blood vessels. Rich in polyphenolic compounds, dietary fiber, healthy fatty acids, selenium, and magnesium, walnuts have beneficial effects on cardiovascular risk, particularly regarding atherosclerosis and arrhythmia[94]. Moreover, walnuts, rich in the bioactive fatty ALA and non-sodium minerals, can lower the risk of myocardial infarction[95].

The de-oiled cakes from nuts are typically protein rich, but their current utilization is largely limited to cattle feed. These mechanically pressed cakes contain 45 %-55 % protein and 30 %-35 % carbohydrates and fiber. Enzymatic hydrolysis derived de-oiled nut cakes could be evaluated for their potential anti-hypertensive, antioxidant, and neuroprotective activities[96]. Regular inclusion of walnuts in the diet can aid in delaying the progression of chronic diseases, including those related to anthropometric and endocrine dysfunctions, as well as neurodegenerative disorders[97].

CONCLUSION

J. regia L. is a medicinal plant that contains fibers, PUFAs, polyphenols (including tannins and ellagic acid), vitamins (such as riboflavin and tocopherols), proteins (including arginine, lysine, and tryptophan), non-sodium minerals (such as calcium, magnesium, potassium, and phosphorus), and trace elements (including copper, zinc, and selenium). These components contribute to its ability to combat inflammation, oxidative stress, aging, cancer, and diabetes mellitus, as well as its antimicrobial properties and cognitive and memory enhancement effects. This review highlights that walnuts are nutritionally rich, pharmacologically active, and therapeutically used in various formulations. It is recommended that future studies focus on the identification of active molecules, pharmacokinetic and pharmacodynamic profiling, gene profiling, and elucidating their mechanisms of action.

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Conflict of interest:

The authors declared no conflict of interests.

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