

A Review Study on Phytochemistry and Pharmacology Applications of *Juglans Regia* Plant

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ABSTRACT

In recent years, the use of medicinal plants increased considerably; so that today, the use of traditional medicine, as well as medicinal plants is necessary for the aim of producing more effective drugs with fewer side effects and determining the effective doses. With the scientific name of *Juglans regia*, walnut plant is a medicinal plant with different properties that is considered less, despite having great therapeutic potential in the traditional medicine. The aim of this study was to review the dispersal of walnut plants, the chemical compounds, and therapeutic effects of walnuts on antioxidant activity, antidiabetic, hypolipidemic, antimicrobial, and antihypertensive activities, as well as liver protection. Data of this review study have been collected from the books and scientific articles published in databases such as Science Direct, Web of Science, Scopus, PubMed, and Scientific Information Database. While this plant having high antioxidant capabilities, walnuts are composed of many chemical compounds such as ascorbic acid, flavonoids, quercetin, and caffeic acid. Experimental studies have shown that walnuts reduced blood glucose and lipids and also decreased blood pressure. They have antioxidant, antidiabetic, antimicrobial, and liver-protective properties. The use of walnuts in traditional medicine and review of experimental studies demonstrated the presence of multiple, effective, and useful compounds which may provide the opportunity for the production of lipid-lowering, antidiabetes, and liver protective drugs. Due to the effects of walnuts on improving the complications of various diseases, the need for doing comprehensive clinical trials for the use of walnuts in the treatment of diseases is necessary.

Key words: Antidiabetic, antihypertensive, antioxidant, *Juglans regia*, pharmacology

INTRODUCTION

The history of using medicinal plants to treat diseases is as long as the history of human being; so that, it has a history of several thousand years in a lot of countries.^[1,2] In the past centuries, natural drugs, especially medicinal plants were considered as the basis of treatment. In the recent decade, it has been shown that there is a great tendency toward and willingness in accepting natural therapies in the developed and developing countries.^[3,4] Many plants used in traditional medicine are indigenous to Iran.^[5] Due to reduced costs and fewer side effects, the use of medicinal plants are preferred to chemical drugs;^[5] and regarding the complications and harmful effects of chemical drugs, the use of natural and herbal medicines have been seriously taken into consideration. In recent years, the use of herbal medicines has significantly increased.^[6] In addition, for the use of plants or their active components, it is repeatedly instructed to make necessary coordination and get the mandatory scientific confirmation.^[7]

In recent decades, the tendency toward using natural materials rather than synthetic materials has increased.^[8] Synthetic products and materials are more in the form of compounds compared to the natural substances; and

their return to nature, in comparison with natural ingredients, needs a lot of time; and this process causes environmental pollution.^[9] Each plant yields secondary metabolites, including compounds such as phenolic compounds, essential oils, terpenoids, glycosides, terpenes, alkaloids, and tannins, which may be responsible for various therapeutics effects. The remedial significance of medicinal herbs enhances with the increased value of certain compounds of the plants.^[10] Many studies have been conducted on the pharmacology of medicinal plants; hence, they are a potential source for the production of new drugs, and may increase the effects of chemical drugs which might reduce the costs and increase the quality of treatment. Natural antioxidants such as phenolic compounds have important and great value for the human health because they reduce the risk of degenerative disease by reducing oxidative stress and inhibit the oxidation of macromolecules.^[11,12]

The results of scientific studies on medicinal plants to treat various diseases including diabetes, infectious diseases, cancer, and atherosclerosis have been helpful.^[6,13] Natural products may lead to better treatments with fewer side effects than synthetic drugs. There is a big focus for hypoglycemia components or other adverse effects caused by the diseases in the use of herbs in traditional medicine.^[14]

Walnut, with scientific name of *Juglans regia*, which belongs to the *Juglandaceae* family, is one of the medicinal plants which, like most herbal medicines of traditional medicine, is considered less despite having great therapeutic potential.^[15] In traditional medicine, walnut roots are used to

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treat diabetes, its leaves are used to treat rheumatic pains, fever, diabetes, skin diseases; and its flowers are used to treat malaria and rheumatic pain.^[16-19] As far as, Iranian traditional medicine is concerned, this plant is widely used in Persian cuisine to treat different diseases. Walnut leaves are used in traditional medicine to reduce blood glucose and improve diabetes.^[17] Based on studies conducted, walnut leaves contain compounds effective on health; and they are widely used in traditional medicine for the treatment of venous insufficiency and hemorrhoid symptoms. In some cases, they are used as anti-diarrhea and anti-parasitic drug, as well as a blood purifier.^[20,21] The results suggest that extensive research in the past two decades has been conducted on the pharmacological effects of walnut. Different parts of this plant such as its leaves, bark, and fruits have hypoglycemic properties in diabetic animals.^[22] Studies on the effects of the walnut leaf on lipid factors in streptozotocin-induced diabetic rats have demonstrated reduced levels of lipids.^[23-25] In addition, recent studies have shown that this plant is associated with analgesic and antimicrobial effects.^[25] Studies have shown that the walnut extract is full with total phenol which have anticancer and anti-inflammatory properties.^[26] According to the studies conducted on walnuts and their properties, the aim of this study was to review the dispersal of walnut, its chemical walnut composition and therapeutic properties [Figure 1].

METHODS

This research is a review study which examines the dispersal, chemical composition, and effects of *J. regia* (walnut) through review of the literature and summing up of experimental studies conducted by the authors of the present study. For the review of literature, the original English resources found in Wiley, Science Direct, PubMed, and Google Scholar databases; equivalent keywords in Persian electronic databases including Scientific Information Database, review of Persian available resources, and articles published in Persian scientific journals were used.

ECOLOGY AND GEOGRAPHICAL DISTRIBUTION OF WALNUT

The vegetative origin of the walnut tree is the Eastern Balkans to the Himalayas and Southwestern China.^[14] The Persian or common

walnut (*J. regia*) is its best-known member, found primarily in the temperate areas and commercially cultivated in the many parts of the world [Figure 2].^[17,18] Now, walnut trees are growing many in parts of the world, including Asia (foothills of the Himalayas, Iran, China and Japan), Southern and Eastern Europe, as well as North and South America. Walnut trees grow in some provinces of Iran such as Fars, Hamedan, Kohgiluyeh and Boyerahmad, and Lorestan.^[14-18] A species of walnut tree with the scientific name of *J. regia* grows in Iran. Walnut tree is sensitive to too hot and too cold weather in summer and winter.^[27] Walnut trees are monoecious plants with a height of about 10–25 m. They have pinnately compound leaves; with male and female flowers appeared on them separately. During the period of winter dormancy, walnut trees can stand the cold weather up to -11°C . The puberty of walnut trees has a direct relationship with the species, breed, weather, and the location of its growth.

CHEMICAL COMPOSITIONS OF WALNUT

Depending on the different factors such as geographic location, temperature, time, and other factors, a plant has a different chemical composition in different countries. Today, different parts of the walnut tree such as leaves, bark, and fruits are used in the world. Researchers have reported that chemical compounds found in walnuts are different in different climates. Fruits of walnut trees are valuable and edible; and their oil is rich in polyunsaturated fatty acids, tocopherols, and phytosterols.^[14] Walnuts are a good source of essential fatty acids and tocopherols. Chemical compounds of different parts of the walnut are shown in Table 1. Zahoo reported that 17 compounds have been identified in walnut leaves; nine of them are epicatechin, syringetin-o-hexoside, myricetin-3-o-glucoside, myricetin-3-o-pantocid, aesculetin, taxifolin-pantocid, quercetin glucuronide, kaempferol pantocid, and kaempferol rhamnoside.^[14] The leaves of this plant contain phenolic acids, tannins, essential fatty acids (linoleic acid is its major fatty acid), ascorbic acid, flavonoids, caffeic acid, and paracomaric acid. The most

Table 1: Compound of *Juglans regia*

Part	Compound	References
Leaf	Phenolic acids, tannins, essential fatty acids, ascorbic acid, flavonoids, caffeic acid, paracomaric acid, juglone Flavonoids: Quercetin galactoside, quercetin pantocid derivatives, quercetin arabinoside, quercetin xyloside, and quercetin rhamnoside	[14,16,20,28-30]
Green husk of fruit	Emulsion, glucose, organic materials such as citric acid, malic acid, phosphate, and calcium oxalate	[29-32]
Fruit	Fatty acids, tocopherols, phytosterols, total phenolic (tannin), antioxidant activity	[10,14]

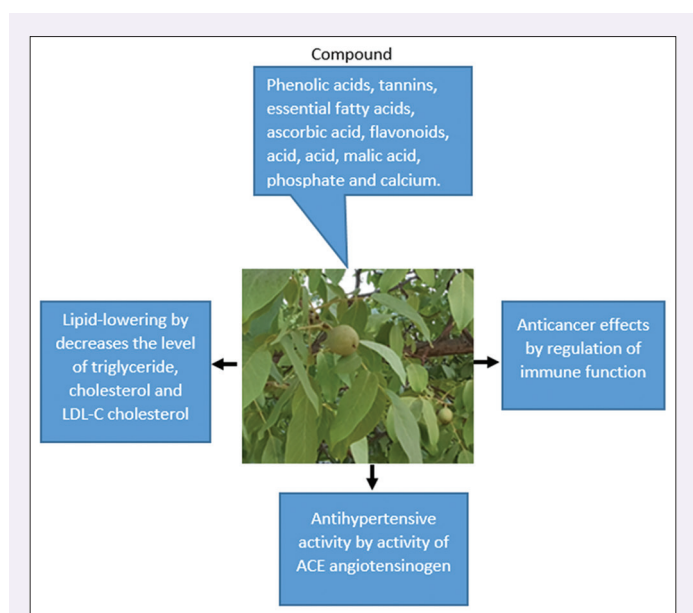


Figure 1: Scheme of *Juglans regia* compounds and several positive influence properties

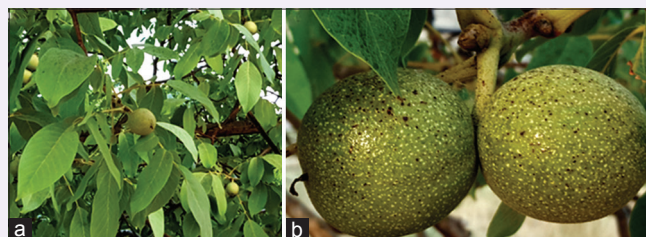


Figure 2: (a) Leaves of *Juglans regia* (b) Fruits of *Juglans regia*

important flavonoids in the walnut leaves include quercetin galactoside and quercetin pantocid derivatives, quercetin arabinoside, quercetin xyloside, and quercetin rhamnoside.^[16] Furthermore, Shah *et al.* also reported phytochemical screening of the crude leaf extracts of *J. regia* revealed the presence of carbohydrates, cardiac glycosides, phenolics, flavonoids, alkaloids, proteins, steroids, and tannin.^[19] Amaral *et al.* reported that there are phenolic compounds including 3- and 5-caffeoylquinic acid, 3- and 5-p-coumaroylquinic acid, quercetin 3-galactoside, quercetin 3-pantocid derivatives, quercetin 3-arabinoside, quercetin and quercetin 3-o-xyloside, and quercetin 3-rhamonocid in the walnut leaves.^[28] Quercetin 3-galactoside is the main ingredient among the mentioned compounds.^[28,29] Furthermore, it has been reported that the leaves of this plant contain naphthalene derivatives, particularly 5-hydroxy-1-4-naphthoquinone. Juglone (5-hydroxy-1, 4-naphthoquinone) is a naphthoquinone compound found in the fresh leaves and green husk of the walnut tree fruits. Juglone is the most obvious ingredient in different organs of the walnut tree, with molecular weight of 174.16, and formula C₁₀H₅O₂ (OH), the precursor of which is a glycoside that is found as a compound in aerial parts of the plant, especially leaves, which is then converted to juglone through hydrolysis.^[30,31] Juglone is an alkaloid substance which is slightly dissolved in the hot water and moderately in the alcohol; therefore, it can be one of the effective compounds in the walnut leaves because other substances in the leaves of the walnut are often water-soluble or fat-soluble. The green husk of walnut tree fruits has emulsion, glucose, and organic materials such as citric acid, malic acid, phosphate, and calcium oxalate. Juglone and phenolic compounds are the most important compounds found in the leaves and green husk of walnuts.^[29-31] Juglone, as a toxic compound, is only found in fresh and green walnuts, but there is no such property in its dried leaves.^[29,32,33] Walnut green husk has a byproduct with little use. It has been demonstrated that due to its phytochemical source, walnut husk increases the value of the walnut products; compared to the use of a by-product produced in a large quantity.^[8,33,34]

THERAPEUTIC TREATMENT

Antioxidant activity

Possible mechanisms of the effectiveness of pharmacological properties of different parts of walnuts are shown in Table 2. Several studies have demonstrated the antioxidant potential of walnut products, particularly their fruits, leaves, and alcoholic substances produced from green fruits.^[31-34] In biological systems, oxidative stress resulting from an imbalance between the production of reactive oxygen species (ROS) and antioxidant defense systems are some of the effects of major cellular components, including lipids, proteins, and DNA. Overproduction of ROS or reduced antioxidant defense may be involved in creating several dangerous diseases.^[34-36] Green walnut husk extract shows a strong effect of lowering oxidative stress. The reduction capability of a compound is based on its potential antioxidant activity.^[36] In their study, Ahmad *et al.* reported that walnuts are associated with antioxidant properties that are useful in the treatment of chronic diabetic patients.^[37] Some studies have shown that the fruits of walnut trees contain Vitamin C and polyphenols, with antioxidant effects.^[38,39,85] Based on recent empirical research, the leaves of walnut trees have secondary metabolites that provide a powerful antioxidant effect.^[39] The existence of antioxidant compounds in walnuts may lead to the collection of free radicals and inactivation of them; and consequently, the protection of cell membranes and various compounds of alive organism against harmful effects. In addition, the selections with relatively antioxidant activity may offer significant marketing advantage, due to consumer preference for antioxidant rich products.

Antidiabetic activity

Due to its fatal complications, diabetes mellitus is the seventh leading cause of death in the human society and the third in the world.^[16,17] Although the most common way to treat diabetes is the use of insulin, nutritional approach to the treatment of diabetes is very effective in the developing countries.^[40] Several studies have confirmed the therapeutic potential of some medicinal plants in the treatment of diabetics.^[40-44] So far, the positive effect of more than 1200 medicinal plants in reducing blood glucose levels or reducing complications of diabetes has been identified.^[44,45] The use of different types of medicinal plants in Morocco indicates how fourteen plant samples such as walnut leaves are used to treat diabetics.^[45]

In the resources of Iranian traditional medicine, the medical uses of walnuts have repeatedly been mentioned. In Al-Hawi reported, the walnut leaves has been introduced by Zakaria Razi M. Alhavi as a performance-enhancing substance which disposes of parasites; and is useful in the treatment of tuberculosis and diabetes.^[46] Walnut leaves are among natural remedies that are recommended to patients with diabetes in traditional medicine. One of the major compounds in different parts of the walnut plant is juglone on which limited research has been conducted. In a research, it has been reported that walnut bark extract reduces the complications of diabetes.^[47] Leaves and fleshy green fruits of walnut trees are used as hypoglycemic agents in Iranian traditional medicine.^[15,37] The results of some previous studies have shown that the infusion of walnut and olive leaves has blood glucose lowering effect in patients with diabetes.^[2] In another study, it has been proven that the infusion of walnut leaves has been effective in lowering the blood glucose levels in patients with diabetes.^[47,48] Fathi Azad *et al.* have also reported that the consumption of hydroalcoholic dose-dependent extract of walnut leaves decreases the level of blood glucose in diabetic rats. They also believed that the impact of hydroalcoholic extract of walnut leaves in lowering the blood glucose level is comparable with drugs such as metformin.^[49]

It has also been reported that a mixture of walnut leaves powder, *Salsola rigida*, and *Urtica dioica* can reduce the absorption of glucose from the intestine and reduce the level of glucose in normal and diabetic rats.^[50] Some researchers have reported that the administration of walnut leaf extract on diabetic rats was led to the significant decrease in the glucose levels and improvement of diabetes.^[16,17,51-54] In a study, Asgary *et al.* reported that the administration of 200 mg of walnut leaf extract for 4 weeks before becoming diabetic and 4 weeks after becoming diabetic was effective in improving diabetes in diabetic rats.^[56] In another study on the effect of walnut leaf, extract on blood biochemical parameters in alloxan-induced diabetic rats, Jelodar and Nazifi-Habibabadi reported a drop in glucose level.^[53] In another study, the effect of ether, ethanol, and the cyclohexane extract of walnut leaves on blood biochemical parameters in diabetic rats was examined and the results showed a drop in glucose, cholesterol, triglyceride, and blood urea nitrogen (BUN).^[54] In their study, Mohammadi *et al.* reported that the administration of hydroalcoholic extract of walnut leaves on the changes in the pancreas tissue of streptozotocin-induced diabetic rat was led to the improved islets of Langerhans and restoration of β -cell function.^[16,17] In another study, it has been reported that the administration of hydroalcoholic extract of walnut leaves to the nicotinamide-induced and streptozotocin-induced type-2 diabetic rats was led to the improved islets of Langerhans and restoration of β -cells; so that the level of insulin in diabetic rats treated with the extract increased; and the level of glycosylated hemoglobin, triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) decreased significantly.^[18]

In another study, it was also reported that the administration of hydroalcoholic extract of walnut leaves to the groups with type-1 diabetes led to the decreased level of cholesterol, triglycerides, hemoglobin A1c (HbA1c), LDL, and increased level of high-density lipoprotein

Table 2: Pharmacological effect of walnut

Pharmacological effect	Effectiveness	References
Antioxidant effects	The leaves of walnut trees have secondary metabolites that provide a powerful antioxidant effect The existence of antioxidant compounds in walnuts may lead to the collection of free radicals and inactivation of them; and consequently, the protection of cell membranes and various compounds of the alive organism against harmful effects	[31-39]
Anti-diabetic effects	Flavonoids such as quercetin increase insulin secretion and they are a strong inhibitor of sorbitol accumulation in tissues of the body Administration of walnut leaf extract on diabetic rats was led to the significant decrease in the glucose levels and improvement of diabetes Alkaloids are among the substances that are capable of lowering the level of blood glucose Methanolic extract of the <i>walnuts</i> bark and leaves in streptozotocin-induced diabetic rats increases the number of beta cells, the level of insulin; and reduces the level of glucose and has proliferative effects The positive impact of flavonoids is due to the intracellular Vitamin C, prevention from permeability and capillary rupture, strengthening of the immune system of cells and improvement of diabetes in patients	[16,17,21,40-60]
Lipid-lowering effects	Several studies showed that a chemical compound such as juglone has antidiabetic effects Dose-dependent consumption of Persian walnut oil extract decreases the level of triglyceride, cholesterol and LDL-C cholesterol in nondiabetic rats with high cholesterol. The results of the administration of alcoholic extract of walnut leaves on the level of triglyceride and serum cholesterol indicate that the active ingredient in walnut leaves somehow has managed to reduce the level of triglyceride and total serum cholesterol and increase the level of HDL	[16,17,30,53,60-64]
Anti-hypertensive activity	Walnut leaf aqueous extract reduced systolic, diastolic, and mean arterial pressure Flavonoids, especially quercetin reduces blood pressure Flavonoids of plants inhibit <i>in vitro</i> activity of ACE and are involved in the regulation of high blood pressure	[21,46,63,66-79]
Antimicrobial effects	Walnut products, particularly husks, barks, leaves, fruits, and special compounds of juglone are associated with antimicrobial activities Several studies have demonstrated that apart from antioxidant activities of phenols and/or phenolic extracts, their antimicrobial activities have led the researchers to consider them as an alternative to antibiotics and chemical protection	[11,24,82]
Liver and kidney protective	Walnut leaves can protect liver against oxidative damages induced by carbon tetrachloride. This liver protective effect is likely effective in meeting the changes in detoxifying and antioxidant enzymes and sweeping free radicals away The administration of walnut extract had a significant impact in the treatment of acute renal failure and could be effective in nephron cell regeneration, <i>in vivo</i> or <i>in vitro</i> The intra peritoneal injection of walnut extract into rats reduced the amount of ALT, AST, total protein and plasma albumin	[11,20,78]
Anticancer effects	Flavonoids have antioxidant properties that are involved in the regulation of immune function and increase in the anticancer activities of the body Juglone in the walnut leaves on colon cancer cells of the rats indicated its anticancer role in inhibiting the formation of benign or malignant intestinal tumors	[7,83-87]

LDL=Low-density lipoprotein, HDL=High-density lipoprotein, ACE=angiotensin converting enzyme, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase

(HDL) and hyperinsulinemia.^[54-57] In a clinical trial, Hosseini *et al.* examined the hypoglycemic effects of walnut leaf extract on patients with diabetes and reported that the administration of walnut leaf extract to under-treatment diabetic patients reduced the level of blood glucose, insulin, and HbA1c compared to the placebo group.^[58]

Reduced glucose level caused by the administration of walnut leaf extract may be based on the mechanism of increasing the release of insulin from the remaining β -cells, reproduced β -cells, insulin sensitivity, interfering with the absorption of dietary carbohydrates in the small intestine and facilitated use of glucose using peripheral-mediated or insulin-dependent-glucose transporter.^[16,17,53-58] A methanolic extract of the walnuts bark and leaves in streptozotocin-induced diabetic rats increases the number of β -cells, the level of insulin; and reduces the level of glucose and has proliferative effects.^[18,57]

The effectiveness of the administration of hydroalcoholic extract of walnut leaves in lowering blood glucose levels in diabetic rats shows that the active ingredient in walnut leaves is soluble in alcohol.^[54-57] Alkaloids

are among the substances that are capable of lowering the level of blood glucose.^[29] Since serum glucose levels in the diabetic control group did not significantly decrease during the experimental period, changes in blood glucose levels cannot be attributed only to the changes in beta cells; and the effects of hydroalcoholic extract of walnut leaves on blood glucose levels in diabetic rats can be attributed to the active substances contained in the extract. Flavonoids such as quercetin increase insulin secretion and they are a strong inhibitor of sorbitol accumulation in tissues of the body.^[14,55,59] The positive impact of flavonoids is due to the intracellular Vitamin C, prevention from permeability and capillary rupture, strengthening of the immune system of cells, and improvement of diabetes in patients.^[59] The results of several studies showed that a chemical compound such as juglone has antidiabetic effects.^[28] Previous research also indicates that polysaccharides, flavonoids, polypeptides, steroids, alkaloids, and pectin in the medicinal plants can well justify the blood glucose, and cholesterol lipid lowering properties of some herbs in the treatment of diabetes by preventing the blood biochemical changes.^[26,29,60,61]

Lipid lowering activity

Researchers have reported that dose-dependent consumption of the Persian walnut oil extract decreases the level of triglyceride, cholesterol, and LDL-C cholesterol in nondiabetic rats with high cholesterol.^[52] The results of the administration of alcoholic extract of walnut leaves on the level of triglyceride and serum cholesterol indicate that the active ingredient in walnut leaves somehow has managed to reduce the level of triglyceride and total serum cholesterol and increase the level of HDL.^[16,17,30] The results of previous studies shown that walnut administration would change the distribution of lipids in different lipoprotein groups; and the use of walnuts is likely associated with anti-atherogenic effects.^[60-63]

It was also reported that a diet containing walnuts will lead to a better distribution of fats among fat subgroups, even when the amount of total fat has not changed.^[30] This effect of walnuts may be an additional process involved in the prevention of vascular plaque formation.^[61] As far as the effects of hydroalcoholic extract of walnut leaves in lowering blood glucose level is concerned, it is likely that juglone, as an effective factor in the walnut leaf extract, causes higher reduction of blood glucose level by stimulating the insulin-producing system, or enhancing the response of cells to insulin.^[30,60] At the beginning of the experiment, more urea is produced due to the development of diabetes in the rats. But with the increase in blood glucose consumption and decreased the level of protein, urea production is also reduced.^[62] Therefore, the existence of multiple chemical compounds in walnuts and their mechanism of action is a factor to reduce the level of fats.

Antihypertensive activity

In a study in Morocco, 320 diabetic patients and 380 patients with high blood pressure and cardiovascular disorders were interviewed. Eighty percent of patients were taking herbal medicine to treat their illness.^[45,62] They reported that herbal therapy is cheaper and better than the treatment with synthetic drugs.^[21] It has been reported that in young people prone to heart disease, eating walnuts play an important role in changing blood lipid concentrations.^[62-68] In another study, it has been reported that the administration of walnut leaf aqueous extract reduced systolic, diastolic, and mean arterial pressure compared to the control group.^[68] In a study, Perusquia *et al.* examined the effect of walnut leaf aqueous extract on aortic segments of rats and reported that their blood pressure and noradrenaline-induced contraction in isolated aorta were reduced. This reduction in blood pressure is attributed to the relaxant effects of the extract on the muscles of arterial walls.^[69] Perez-Vizcaino *et al.* demonstrated that a diet rich in flavonoids, especially quercetin reduces blood pressure.^[70] Furthermore, in another study, it was reported that the ethanol extract of the thin husk around the walnut fruit can inhibit the effect of angiotensin converting enzyme CE by 40%.^[71] In a study, Javadi *et al.* reported that the extract of walnut blades decreased systolic and diastolic blood pressure.^[72] In another study, it has been reported that coadministration of walnut leaf aqueous extract and acetylcholine reduced systolic, diastolic, and mean arterial pressure compared with the control group; and pretreatment with walnut leaf aqueous extract reduced blood pressure caused by the injection of adrenaline.^[73]

Duarte *et al.* reported that flavonoids cause the relaxation of contractile activity induced by noradrenaline and potassium chloride on isolated aortic smooth muscle.^[74] Ajay *et al.* demonstrated that flavonoids prevent contractions induced by phenylephrine in the isolated rat aorta.^[75] Some researchers have reported that quercetin reduces noradrenaline-induced vasoconstriction through engaging the L-type calcium channels in the rat arteries.^[76] In a study, Balasuriya and Rupasinghe reported that flavonoids of plants inhibit *in vitro* activity of ACE angiotensinogen converting enzyme; and are involved in the regulation of high blood

pressure.^[77] According to the results of the mentioned studies, it can be assumed that the walnut leaf hydroalcoholic extract has blood pressure lowering effects; and chemical compounds in this plant reduce the level of blood pressure. Walnut leaves contain compounds such as phenolic acids and flavonoids. The most important flavonoids in walnut leaves are quercetin galactoside, quercetin pantocid, quercetin arabinoside, quercetin xyloside, and quercetin rhamnoside.^[27,78] Reduced blood pressure may be due to the interaction with the adrenergic system. Thus, according to the results of a lot of research, it can be said that the walnut leaf extract is effective in reducing the level of blood pressure because of having multiple flavonoid compounds.

Antimicrobial and antifungal activity

The use of natural antimicrobial compounds for the production of food additives in the factories is increasing because of the desire of consumers to avoid chemical preservatives, and increased resistance to antibiotics.^[19,28] Various components of walnuts such as their green husks, barks, leaves, and fruits have been used in the pharmaceuticals.^[19,20] Studies have demonstrated that walnut products, particularly husks, barks, leaves, fruits, and special compounds of juglone are associated with antimicrobial activities.^[14,20,25] But so far there is no information about the effects of the green husk of walnuts.^[19] With its antioxidant activity, the Portuguese walnut extract significantly inhibited the growth of Gram-positive bacteria, in particular, *Bacillus cereus*.^[19] Some researchers demonstrated, that walnut green husks aqueous extracts presented a strong antioxidant activity and inhibited the growth of different pathogenic bacteria.^[28] Several studies have demonstrated that apart from antioxidant activities of phenols and/or phenolic extracts, their antimicrobial activities have led the researchers to consider them as an alternative to antibiotics and chemical protection.^[19,20] In a study, Sharafati-chaeshtori *et al.* reported that the walnut leaf extract is effective on *Propionibacterium acnes*.^[86] Mehtanolic components derived from walnut leaves have demonstrated a strong antifungal activity.^[87] In a study, Amaral *et al.* reported that walnut leaves could be useful for employment as an antimicrobial agent against bacteria responsible for human gastrointestinal infections.^[28] Thus, according to the results of a lot of studies, it can be said that, due to having compounds such as juglone and phenolics, walnut leaves are associated with antibacterial activities.

Protective of liver and kidney

eidi *et al.* have reported that the hydroalcoholic extract of walnut leaves can protect liver against oxidative damages induced by carbon tetrachloride. This liver protective effect is likely effective in meeting the changes in detoxifying and antioxidant enzymes and sweeping free radicals away.^[24] Another study showed that after subcutaneous injection of mercuric chloride to rabbits and induction of experimental acute renal failure, the administration of walnut extract had a significant impact in the treatment of acute renal failure and could be effective in nephron cell regeneration, *in vivo* or *in vitro*.^[79] Laboratory studies have shown that the intraperitoneal injection of walnut extract into rats reduced the amount of alanine aminotransferase, aspartate aminotransferase, total protein, and plasma albumin, while there was no significant changes in the levels of bilirubin, BUN, creatinine, and alkaline phosphatase enzyme activity.^[11] The results of several studies have shown that walnuts are associated with a lot of effects due to having antioxidants.

Some other of walnut activity

walnut leaves are the major source of flavonoids. Flavonoids have antioxidant properties that are involved in the regulation of immune function and increase in the anticancer activities of the body.^[7] The

results of a study on the effects of juglone found in the walnut leaves on colon cancer cells of the rats indicated its anticancer role in inhibiting the formation of benign or malignant intestinal tumors.^[80] Hexanic extract of walnut leaves is a strong inhibitor against prostate cancer cells, which could be considered as a supplementary potential against this disease.^[81] Researchers showed that juglone found in different parts of the walnut plant inhibits the growth of human sickle cells, dose-dependently.^[82] The chemical analysis of the composition of alcoholic extract of walnut leaves showed that its main ingredient called juglone, is associated with the insecticidal activity.^[83,84] The kernel of *J. regia* has been used for the treatment of inflammatory bowel disease in Iranian traditional medicine.^[84,88] The results of laboratory experiments on this plant showed that the extract of this plant disrupted sex hormones and caused irregularities in the testicular and ovarian tissue, as well as reduced the activity of the enzymes 3-glucose dehydrogenase and phosphate dehydrogenase.^[54] In a study, Mokhtari *et al.* reported that the administration of walnut leaf extract has an analgesic effect; so that the administration of this extract in the acute phase of pain, could be resulted in a significant reduction of pain.^[89] The administration of walnut leaf extract, together with morphine, causes analgesia in the acute phase.^[89] Some flavonoids such as quercetin have analgesic effect through adrenergic pathways and reduce the sensitivity of the central system and eventually reduce pain.^[89-92] According to studies, it is possible that walnuts are associated with analgesic effects due to having flavonoid compounds such as quercetin.

Side effects of walnut

with an increase in the dose used, this plant, like some poisonous plants, may cause damages; therefore, the amount consumed, and the time course of therapy should be determined by a physician. Taking this herb as a medicine to prevent and cure numerous diseases needs supplementary clinical trials.

CONCLUSION

The results of several studies have shown that plants belonging to the *Juglandaceae* family contain alkaloids, flavonoids, and terpenoids. Walnut is a medicinal plant belonging to this family that has been used in traditional medicine for the treatment of a lot of diseases. Due to having monoterpenes, coumarin, flavonoids, tannins, saponins, alkaloids, and other components, it has many medicinal properties. This component has been suggested to reduce the risk of hypertension, diabetes mellitus, cancer, and microbial activity. The data reported in the previous studies confirmed that walnuts are a rich source of important nutrients that can be beneficial to human health as well. Because of its multiple compounds and pharmacological properties, it is necessary to conduct further studies on other unknown useful properties of this plant; so that it could be used as a drug to treat human diseases. It is also recommended more research and clinical trials to be conducted to identify molecules, information pathways, and related genes. A key issue that can be used in these studies is to evaluate the therapeutic effects of walnuts on diseases such as diabetes, hypertension, infectious, and liver diseases which should be investigated in clinical trials.

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Conflicts of interest

There are no conflicts of interest.

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