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A review on walnut: Its pharmacological properties and role in human life

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Abstract

Walnuts have high nutritional and pharmacological properties. They are considered to be a type of natural functional food. Its consumption at recommended amounts has a number of health advantages, including a lower risk of coronary heart disease, obesity, cardiovascular disease, prevention of some cancers, and type 2 diabetes, and also it acts as an antioxidant. The number of bioactive elements in walnuts, such as polyphenols, plant sterols, dietary fiber, proteins, sterols, and essential fatty acids, contribute significantly. This review summarizes the bioactive components present in walnut and how they affect the gut microbiota and also their studies and pharmacological properties.

Keywords: Walnut, anti-microbial, anti-cancer, anti-oxidant, phytochemicals

Introduction

Walnuts belong to the family Juglandaceae and are one of the world's most extensively distributed and economically cultivated tree nuts. Walnuts are one of the world's oldest tree foods, having origins in Persia dating back to 7000 BC. Total global production of walnut stands at about 4.5 metric tons, among which China (56%) stands first followed by the United States (13.7%), Iran (7%), Turkey (5%), and Mexico (3%), India is with 33000 tons at the rank of 11(Shigaeva et al., 2020)^[1]. The presence of phytochemical ingredients such as alkaloids, flavonoids, nitrogen-containing compounds, carotenoids, and other polyphenolic components is responsible for its wide variety of therapeutic benefits (Gupta et al., 2019)^[2]. Almost every component of this plant, including the kernel, bark, flowers, leaves, septum, green husk, and oil, has therapeutic benefits. Juglans regia has anti-histaminic, bronchodilator, anti-fertility, anti-oxidant, analgesic, immunomodulatory, anti-diabetic, hepatoprotective, anti-microbial, anti-ulcer, anti-inflammatory, lipolytic, anti-hypertensive, neuroprotective, anticancer, insecticidal, wound healing, and several other therapeutic properties, according to extensive research. Walnut is considered a "superfood" because they are high in alpha-linolenic acid (ALA), omega-3 fatty acid, antioxidants, phytochemicals, polyphenols, and fibers (Hayes et al., 2016)^[3].

Nutritional Composition of walnut.

Walnuts have a prominent position in the functional food industry, because of their nutritional and functional qualities. Unsaturated fatty acids, vitamin E, fiber, magnesium, and potassium are abundant in nuts. Walnuts are strong in omega-6 and omega-3 polyunsaturated fatty acids (PUFA), which are necessary dietary fatty acids, compared to most other nuts, which contain predominantly monounsaturated fatty acids (MUFA). According to the US Department of Agriculture Nutrient Database (2010), 100g of walnut provides 2738 (KJ) energy. Walnut contains 65.2% fat and most of the calories of walnuts are from fat, of which 8-14% fats are omega-3 fat alpha-linolenic acid (ALA), also walnut is a rich source of omega 6 fatty acid (linoleic acid) (Almario *et al.*, 2001) ^[4]. Walnuts are high in vitamins and minerals, they include copper (found in tissues of the body), phosphorous (involved in the production of bones and teeth), Manganese (found in nuts) (Mason JB *et al.*, 2020) ^[5], vitamin B6, vitamin B9, and vitamin E. Walnuts have a higher concentration of gamma-tocopherol, it's a kind of vitamin E and has a high antioxidant activity and helps to prevent fat oxidation in lipid membranes. The following data in Table 1 is from the Indian Food Composition 2017.

Table 1: Nutritional Composition of walnut (in 100g)

Proximate principle and Dietary Fiber	
Water	3.56±0.22
Protein	14.92±0.62
Ash	1.72±0.08
Total Fat	64.27±0.05
carbohydrate	10.14±0.69
Energy	2809±3
Total Dietary fibre	5.39±0.19
Insoluble Dietary fibre	4.74±0.17
Soluble Dietary fibre	0.65±0.03

Pharmacological properties

Walnut is a medicinal plant. Its roots were used to cure diabetes, walnut leaves were used to treat fever, rheumatic pains, and skin illnesses, and also it helps to improve diabetes by lowering blood glucose levels and walnut blossoms were used to treat rheumatic pain and malaria in traditional medicine. Walnut extract is high in total phenolic components, which have anti-inflammatory and anti-cancer activities, as per studies also it has anti-parasitic, and anti-diarrhoeal, as well as a blood purifier (Delaviz *et al.*, 2017)⁽⁶⁾.



Pharmacological activity of Juglans regia.

Anti-tumor effect

Walnut has pharmacological actions in a variety of severe chronic illnesses, according to the majority of research, cancer is one of these disorders, and it is caused by the active components in plants such as quinones, polyphenols, essential fatty acids, and proteins. Juglans regia extract has been discovered to contain ellagitannins, which have anti-cancer and anti-inflammatory activities (Meshkini et al., 2017) [7], Walnut leaves were traditionally used to cure skin irritation, stomach aches, burns, and wounds due to their qualities. The chloroform extract of walnut root was found to have cytotoxic action against many human cancer cells, including skin, breast, lung, prostate, and colon (Zhang et al., 2015)^[8]. There is currently a lot of knowledge regarding phenolic chemicals, including evidence of their lethal effect on cancer cells, inflammation, angiogenesis, and radiation resistance. A diet high in polyphenols has been found to lower the risk of cancer. By upregulating caspase 8, caspase 3, and Bax gene expression while downregulating Bcl-2 gene expression, chloroform, methanol, and n-hexane extracts of walnut green husk and root bark caused apoptosis in breast cancer cells and prostate cancer cells. The findings showed that bioactive chemicals found in walnut green husks might be used to develop anti-cancer medicines (Croitoru et al., 2019)^[9].

Antimicrobial and Antifungal activity

Microbicidal activity is one of the activities displayed by *Juglans regia*. Several studies have demonstrated that components of walnut products, including barks, husks, and fruits, have antibacterial properties. *Juglans regia* has been demonstrated to have anti-fungal action in addition to antimicrobial activity. Methanolic extracts of *Juglans regia* were

found to be potent against all Candida strains in study papers, suggesting that they may be useful in the treatment of oral candidiasis (Delaviz et al., 2017)^[9]. The antimicrobial activity of the walnut green husk aqueous extract was investigated using an agar streak dilution method based on radial diffusion against Gram-negative (Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia), Grampositive (Bacillus subtilis, Bacillus cereus, Staphylococcus aureus), and fungi (Candida albicans, Cryptococcus neoformans). The results indicated that all of the extracts tested inhibited Gram-positive bacteria, with Staphylococcus aureus being the most susceptible, with a minimum inhibitory concentration (MIC) of 0.1 mg/ml. Only two of the examined extracts reduced the development of Pseudomonas aeruginosa and none of the extracts decreased the growth of fungus when it came to antibacterial efficacy against Gram-negative bacteria (Amaral et al., 2005)^[10].

Using the microdilution technique, an ethanol extract of walnut leaves showed antibacterial action against dental salivarius, plaque microorganisms (Streptococcus Streptococcus mutans, Actinomyces viscosus, and Streptococcus sanguinis). The most susceptible germs were Streptococcus sanguinis and Streptococcus salivarius, according to the findings (Chaleshtori et al., 2011)^[11]. The antibacterial efficacy of walnut stem bark hydro-alcoholic extract against bacterial isolates from mastitis milk was investigated in vitro. Escherichia coli, Staphylococcus aureus, Enterobacter aerogenes, and Streptococcus strains are the most common bacteria that cause mastitis. Some bacteria were suppressed by the hydro-alcoholic extract, while Klebsiella pneumoniae and Escherichia coli were not (Moori Bakhtiari et al., 2015)^[12].

Anti-oxidant activity

Walnut is a healthy nut containing alpha-linolenic acid in its lipid fraction and polyphenolics with significant antioxidant capabilities in its skin. Walnut skins are strong free radical scavengers and may be useful in lowering oxidative stress, among other health benefits that might be utilized for product development (Samaranayaka et al., 2008) [13]. The walnut kernel is abundant in proteins and lipids and is high in nutrients (minerals and vitamins). It includes vitamin E, a powerful fat-soluble antioxidant, as well as a variety of phytochemicals, including phenolic compounds (phenolic acids and flavonoids), which are recognized for their antioxidant properties (Pantsi et al., 2014)^[14]. Walnut leaf methanolic extract has antioxidant and anticancer properties, and it has no toxicity in healthy liver primary cells. Natural compounds such as antioxidants derived from walnut byproducts are becoming increasingly relevant owing to their health advantages. The phenolic chemicals found in walnut fruits are abundant. Flavonoids, Phenolic acids, lignans, and naphthoquinones, are the most significant groups. The method by which phenolic substances kill cancer cells is by interfering with DNA binding protein activity, preventing ATP synthesis in mitochondria, ROS(Reactive oxygen species) formation inside the cell, and apoptosis (Rai et al., 2018) ^[15]. A comprehensive assessment of phenolic compounds in green walnut husk was examined spectrophotometrically using the Folin Ciocalteu's technique and also an individual characterization of phenols was studied using the HPLC method, the primary chemical found was chlorogenic, Gallic, sinapic, juglone. ellagic. and protocatechuic acid were also discovered, Methanol and ethanol were used as solvents for these extractions (Jakopic et al., 2009)^[16].

Antidiabetic activity

With a rising number of people developing diabetes, it's becoming more important than ever to find new strategies to prevent and cure the disease while also decreasing the negative side effects associated with existing diabetic medications. Ayurvedic research has found that over 1200 medicinal herbs have potential outcomes in the treatment of diabetes and its complications. It was first discovered that walnut leaves contain a chemical that kills parasites, making them potentially useful in the treatment of TB and diabetes. Several additional studies have found that infusing walnut leaves with olive leaves or infusing walnut leaves alone can reduce blood glucose levels in diabetic individuals. The mechanism behind the reduction in glucose levels caused by walnut extract administration may be due to increased insulin release from the remaining β -cells of the pancreas, increasing insulin sensitivity, emulate β -cells, by interfering with the absorption of carbohydrates obtained from the diet, particularly in the small intestine, and thus increasing glucose uptake via. Insulin-dependent glucose transporter or peripheral glucose transporter (Mohammadi et al., 2012)^[17]. The anti-diabetic impact of Juglans regia leaves in rats with diabetes streptozotocin-induced was investigated. Glycosylated hemoglobin, Blood glucose, triglyceride, LDL, and total cholesterol levels all decreased significantly after treatment with Juglans regia extracts, while HDL and insulin levels increased significantly (Mohammadi et al., 2011). The effectiveness and safety of walnut hydrosol (WH) in individuals with type 1 diabetes were investigated in research. The study included eight participants with type 1 diabetes

mellitus (DM). They were instructed to drink 250 ml walnut hydrosol twice a day after meals for four weeks. WH may help diabetics regulate their blood sugar levels, but it can also cause minor and serious negative effects (Moravej *et al.*, 2016)^[18].

Cardiovascular activity

Walnut extract had a direct influence on cholesterol, triglyceride, and LDL-C cholesterol levels in hyperlipidaemic rats. Walnut leaf extract has the ability to lower triglycerides and blood cholesterol while raising HDL values (good cholesterol). The lipid-lowering impact of Persian walnut oil (encapsulated in 500 mg capsules, 3 g/day, for 45 days) in the community of southern Iran was evaluated in a randomized, double-blind case-control study. Lipid profiles were evaluated before the trial began, on days 15, 30, and 45 following the start, and 15 days after the study ended Plasma. TG concentrations dropped by19% to 33% of baseline. Other tested parameters showed no statistically significant changes. (Zibaeenezhad et al., 2003)^[19]. Nut eating has been linked to a lower risk of both fatal and non-fatal coronary heart disease and myocardial infarction. According to epidemiological research, those who ate nuts five or more times per week had a 50% lower risk of coronary heart disease than those who never ate nuts (Al-Snafi et al., 2018)^[20].

Effect on oral health

The impact of acetone and aqueous extracts of Juglans regia on salivary samples of individuals with dental caries was investigated. The disc diffusion technique was used to conduct the antimicrobial test. Acetone extract has been discovered to be an efficient anti-cariogenic medication. The antibacterial properties of hot and cold bark extracts from two cultivars of Juglans regia were investigated in vitro against four dental caries-causing pathogens (Streptococcus sobrinus, Streptococcus mutans, Actinomyces viscosus). Although both types of Juglans regia have antibacterial activity, chloroform extracts were more effective. As a result, both kinds of Juglans regia extracts had a strong anti-plaque effect (Nancy et al., 2011) ^[21]. Using microdilution and agar-diffusion techniques, the antibacterial activities of ethanolic walnut leaf extract were compared to those of chlorhexidine mouth rinse against Streptococcus mutans and Streptococcus sanguinis. The MIC of ethanolic extract of walnut leaf against Streptococcus sanguinis and Streptococcus mutans was 15.6 and 125 mg/ml, respectively. There was a significant difference in the inhibitory zone between ethanolic extract and chlorhexidine against Streptococcus mutans (P=0.000), but not against Streptococcus sanguinis (P=0.058) (Sharafati et al., 2011)^[22].

Immunological effect

In an experimental model of leukopenia generated by a single dose of cyclophosphamide in white mice, the immuno protective effects of the aqueous extract of walnut septa were investigated. The results showed that walnut septa extract restored myelopoiesis in white mice that had been inhibited by cyclophosphamide injection. The rapidly rising number of immature (band neutrophil) and mature neutrophils in the peripheral blood enabled the blood formula normalization procedure by the indicated extract. In the bone marrow of mice with leukopenia, walnut septa extract enhanced the division, differentiation, and maturation of blast forms of myeloid and lymphoid line cells (Dzidziguri *et al.*, 2016)^[23].

Anti-inflammatory and analgesic effects

In rats, the nociceptive effect of an alcohol extract of *Juglans regia* leaves (0.5, 1, and 1.5 mg/kg) was investigated alone and in conjunction with morphine. In the acute phase of the formalin test, an alcohol extract of walnut leaves at a concentration of 1.5 mg/kg reduced nociception significantly, and this effect was dose-dependent. Furthermore, rats given a combination of morphine and alcohol extract demonstrated increased nociception, particularly in the acute phase of the formalin test, as compared to rats given either drug separately. Against a carrageenan-induced hind paw edema model in mice, ethanolic extracts of *Juglans regia* leaves displayed a strong anti-inflammatory effect (as powerful as indomethacin) without causing any gastrointestinal damage (Mokhtari *et al.*, 2008)^[24].

The protective effects

Wistar rats were used to test the preventive effects of Juglans regia kernel extract against cigarette smoke extract (CSE)induced lung toxicities. Wistar rats were administered a prophylactic therapy of methanolic extract of Juglans regia kernel at dosages of 50 mg/kg bw and 100 mg/kg bw by gavage for one week prior to CSE exposure. In lung tissue, Juglans regia extract considerably reduced LDH, total cell count, total protein, and boosted GSH levels, as well as significantly restoring GR, catalase, and reducing XO activity (Qamar et al., 2011)^[25]. The hepatoprotective effect of a polyphenol-rich fraction (WP, 45 percent polyphenol) produced from walnut kernel pellicles was tested in mice. WP (200 mg/kg) inhibited serum glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) increase in carbon tetrachloride-induced liver damage, but not in D-galactosamine (GalN)-induced liver injury, after a single oral treatment. Only ellagitannins having a galloylated glucopyranose core, such as tellimagrandins I, II, and rugosin C, significantly reduced CCl 4-induced hepatocyte damage among the separated components (Shimoda et al., 2008)^[26].

Anti-hypertensive effect

Another study found that eating walnut lowers diastolic, systolic, and mean arterial pressure when compared to the control group. Flavonoids have been shown to produce the relaxation of constricted muscle (e.g. aortic smooth muscle) driven by non-adrenaline activity and potassium chloride. The majority of these investigations in in-vivo and in-vitro models showed that walnut leaf extracts had a hypotensive impact, suggesting that they may be useful in hypertension and associated consequences. The presence of flavonoids and phenolic chemicals accounts for the majority of its hypotensive action. Flavonoids such as quercetin pantocid, quercetin arabinoside, quercetin rhamnoside, and quercetin galactoside are the most common flavonoids (Joukar *et al.*, 2017)^[27].

Conclusion

The current review paper presents a summary of recent research on walnut, their active ingredients, and their pharmacological effects. This article highlights the plant's traditional usage in a variety of diseases, as well as scientific support for its claimed pharmacological action *in vivo* and *in vitro* research. Recent findings from clinical studies suggest that walnut has the potential to be employed in a variety of medical diseases due to the presence of additional active elements such as tannins, monoterpenes, polyphenols, saponins, alkaloids, flavonoids, and other components. Furthermore, it is claimed that using this plant might help reduce the risk of hypolipidemia, hypertension, diabetes, cancer, and microbial activity.

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