

Review

Significance and use of walnut, *Juglans regia* Linn: A review

Nael Abu Taha and Mohammed A. Al-wadaan

Chair of Advanced Proteomics and Cytomics Research, Faculty of Science, King Saud University, Riyadh
11415, Saudi Arabia.

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Juglans regia Linn is a medicinal plant that has been widely used in traditional medicine for a wide array of ailments that include helminthiasis, diarrhea, sinusitis, stomachache, arthritis, asthma, eczema, scrofula, skin disorders, and various endocrine diseases such as diabetes mellitus, anorexia, thyroid dysfunctions, cancer and infectious diseases. The present review, attempts to provide comprehensive information on the ethnobotanical use, pharmacology, nutritional value, preclinical and clinical studies, toxicity, other uses and current research prospects of the *Juglans regia* L. Currently, there is a renewed interest in walnut, and several investigations aimed at scientific validation of its traditional uses and a humble scientific investigation aimed at isolation and identification of active constituents of crude extracts.

Key words: *Juglans regia*, nutritional value, bioactivity, clinical trial, traditional use, toxicity.

INTRODUCTION

Origin and distribution

Walnut (*Juglans regia* L.) is the most widespread tree nut in the world. The tree is commonly called as the Persian walnut, white walnut, English walnut or common walnut. It belongs to juglandaceae and has the scientific name *Juglans regia*. The walnut tree species is native to the old world. It is native in a region stretching from the Balkans eastward to the western Himalayan chain (Fernandez-Lopez et al., 2000) and was cultivated in Europe as early as 1000 BC. At present, walnut is cultivated commercially

throughout southern Europe, northern Africa, eastern Asia, the USA and western South America. World production of whole walnut was around 1.5×10^6 t in 2008 (FAO, 2008). China is the leading world producer, followed by the USA, Iran, Turkey, Ukraine, Romania, France and India, but production in other countries such as Chile and Argentina has increased rapidly in recent years (Martinez et al., 2010).

Walnut composition and nutritional value

Walnut has been used globally in human nutrition since ancient times. The high protein and oil contents of the kernels of *Juglans regia* L. (Juglandacea) make this fruit indispensable for human nutrition. Therefore, the walnut is classified as a strategic species for human nutrition and is included in the FAO list of priority plants (Gandev, 2007). The seed part of the fruit (kernel) is consumed fresh, toasted, or mixed with other confectionaries. In the Middle East walnuts are added alone or along with almonds, date, and raisin as a special pastry preparation called Ma'moul. Walnuts are nutrient-rich food due to high contents of fats, proteins, vitamins and minerals. They are also good source of flavonoids, sterols, pectic

*Corresponding author. E-mail: nabutaha@ksu.edu.sa.

Abbreviations: **FAs**, Fatty acids; **PUFAs**, polyunsaturated fatty acids; **AA**, amino acid; **MICs**, minimum inhibitory concentrations; **IC₅₀**, half maximal inhibitory concentration; **TMV**, tobacco mosaic virus; **DPPH**, 2,2-diphenyl-1-picrylhydrazyl; **LDL**, low-density lipoprotein; **CCl₄**, carbon tetrachloride; **LDH**, lactate dehydrogenase; **GSH**, glutathione; **GR**, glutathione reductase; **GOT**, glutamyl oxaloacetic transaminase; **GPT**, glutamyl pyruvic transaminase; **TG**, triglycerides; **EDV**, endothelium-dependent vasodilation; **CP**, cyclophosphamide.

Table 1. Nutritional value of *Juglans regia* L.

Principle	Value per 100 g
Vitamins (USDA, 2010)	
Folates	98 mcg
Niacin	1.125 mg
Pantothenic acid	0.570 mg
Pyridoxine	0.537mg
Riboflavin	0.150 mg
Thiamin	0.541 mg
Vitamin A	20 IU
Vitamin C	1.3 mg
Vitamin E-y	20.83 mg
Vitamin K	207 mcg
Minerals	
Potassium	441 mg
Phosphorus	346 mg
Calcium	98 mg
Magnesium	158 mg
sodium	2 mg
Iron	2.9 mg
Copper	1.5 mg
Manganese	3.8 mg
zinc	3.09 mg
Aluminum	0.58 mg
Fatty acids (Muradoglu et al., 2010)	
Unsaturated fatty acids	
Palmitoleic acid C16:1	0.77
Oleic acid C18:1	25.26
Gadoleic acid C20:1	0.05
Total MUFA	22.37
Linoleic acid C18:2	57.10
Linoleic acid C18:3	10.34
Total PUFA	4.29
Saturated fatty acid	
Myristic acid C14:0	0.24
Palmitic acid C16:0	4.28
Stearic acid C18:0	1.85
Arachidic acid C20:0	0.19
Total SFA	7.21
PUFA/SFA	9.91

substances, phenolic acids and related polyphenols. The nutritional contents differs from a cultivar to another which can be influenced by genotype, cultivator, different ecology and different soil (Caglarirmak, 2003; Crews et al., 2005; Martinez et al., 2010; Muradoglu et al., 2010). The major components of walnut oil are triacylglycerols (980 g/kg oil), in which monounsaturated fatty acids (FAs) (mainly oleic acid) and polyunsaturated FAs (PUFAs; linoleic and α -linolenic acids) are present in high amounts in all genotypes (Table 1). Oil contents reported by

Pereira et al. (2008) (78.83 to 82.4%) were higher than those reported by other researchers (Savage, 2001; Muradoglu et al., 2010). In general, the FA composition of walnut oil resembles that of soybean oil, but walnut oil contains a greater concentration of linolenic acid. In fact, among vegetable oils, walnut oil has one of the highest amounts of PUFAs (up to 78% of the total FA content).

Walnuts have high amount of omega-6 and omega-3 PUFA, which are essential dietary fatty acids. Clinical studies suggest that omega-3 PUFA have significant role in prevention of coronary heart disease (Davis et al., 2007). Oil rich in oleic acid displays greater oxidative stability therefore; it could be widely used as frying oil. According to an investigation conducted by several researchers, It was found that the average value for protein was 18.1% (Amaral et al., 2003); Muradoglu, 2005; Mitrovic et al., 1997; Muradoglu, 2010; Savage, 2001). They are mainly composed of glutelins (about 70% of the total seed proteins) together with lesser amounts of globulins (18%), albumins (7%) and prolamins (5%) (Martinez et al., 2010). The amino acid (AA) composition of walnut flour is dominated by the acidic AA residues of aspartate and glutamate together with relatively high levels of arginine. Walnut proteins contain all essential AAs required for the needs of a human adult. The lysine/arginine ratio in walnut proteins is lower than those observed in other common vegetable proteins, and this fact has been identified as a positive feature in the reduction of atherosclerosis development (Sza-Tao et al., 2000; Venkatachakm and Sathe; 2006; Martinez et al., 2010). Walnut cultivars analyzed have recorded rich mineral composition, especially potassium, magnesium, and calcium. The minimum and maximum macro and micro nutrient contents of walnut are presented in Table 1 (Ravai, 1992; Payne, 1985; Souci et al., 1994; Cosmulescu et al., 2009). Walnuts contain high levels of potassium, phosphorus and magnesium and lower sodium. These elements play an important role for many enzymes activity especially as cofactor.

Ethnobotanical use

Juglans regia leaves have been used mostly in worldwide traditional medicines as antimicrobial, antihelmintic, astringent, keratolytic, antidiarrhoeal, hypoglycaemic, depurative, tonic, carminative, and for the treatment of sinusitis, cold and stomach ache (Girzu et al., 1998; Mouhajir et al., 2001; Vaidyaratnam, 2005). In Turkish folk medicine, fresh leaves applied on the naked body or forehead to reduce fever or on swelled joint to alleviate the rheumatic pain (Fujita et al., 1995; Yesilada, 2002). The kernel of *J. regia* has been used for the treatment of inflammatory bowel disease in Iranian traditional medicine (Kim et al., 2006). In Palestine, it is used for treatment of diabetes and asthma (Jaradat, 2005; Kaileh et al., 2007) and to treat prostate and vascular disturbance (Spaccarotella et al., 2008). The plant is

used as a topical remedy for dermal inflammation and excessive perspiration of the hands and feet. It is also a common home remedy for the treatment of chronic eczema and scrofula. The leaves of this plant is used topically to treat scalp itching and dandruff, sunburn and superficial burns as well as an adjunctive emollient in skin disorders (Gruenwald et al., 2001; Robbers et al., 1999; Ali-Shtayeh and Abu Ghdeib, 1999; Blumenthal, 2000; Baytop, 1999). It also has high anti-atherogenic potential and a remarkable osteoblastic activity that adds to the beneficial effect of a walnut enriched diet on cardioprotection and bone loss (Papoutsis et al., 2008). The bark, branches and exocarp of the immature green fruit of this medicinal plant have been used to treat gastric, liver and lung cancer a long time in China (Liu et al., 2004; Baytop, 1999). It is used by traditional healer in northeastern region of Mexico to protect against liver damage (Torres-gonzalez et al., 2011). The bark is used as miswaks for teeth cleaning (Ibrar et al., 2007). In Nepal the bark paste is useful in arthritis, skin diseases, toothache, and hair growth. Seed coat is used for healing wounds (Kunwar and Adhikari, 2005). The shell of *Juglans regia* is used in Calabria folk medicine to heal malaria (Tagarelli et al., 2010).

Antibacterial activity

Hot and cold solvent and aqueous extract of leaves, barks, fruits and green husks of *J. regia* from different countries revealed broad spectrum antibacterial activity against gram-positive and gram-negative bacteria viz. *Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, *Micrococcus luteus*, *Salmonella typhimurium*, *Enterococcus faecalis*, *Bacillus thuringiensis*, *Protomonas extroquens*, and *Proteus* sp. using agar streak method, disc diffusion method and microplate alamar blue assay (Deshpande et al., 2011; Poyrazolu et al., 2010; Pereira et al., 2008; Oliveira et al., 2008; Pereira et al., 2007; Qa'dan et al., 2005a b; Citoglu and Altanlar, 2003; Upadhyay et al., 2010b). The antimicrobial activity against gram-negative bacteria were selective since not all the fruit extract of *J. regia* cultivator inhibited the growth of *Pseudomonas aeruginosa* and *E. coli*. cv. Lara inhibited the growth of *K. pneumoniae* (MIC of 100 mg/mL), cv. Mayette inhibited the development of *P. aeruginosa* and *E. coli* with minimum inhibitory concentrations (MICs) of 50 and 10 mg/mL, respectively, and cv. Mellanaise inhibited the growth of *E. coli* and *K. pneumoniae* at concentration of 100 mg/mL (Ali-Shtayah et al., 1999). Mexican aqueous bark and leaves extract exhibited no antimycobacterial activity. Only the hexane and methanol extract showed antimycobacterial activity with MIC of 100 and 125 mg/ml, respectively using Soxhlet extractor (Cruz-Vega et al., 2008). Over 45% of Iranian clinical isolates of

Helicobacter pylori strain were inhibited by *J. regia* aqueous and equal mixture of methanol, diethyl ether and petroleum benzene extract (Nariman et al., 2004). In a recent study, juglone was shown to potently inhibit the three key enzymes from *Helicobacter pylori*, cystathionine γ -synthase (HpCGS), malonyl-CoA:acyl carrier protein transacylase (HpFabD), and β -hydroxyacyl-ACP dehydratase (HpFabZ) with the half maximal inhibitory concentration (IC₅₀) values of 7.0±0.7, 20±1, and 30±4 μ mol/L, respectively. Therefore, HpCGS, HpFabD, and HpFabZ are considered to be the potential targets of juglone (Kong et al., 2008). The antibacterial activity of Jordanian *J. regia* leaves extract to acne developing organism revealed that 12.5% *S. epidermidis* isolates were resistant to the leaf extract where as all *Propionibacterium acnes* isolates were sensitive even to 10% of the extract (Qa'dan et al., 2005b).

Antifungal activity

J. regia fruits, leaves and bark aqueous and solvents extract exhibited antifungal activity against wide range of fungi using disc diffusion method, agar dilution method, agar streak dilution and Raddish method. Pereira et al. (2008) reported that all the walnut varieties exhibited antifungal activity against *Candida albicans* and *Cryptococcus neoformans* when soxhleted with light petroleum ether (b.p. 40-60°C). The higher inhibition was observed with cv. Lara extract (MIC of 1 mg/mL). However, *C. albicans* and *C. neoformans* were only resistant to cv. Mellanaise extract. Cold extraction of fruit, leaves and bark inhibited the growth of *Microsporium canis*, *Trichophyton mentagrophytes*, and *Trichophyton violaceum* (Ali-Shtayah et al., 1999). On the other hand, the aqueous extract of green husks showed no antifungal activity against *C. albicans* and *C. neoformans* (Oliveira et al., 2008). Methanol, acetone, chloroform and ethyl acetate bark extract revealed antifungal activity against *A. niger*, *Alternaria alternata*, *Triphoderma viresn*, *fusarium solani*, *Pichia guilliermondii*, *Pichia jadinii* and all *Candida* species tested (Upadhyay et al., 2010c; Ahmad et al., 1973).

Antiviral activity

Mei-zhi et al. (2007) reported that 95% ethanol and ethyl acetate leaves extract of *J. regia*, inhibited tobacco mosaic virus (TMV). The methanol extract of *J. regia* inhibited *Sindbis* virus at a minimum concentration of 1.5 μ g/ml (Mouhajir et al., 2001).

Antioxidant activity

The antioxidant potential of ethyl acetate, butanol, meta-

nol, ether and aqueous methanol extract of walnut kernels, husks and leaves were measured by different methods such as reducing power, scavenging activity on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals and lipid oxidation inhibition by β -carotene linoleate system. All the extracts showed strong antioxidant activity (Qamar and Sultana, 2011; Carvalho et al., 2010; Abbasi et al., 2010; Rahimipannah et al., 2010; Zhang et al., 2009b; Almeida et al., 2008; Oliveira et al., 2008; Pereira et al., 2008; Pereira et al., 2007; Fukuda et al., 2003). Bullo et al. (2010) reported a decrease in the antioxidant burden observed in enzymatic and non-enzymatic antioxidant systems after the consumption of a whole-walnut or a walnut-skin diet in C57BL/6 mice. The same author also reported that consumption of walnuts and walnut skins have no deleterious effect on low-density lipoprotein (LDL) oxidizing capability, despite their higher contents of omega-6 PUFAs. Several phenolic compounds isolated from *J. regia* such as pyrogallol, p-hydroxybenzoic acid, vanillic acid, ethyl gallate, protocatechuic acid, gallic acid, 3,4,8,9,10-pentahydroxydibenzo pyran-6-one, tannins, glansrins, adenosine, adenine, etc, could provide a chemical basis for some of the health benefits claimed for *J. regia* in foods and folk medicine (Zhang et al., 2009a; Fukuda et al., 2003).

Antidiabetic activity

Fukuda et al. (2004) demonstrated a strong inhibitory activity of walnut polyphenols and the polyphenolic components like Casuarictin, tellimagradin II and Tellimagradin I on different enzymes like glycosidase, sucrose, maltase and amylase. In addition to the above findings, researchers also noticed that walnut polyphenol-rich fraction has triglyceride lowering effect and urine peroxide lowering effect in genetically inherited Type II diabetes mellitus (*db/db*) mice at the dose of 200mg/kg/day. The consumption of walnut leaf pellets in alloxan induced diabetic rats at the dose of 185 mg/kg reduced fasting blood sugar significantly and the histomorphometric study of pancreas showed a sign of regeneration of β -cells in the treated group (Jelodar et al., 2007). *J. regia* leaves methanolic extract at dose of 250 mg/kg decreases the postprandial plasma blood glucose levels in both short and long term models. The plant extract significantly inhibited α -glucosidase activity *in vitro* for both maltase and sucrase enzymes and showed no changes in the insulin and glut-4 genes expression. The author attributed the inhibitory action of the plant extract to gallic acid and caffeoylquinic acid in the leaves (Teimori et al., 2010).

Anthelmintic activity

Kale et al. (2011) reported that stem park of *J. regia*

acetone extract exhibited significant activity at all dilution tested when compared to the Albendazole standard against *Eicinia feotida*. The benzene, methanol and ethanol soxhlet extracts of *J. regia* stem bark on adult Indian earthworm, *Pheretima posthuma* exhibited significant anthelmintic activity as comparable to that of standard drug Piperazine citrate (Upadhyay et al., 2010a). The 95% ethanol, petroleum ether and ethyl acetate extract of green walnut hull have obvious anti-feeding effect on armyworm and the small vegetable-moth. The research group indicated that anti-feeding rate, death rates as well as growth inhibition rate of armyworm have correspondingly changed in dose dependant manner (Me-zhi et al., 2006).

Anti-inflammatory activity

The ethanolic extracts of *J. regia* leaves exhibited potent anti-inflammatory activity as potent as indomethacin against carrageenan-induced hind paw edema model in mice without inducing any gastric damage (Erdemoglu et al., 2003). Mokhtari et al. (2008) stated that the alcohol extract of walnut leaves in dose of 1.5 mg/kg caused a significant nociception decrease in acute phase of formalin test where as the aqueous (2.87 and 1.64 g/kg) and ethanolic (2.044 and 1.17 g/kg) extracts of leaves showed antinociceptive activity in hotplate test suggesting a promising analgesic and anti-inflammatory agents against diseases such as rheumatoid arthritis. On the basis of Qamar and Sultana (2011) result, a protective role of methanolic *J. regia* extract against CSE-induced acute lung toxicity in Wistar rats was suggested. The extract significantly decreased the levels of Lactate dehydrogenase (LDH), total cell count, total protein and increased the glutathione (GSH) level in bronchoalveolar lavage fluid. It also significantly restored the levels of Glutathione reductase (GR), catalase and reduced the xanthine oxidase (XO) activity in lung tissue.

Antidepressant activity

The macerated hexane extract of *J. regia* fruit produced significant antidepressant activity at both doses of 100 and 150 mg/kg body weight when compared with standard drug fluoxetine on male Wistar rats. The antidepressant activity was evaluated by forced swimming and tail suspension test (Rath and Pradhan, 2009).

Antityrosinase activity

Ozer et al. (2007) suggested that gel formulation containing ellagic acid and plant leaves extract of *J. regia* is effective in treating uneven skin pigmentation. The ethanolic leaves extract could be suggested as new

sources of skin-whitening agents. Aitani and Shimoda (2005) reported that melanin formation was inhibited at concentration 1 to 30 $\mu\text{g/ml}$ in Pre-cultured B16 melanoma cells incubated with medium containing walnut polyphenols and their result indicated that walnut polyphenols is more superior to the popular skin-lightening agent, ascorbic acid and arbutin upon data comparison.

Hepatoprotective activity

Orally fed Walnut polyphenols prepared from the kernelpellicle demonstrated a dose dependent lowering effect in glutamyl oxaloacetic transaminase (GOT) and glutamyl pyruvic transaminase (GPT) in carbon tetrachloride (CCl_4) induced liver damage in mice model after a single oral administration (200 g/kg). Result indicated that walnut polyphenols is more superior to Curcumin, a commonly used hepatoprotective agent. The effect of each active component of *in vitro* evaluation of walnut polyphenols on CCl_4 -induced cytotoxicity in primary cultured rat hepatocytes showed that tellimagrandin I, casuarictin, tellimagrandin II, and rugosin C (Figure 1) are inhibitory on CCl_4 -induced cytotoxicity in primary cultured rat hepatocytes however, tellimagrandin I of walnut polyphenols is believed to be the most important active compound responsible for hepatoprotective effect (Hiroshi et al., 2008). The same author, Hiroshi et al. (2006) reported that 50% EtOH extract from endocarps of walnuts on mice liver injury models induced by carbon tetrachloride at the dose of 100 and 200 mg/kg significantly suppressed GOT and GPT deviations. Polyphenolic constituents, tellimagrandins I and II, rugosin C and casuarictin were found to be principal constituents with hepatoprotective activity against oxidative damage.

Hypotriglyceridemic activity

Oral administration of a polyphenol-rich extract (WP) from walnuts (100 and 200 mg/kg) in high fat diet fed mice significantly reduced liver weight and serum triglycerides (TG) where as hepatic β -oxidation in cytosol, including peroxisome, was enhanced by WP (50-200 mg/kg). A polyphenol-rich extract was found to possess hypotriglyceridemic activity via enhancement of peroxisomal fatty acid β -oxidation in the liver. These results suggest that tellimagrandin I is involved in the hypotriglyceridemic mechanism (Shimoda et al., 2009).

Anticancer activity

Juglone has been reported to inhibit intestinal carcinogenesis induced by azoxymethane in rats and

might be a promising chemopreventive agent in human intestinal neoplasia (Sugie et al., 1998). Juglone was also proven to be a potent cytotoxic agent *in vitro* in human tumor cell lines, including human colon carcinoma (HCT-15) cells, human leukemia (HL-60) cells and doxorubicin-resistant human leukemia (HL-60R) cells (Kamei et al., 1998; Segura-Aguilaretal, 1992). In a recent study, Juglone inhibited the growth and induce apoptosis of sarcoma and 180 SGC-7901 cells *in vivo*. The mechanism is mediated by the activation of the mitochondrial death pathway, which requires the generation of reactive oxygen species (ROS), down-regulation of Bcl-2 protein expression and up-regulation of Bax protein expression (Ji et al., 2011). Walnut methanolic extracts obtained from *J. regia* seed, green husk and leaf showed concentration dependent growth inhibition against human renal cancer cell lines A-498, 769-P and the colon cancer cell line Caco-2. Concerning A-498 renal cancer cells, all extracts exhibited similar growth inhibition activity (IC_{50} values between 0.226 and 0.291 mg/mL), while 769-P renal and Caco-2 colon cancer cells, walnut leaf extract showed a higher antiproliferative efficiency (IC_{50} values of 0.352 and 0.229 mg/mL, respectively) than green husk or seed extracts (Carvalho et al., 2010). The tested dried fine powder of *J. regia* light petroleum seed extract in cancer induced in Swiss albino mice with the help of 7,12-Dimethylbenz(a)anthracene (DMBA) and croton oil showed the petroleum extract was significant in reducing the cancer cells (Kumudhavalli et al., 2010).

Other medicinal uses

Willis et al. (2009) examined the effects of walnut diet on motor and cognitive ability in aged rats for 8 weeks. The three treated groups (2, 6 and 9%) revealed that the 2% walnut diet improved performance on rod walking, while the 6% walnut diet improved performance on the medium plank walk; the higher dose of the 9% walnut diet impaired reference memory, however the researcher attributed this to the number of polyphenolic compounds that could be negatively effecting reference memory at a higher dose. A 2004 study by the NYS Institute for Basic Research in Developmental Disabilities (OMRDD) revealed that methanolic extract of walnut was able to inhibit and defibrillize fibrillar amyloid β - protein (the principal component of amyloid plaques in the brains of patients with Alzheimer's). It is proposed that polyphenolic compounds present in walnuts may be responsible for its anti-amyloidogenic activity (Chauhan et al., 2004). Similarly, it was found that two of its major components in walnuts, gallic and ellagic acid, act as "dual-inhibitors" of the enzyme acetylcholinesterase which, in association with amyloid inhibits protein aggregation, and inhibit the site of acetylcholinesterase responsible for the breakdown of acetylcholine. These results suggest that walnuts may reduce the risk or delay

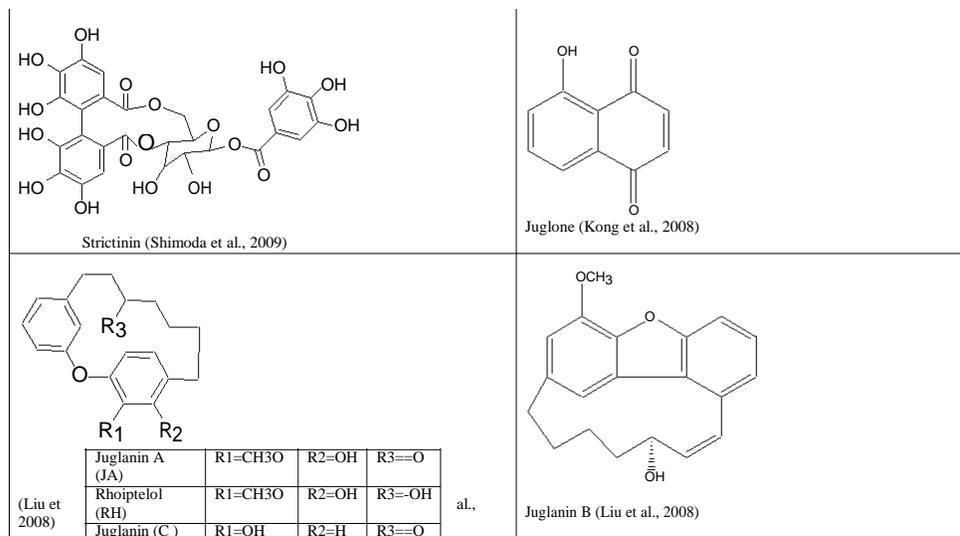


Figure 1. Chemical structures of compounds isolated from *Juglans regia* L.

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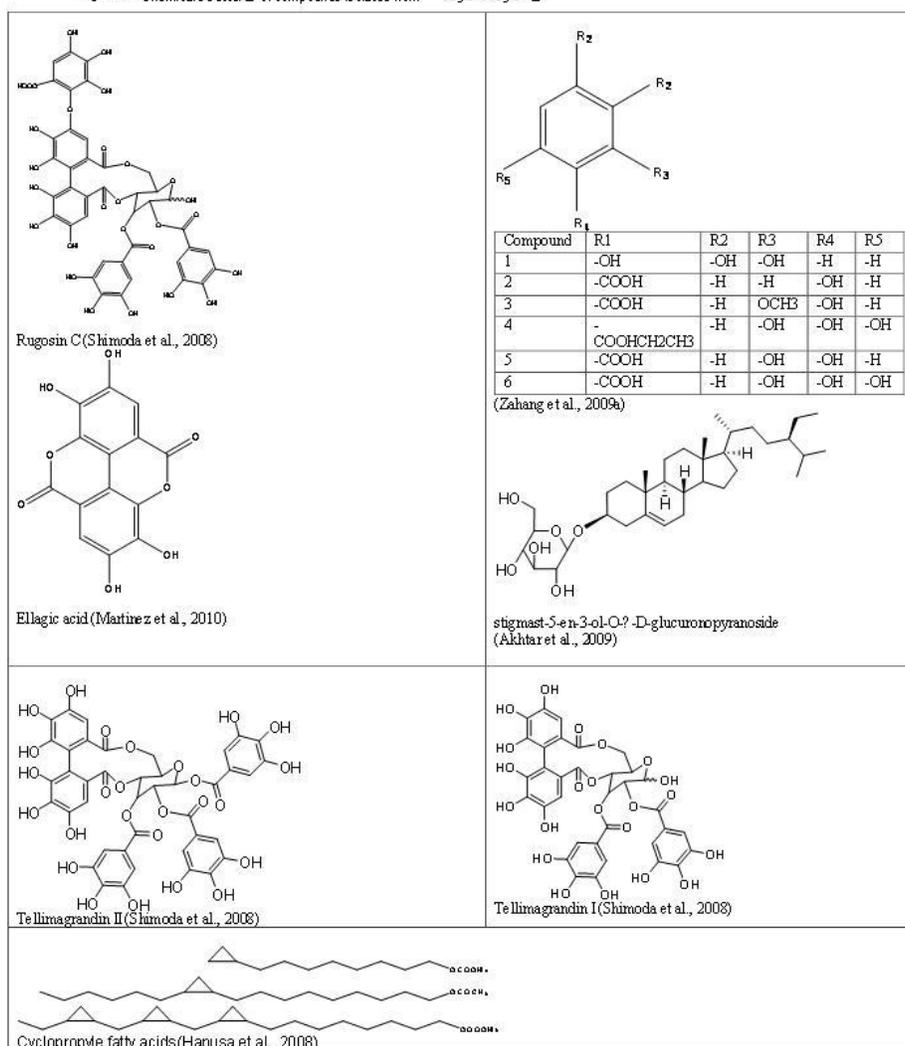


Figure 1 contd.

the onset of Alzheimer's disease by maintaining amyloid-protein in the soluble form and prevent the breakdown of acetylcholine (Society for Neuroscience, 2007).

Clinical study

A daily intake of 43 to 57g of walnuts incorporated into Japanese diet for 4 weeks to 40 healthy Japanese men and women lowered blood cholesterol, particularly in women (Iwamoto et al., 2000). In double-blind case with either plasma triglyceride (TG) concentration more than 350 mg/dl or total cholesterol concentration more than 250 mg/dl were randomized into two groups, group A subject were administered 6 capsules, each filled with 500 mg of the extracted walnut oil, per day for 45 days, group B individual serve as control and received placebo for 45 days. The result of this lowered plasma triglyceride level by 19 to 33% (Zibaenezhad et al., 2003). Ros et al. (2004) reported that substituting walnuts for monounsaturated fat in a Mediterranean diet improves endothelium-dependent vasodilation (EDV) in hypercholesterolemic subjects. A daily intake of 8-13 walnuts for 4 weeks significantly improves the EDV of 21 hypercholesterolemic males and females.

On the other hand, walnut-enriched meals effectively prevented post prandial lipidemia where triacylglycerol was significantly reduced (Bellido et al., 2004). Spaccarotella et al. (2008) assessed the effect of walnuts on markers of prostate cancer between 45 and 75 years of age. Results suggest that walnuts improved serum γ -T and α -T: γ -T, two biomarkers that are important in prostate and vascular health. Total bilirubin, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), leucine aminopeptidase (LAP), gamma-glutamyltranspeptidase (γ -GTP), cholinesterase, amylase, lipase, Lecithin: cholesterol acyltransferase (L-CAT), LDL-cholesterol, total cholesterol, triglyceride, phospholipid, free fatty acid (FFA), high-density lipoprotein (HDL)-cholesterol, Na, K, serum Fe, total iron binding capacity (TIBC), unsaturated iron binding capacity (UIBC), urea nitrogen, uric acid, glucose, hemocytes revealed no abnormal reading for four male volunteers were given oral walnut polyphenols at the dose of 50 mg/day for 4 weeks (Oryza, 2007).

Toxicity

A review of the literature showed that juglone can cause irritant reactions as well as skin hyper pigmentation but, although it has been found to be a strong sensitizer in guinea pigs, contact allergy is considered a very rare event in man (Wood and Calnan, 1976; Hausen, 1981). However, a case report of 65-year-old woman complaints of skin hyper pigmentation and large tense blisters involving the palms and fingers caused by the

cumulative effect of 15 kilos of walnuts shelled in the 3 days was reported by Bonamonte et al. (2001). Haque et al. (2003) investigated the modulatory effects of walnut aqueous extract on the toxicity of an anticancer drug, cyclophosphamide (CP) with special reference to protection against disruption of drug metabolizing and antioxidant enzymes during the chemotherapy. The extract showed a significant increase in the activity and level of glutathione and glutathione peroxidase in both liver and kidney tissues and catalase in liver only. While the extract CP treated group showed a significant decrease in the lipid peroxidation in liver and kidneys when compared with the CP-treated group. Aqueous extract from *J. regia* leaves reduced 3-(4,5-Dimethyl thiazol-2yl)-2,5-diphenyl tetrazolium bromide (MTT) formation by about 60% at concentration of 500 μ l/ml on HepG2 cell. Additionally, the co-culture of HepG2 with THP1 revealed no sign of any negative effect at all concentration tested after exposure to the extract. The investigator also reported no significant changes of LDH and albumin levels on the culture medium after 24 h of exposure to the extract (Saad et al., 2006). Hosseinzadeh et al. (2011) calculated the half-maximal lethal dose (LD₅₀) values of intraperitoneal injection of *J. regia* aqueous and ethanolic leaves extract and found it to be 5.5 and 3.3 g/kg, respectively. Acute dermal toxicity studies showed that petroleum ether extract of *J. regia* gives lethal effect at 2000 mg/kg (Kumudhavalli et al., 2010).

Other uses

The seeds contain unusual fatty acids which are industrially important, as they are used in protective coatings, dispersants, pharmaceuticals, cosmetics, soaps and a variety of synthetic intermediates as stabilizers in plastic formulations (Hosamani et al., 2000; Eganathan et al., 2006). The wood is of very high quality, and is used to make furniture, and gunstocks. The dye is used as a coloring and tonic for dark hair (Brwon, 1995). The unripe fruits are pickled in vinegar (Facciola, 1990).

Conclusions

The present review article documents the publications on walnut and its constituents in the recent and last few years. The paper highlights the traditional use of this plant and some scientific validation of the claimed biological activity *in vivo* as well as *in vitro*. To best of our knowledge and internet survey only one case of contact dermatitis was reported after shelling 15 kilos of walnuts. The toxicological studies of various secondary metabolites which contribute to its medicinal value are still in its infancy and are becoming an important limiting factor for utilizing the metabolites as therapeutic agent.

Besides, isolation and characterization of active

secondary metabolites responsible for various biological activities have not yet been structurally elucidated, mode of action, target organ of toxicity and molecular mechanism also need to be investigated. Further trials in humans are required to determine the efficacy of walnut extract or one or more of its constituents and to establish what, if any, adverse effects are observed.

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