



CHARACTERIZATION OF BIOACTIVE COMPONENTS, ETHNOMEDICINAL USES, NUTRACEUTICAL POTENTIAL, AND PHARMACOLOGICAL ASPECT OF *JUGLANS REGIA* L. IN UNANI MEDICINE: A NARRATIVE REVIEW

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ABSTRACT

Background: Foods high in immunonutrients, such as walnuts, are considered nutraceuticals and may have therapeutic properties. Utilizing these has been linked to a number of health benefits, such as a lower risk of coronary heart disease, cardiovascular disease, type II diabetes treatment, prevention and treatment of specific cancers, and a reduction in symptoms associated with age-related and neurological conditions.

Aim of the study: The current study recapitulates the most recent research on the relationship between chemical components and pharmacological activities as well as the nutraceutical benefits of walnuts.

Materials and Methods: Nutraceutical information about walnuts was gathered from published works, historical and contemporary documented classical scripts, Unani pharmacopeias, and databases including Pub Med, Web of Science, Science Direct, and Google Scholar.

Results: The walnut has been recognized to be a commercial, dietary, and medical plant that can be utilized to cure common medical conditions. According to the Unani medical system, walnuts are a great dietary food that can be utilized as nutraceuticals. It has been found to possess pharmacological actions like Muqawwi-i-A'da' Ra'isa (Tonic for vital organs), Muqawwi-i-A'sab (Nervine tonic), Mulayyin-i-Am'a' (Laxative), Muqawwi Dimagh (Brain tonic) which is validated through the presence of several pharmacological activities like anti-diabetic, anti-bacterial, cardioprotective, hepatoprotective, immune booster and memory enhancer properties. Amongst the many bioactive substances found in different plant parts, juglone has been identified as having a major anti-cancer effect in the treatment of fatal cancer.

Conclusion: It is imperative to provide scientific evidence for the fundamental advantages of walnuts as a nutritional food source, as well as to clarify and validate any possible medicinal use.

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The cornerstone of treatment was thought to be natural medications, particularly those derived from medicinal plants. Research conducted over the past years has demonstrated that both developed and developing nations have a strong inclination toward and readiness to accept alternative therapies.¹ Traditional diets and herbal extracts have long been acknowledged as essential components of a holistic strategy for achieving total wellbeing and health, particularly in the context of ancient Greek medicine. The idea that food might serve as medicine was taken up by the Greek physician Hippocrates, who is famous for saying, "Let food be the medicine and medicine be the food." Throughout human history, a wide range of natural resources including nuts, cinnamon, saffron, vegetables, honey, garlic, ginger, pomegranate, mint, and many more have been used for their curative and strength-restoring properties when consumed.² Nutraceuticals are defined as bioactive molecules found in regular foods or in sources derived from plants. These substances can be administered in the form of functional foods or dietary supplements, offering additional benefits to important nutritional components. Nutraceuticals are a diverse group of bioactive compounds found in food sources, such as probiotics, fatty acids, amino acids, antioxidants, and phytonutrients. Nutraceuticals are well known for their involvement in diseases treatment and prevention, anti-aging qualities, and cancer prevention, with either proven prior or potential effects.³ For example, garlic has been proposed as an adjunctive treatment for high blood pressure and cholesterol.⁴

Numerous studies have clearly demonstrated the advantages of nutraceutical substances for immune system functions. These include improving immunomodulatory activity, strengthening the infection response mechanism, and lessening the effects of autoimmune diseases and hypersensitivity. Additionally, studies have demonstrated the lipid-lowering, anti-cancer, anti-inflammatory, and antioxidant effects of nutraceuticals.⁵ The

immune system is an intricate host defense system made up of various specialized cells and components of proteins that work together to protect the body from sickness. The two subsystems that collectively make up the immune system are the innate and adaptive immune systems. Cellular and humoral responses are involved in both subsystems. As T cells are in charge of identifying and eliminating infections, this will consequently cause a commensurate reaction that is controlled by a number of cell-mediated responses. Apart from B lymphocytes that generate certain antibodies in response to antigens or diseases, it will also offer a neutralizing impact and defense against any damage the body may experience.⁶ The field of nutraceuticals is becoming more and more appreciated, and there is a growing desire to discover new therapeutic choices through the use of cutting-edge science and technology. While numerous studies have documented the beneficial effects of nutraceuticals on the immune system. Numerous herbs with several phytochemicals have been researched; walnut is one such medication utilized in nutraceuticals.⁷

Geographical distribution of walnut

Juglans Regia L., a member of the Juglandaceae family, is a fragrant, ephemeral tree, a massive, monoecious, deciduous tree that grows to a height of 900–3300 meters that grows abundantly in Kashmir's North-Western Himalayas.⁸ It yields approximately 88 percent of the world's walnut supply. It is native from the region from Balkans eastward to the Himalayas and southwest China. 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 Boyer-Ahmad, and Lorestan.⁹ The Indian Western Himalayan zone offers ideal agricultural climates for walnut production of superior grade. The center of walnut production in India is the Union Territory of Jammu and Kashmir, which produces a

significant portion of walnuts of an export-quality product. JKUT has two sections that manufacture walnuts. It is grown in the Jammu division's Ramban, Kisthwar, Doda, Rajouri, and Poonch districts in addition to all of the Kashmir division's districts. Since walnuts are a high-quality fruit that is sold to other nations, the walnut trade is very important to Jammu & Kashmir and is regarded as the main pillar of the state's economy. Locals who live in the region's more remote parts depend heavily on the walnut trade for their livelihood.¹⁰ The leaf, flower, and kernel have been used in Unani medicine for medicinal as well as dietary purpose. The Temperament (Mizaj) described to be of Hot and Dry type.⁸

Description of the plant

Macroscopic characteristics:

The tree has gray bark and alternate, imparipinnate, mobile, elliptical or oblong-lanceolate leaflets that are longitudinally fissured. There are approximately two genera and fifteen species in the family of flowers, which are unisexual. Featuring five to nine leaflets that are unevenly pinnate and arranged in a regular pattern, the leaves are uniformly arranged and range in length from 25 to 40 cm.¹¹ Cotyledons are cream-brown in color, 2-3 cm long, slightly curving, coriaceous, sporadically corrugated, fragmented pieces, and have an oily, sweet flavor.⁸

Microscopic characteristics include small almond grains and fat in both the endosperm and cotyledons, as well as a broad zone of oval to a polygonal, thin-walled, radially extended parenchymatous cells.⁸

Powder: Cream colored; displays a profusion of spherical oil globules and clusters of cotyledon cells.⁸

This review delves deeply into the phytochemical action, ethnomedical use, and pharmacological action of these nutraceuticals within the Unani medical system.

2. Methodology

The data from publications pertaining to immunity enhancer were evaluated using bibliographic searching. The classical texts (Arabic, Persian, and Urdu) cited in Unani literature were thoroughly examined and scrutinized. A thorough analysis of the botanical herbs employed in the Unani medical system, especially in the form of nutraceuticals, as immunomodulators has been conducted. The Indian Medicinal Plants reference book and other indexed publications were used to meticulously translate the names of the medicinal plants into English. The study's sources included books with a modern bent, pertinent articles, periodicals, and indexed journals from Pub Med, Science Direct, and Scopus. The contents were searched using the following keywords: "Anti-inflammatory," "Walnut," "Antioxidant," "Anti-cancer," and "Unani Medicine." The study excluded the thesis, letters to the editor, non-English language articles, and dissertations.

3. Results and Discussion

Chemical composition and phytochemistry

Walnuts are nutrient-rich because they include a lot of fatty acids, proteins, vitamins, and minerals. They are a good source of flavonoids, phenolic acids, and polyphenols in addition to these. The kernels of walnut fruits have been found to contain larger concentrations of fats (68%), with proteins (16%) of the total.¹² Walnuts are a rich source of essential fatty acids and tocopherols. According to Zahoo et al., 17 chemicals have been found in walnut leaves; nine of these include epicatechin, aesculetin, taxifolin-pantocid, syringetin-o-hexoside, myricetin-3-o-glucoside, myricetin-3-o-pantocid, quercetin glucuronide, kaempferol pantocid, and kaempferol rhamnoside.¹³ Additionally, it has been reported that this plant's leaves contain derivatives of naphthalene, specifically 5-hydroxy-1-4-naphthoquinone. One naphthoquinone chemical that is present in the new leaves and green shell of walnut tree fruits is called juglone (5-hydroxy-1, 4-

naphthoquinone). With a molecular weight of 174.16 and a formula of $C_{10}H_5O_2$ (OH), juglone is the most noticeable component in all of the walnut tree's organs. Its precursor is a glycoside, a compound that is present in the aerial parts of the plant, particularly the leaves, and is hydrolyzed to become juglone. The fruits of the walnut tree include lipids, glucose, and organic elements such as calcium oxalate, phosphate, citric acid, and malic acid in their green shell. The two main components present in the leaves and green shell of walnuts are juglone and phenolic compounds.¹⁴ Triacylglycerols, which include polyunsaturated and monounsaturated fatty acids, make up the majority of the oil extracted from walnuts (MUFAs). Oleic and linoleic acids can also be found in walnut oil. There are two types of saturated fatty acids: palmitic acid and stearic acid. Other elements included in kernels include magnesium, calcium, potassium, phosphorus, iron, and sodium. Walnut is a rich source of essential fatty acids and tocopherols, and it also contains a variety of potentially neuroprotective ingredients, including long-chain omega-3 fatty acids and gamma-tocopherol (vitamin E). Additionally, the earlier research had demonstrated its effectiveness in treating dementia and Alzheimer's disease.¹⁵

Pharmacological Actions: Muqawwi-i-A'da' Ra'isa (Tonic for vital organs), Muqawwi-i-A'sab (Nervine tonic), Mulayyin-i-Am'a' (Laxative), Muqawwi Dimagh (Brain tonic), Muhallil (Resolvent), Jali (Detergent) and Mulattif (Demulcent).¹⁶⁻¹⁹

Ethnomedicinal uses

Kernel: About half of the fruit's total weight is composed of its edible part, walnut kernels. Nuts like walnuts are a great source of energy and are high in minerals, fats, and protein. It has the highest concentration of vitamin B-6 and a significant number of B group vitamins. These are consumed raw and make a healthy brain tonic. It helps prolong life and improve memory. It inhibits bone loss and has cardioprotective effects.²⁰

Leaves In addition to treating skin conditions, eye irritations, eye pain, and conjunctivitis, the green leaves of walnuts are used to boost appetite in people who have low appetites. To relieve irritation and treat conjunctivitis, an infusion is prepared from leaves that are used in eye wash. Moreover, cuts, acne, and skin allergies are treated with the same leaf infusion to cure skin conditions.²⁰

Shell Its powder is one of the key components found in cosmetics meant to cure sunburn and suntans on the skin.²⁰

Bark: interior bark Walnut inner bark can be used to make a tincture or a stew. It is possible to use the decoction as a liver stimulant, to treat skin disorders, and to cure constipation and poor digestion.²⁰

Unani medicinal uses: The kernel of the fruit can be taken alone or with raisin with help in the cure of Du'f al-Bah (Anaphrodisia/ loss of libido), Du'f al-Dimagh (Cerebrasthenia), Suda (Headache), Du'f al-Hafiza (Memory loss), and Naqahat-i-Umoomi (General weakness). The kernel is usually taken with figs and raisins acts as laxative and brain tonic specifically. If taken in roasted form helps cure cough due to cold temperament. If chewed empty stomach and applied on dermatophytosis lesion it removes and treats. The shell of walnut is particularly useful in treating bleeding piles if taken in roasted powdered dosage.¹⁶⁻¹⁹

Therapeutic dose: 10-20 g.¹⁶⁻¹⁹

Adverse effects: If taken in huge quantity it produces ulcers in mouth and pharynx, inflammation of oral cavity, flatulence and headache.¹⁶⁻¹⁹

Pharmacological activities

Antioxidant Activity

By decreasing power, oxidizing lipids, and scavenging free radicals, the extracts of ethyl acetate, butanol, methanol, ether, and alcohol derived from various sections of the walnut plant,

such as the leaves, husks, and kernels, demonstrated their antioxidant ability. Walnut phenolics had a remarkable antioxidant impact, with the walnut pellicle showing the greatest level of protection. The ability to bind Fe^{2+} protects tissues and cells from oxidative damage and facilitates the simple transit of hydroxyl radicals across cell membranes. Thus, one important factor considered to determine antioxidant activity is the capacity to bind ferrous ions and quench hydroxyl radicals.²¹

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity assay, the copper ion reduction assay (CUPRAC), metal chelating ability (ChA), and the capacity to scavenge hydroxyl (OH^-) and superoxide (O_2^-) radicals were used to measure the antioxidant activity. These techniques are thought to be significant predictors of the antioxidant capacity of plant samples. In this investigation, the compound that scavenges free radicals, DPPH, had the strongest antioxidant activity and the lowest IC_{50} value. The ascorbic acid (5.00, 0.01 g/mL) positive control was surpassed by the computed half maximal inhibitory concentration (IC_{50}) value of 22.34, 2.70 g/mL. Low IC_{50} values for the hydroxyl radicals test (41.85, 0.09 g/mL), superoxide scavenging test (147.06, 0.27 g/mL), and chelating capacity test (71.69, 0.02 g/mL) all indicated high antioxidant activity. The results showed that flowers of *J. regia* were found to have a high capability to forage free radicals.²²

Antibacterial activity

Several studies have used the agar streak and disc diffusion methods to report the antibacterial activity of walnut extracts. When tested against gram+ and gram- strains of bacterial cultures, the aqueous extract of leaves, bark, fruits, and fruit green husk produced in hot and cold solvent showed antibacterial activity. The walnut's water-based extract and chloroform exhibit microbicidal activity against airborne microorganisms, and the extract from the leaves of the walnut tree is highly effective in treating acne by inhibiting the *Propioni* bacterium, which

causes acne, as well as other bacteria that cause acne.²³ The essential oil for this investigation was extracted from *J. regia* leaves and subjected to GC-MS analysis. All essential oils and individual components were tested for antibacterial activity against a set of Gram-positive and Gram-negative microorganisms using disc diffusion and microdilution techniques. Strong substances in the maximal inhibition group include Germacrene D, β -pinene, β -caryophyllene, and α -pinene. *S. epidermidis*, *B. subtilis*, and *S. aureus* were the most inhibited Gram-positive bacteria, with MIC values of 15.62, 15.62, and 15.62 g/mL for *J. regia* essential oil, 48.31, 47.21, and 45.62 g/mL for α -pinene, and 46.55, 46.55, and 41.33 g/mL for β -pinene, respectively.²⁴

Antiviral Activity

After researching walnut pellicle extracts, Angeli et al.²⁵ isolated a small number of antiviral chemicals that had the ability to suppress the replication of HSV-1 and HSV-2. For HSV-1 and HSV-2, the ID_{50} (con. which blocked 50% virus production) was determined to be 10 and 8 $\mu\text{g/mL}$, respectively. Nevertheless, the walnut pellicle extract showed no efficacy against Adenovirus (Adenoid), Coxsackievirus B1 (coxsackie B1), Poliovirus1 (polio1), or Echovirus 9 (ECHO-9). It turned out that the substances taken out of walnut pellicle extract were effective against viral illnesses.

Anticancer Activity

Juglone may be a viable chemotherapy preventive drug for neoplasia in human intestines, since it has been shown to reduce intestinal carcinogenesis in animals. Jurunene is a potent cytotoxin that has been shown by the human cancer cell lines HCT-15 cells, HL-60 cells, and doxorubicin-resistant HL-60R cells.²⁶ The carcinogenic and anti-proliferative properties of *J. regia* leaf extracts (methanol and aqueous extracts) at varying doses on the growth inhibitions of human (A375) and mouse (B16F10) melanoma cell lines. In the present research, the following extract concentrations were prepared: 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.40,

0.45, and 0.5 mg/mL of extract/mL. It was shown that the normal lymphocyte cell lines had very little sensitivity to the extracts. After treating the (B16F10) and (A375) cell lines for 72 hours, the cytotoxic activity was assessed, and it was determined that methanolic extracts, at various concentrations, demonstrated strong activity (cell anti-proliferation) against mouse melanoma, with an IC₅₀ of 0.234 mg/mL, as opposed to 0.304 mg/mL on human melanoma cell lines. Similarly, water-based extracts from the aforementioned doses likewise demonstrated favorable (IC₅₀ = 0.298 and 0.350 mg/mL) compared to mice and human cell melanoma. The carcinogenic and anti-proliferative properties of *J. regia* leaf extracts (methanol and aqueous extracts) at varying doses on the growth inhibitions of human (A375) and mouse (B16F10) melanoma cell lines. In the present research, the following extract concentrations were prepared: 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.40, 0.45, and 0.5 mg/mL of extract/mL. It was shown that the normal lymphocyte cell lines had very little sensitivity to the extracts. After treating the (B16F10) and (A375) cell lines for 72 hours, the cytotoxic activity was assessed, and it was determined that methanolic extracts, at various concentrations, demonstrated strong activity (cell anti-proliferation) against mouse melanoma, with an IC₅₀ of 0.234 mg/mL, as opposed to 0.304 mg/mL on human melanoma cell lines. Similarly, water-based extracts from the aforementioned doses likewise demonstrated favorable (IC₅₀ = 0.298 and 0.350 mg/mL) compared to mice and human cell melanoma.²⁷

Brain tonic Activity

A plant-based omega-3 fatty acid, phenolic acid (ellagic acid), gamma tocopherol (vitamin E), folate, melatonin, and flavonoids are among the many compounds found in walnuts that have the potential to be neuro-regenerative. n-3-linolenic acid (ALA) is also abundant in walnuts. Of the 1113 foods whose antioxidant levels were examined, it is noteworthy that walnuts came in

second. Another study found that male rats protected against cisplatin-induced neurotoxicity received a walnut diet comprising 6% walnut oil. The findings showed that the consumption of walnuts improved cognitive and motor abilities, suggesting that consuming walnuts may help prevent the motor and cognitive impairment brought on by chemotherapy. Additionally, it was discovered that walnuts improved the transgenic mice model against Alzheimer's disease by 6-9% in terms of learning abilities, locomotor activity, memory, nervousness, and motor control.²⁸

Cardiovascular Activity

Omega-3 and omega-6 polyunsaturated fatty acids (PUFA) have been reported to be present in high concentrations in walnuts. The majority of research has shown that omega-6 PUFA has no negative effects on human cardiovascular health, despite some studies linking it to an increased proinflammatory vascular reaction. Additionally, frequent walnut consumption (30–100 g/day) has been found to reduce cardiovascular risk factors in non-hyperlipidemic individuals.²⁹ Regular nut consumption has been associated with a decreased risk of myocardial infarction, both fatal and non-fatal. Epidemiological studies have shown that individuals who ate nuts five or more times a week had a 50% decreased risk of coronary heart disease compared to those who never did.³⁰

Antidiabetic activity

Polyphenols found in walnuts are abundant and have been shown to exhibit potent inhibition of many enzymes, including amylase, sucrose, maltase, and glycosidase. In individuals with Type II genetically inherited diabetes mellitus, the polyphenolic compounds casuarictin, tellimagradin I, and tellimagradin II have been shown to have antidiabetic efficacy and to reduce urine peroxidase and triglycerides.³¹

Immunity booster activity

There is evidence of recent researches that suggest that walnut fruits strengthen the immune system by promoting lymphocyte growth and phagocytosis of different macrophages.³²

Hepatoprotective activity

According to certain research, oral administration of walnut polyphenols from the kernel pellicle causes liver injury in mice modelled by CCl₄. This finding demonstrated that polyphenols have a greater hepatoprotective effect than the widely used, well-known curcumin. It was discovered that the primary phytoconstituents detected in various walnut portions were polyphenolic contents, which are

also in charge of oxidative damage and hepatoprotective function. One polyphenolic, tellimagrandins I, was shown to be one of the essential components of a hepatoprotective agent.³³

Figure 1 depicted the phytochemistry, pharmacological action and pharmacological activities of *Juglans Regia* L.

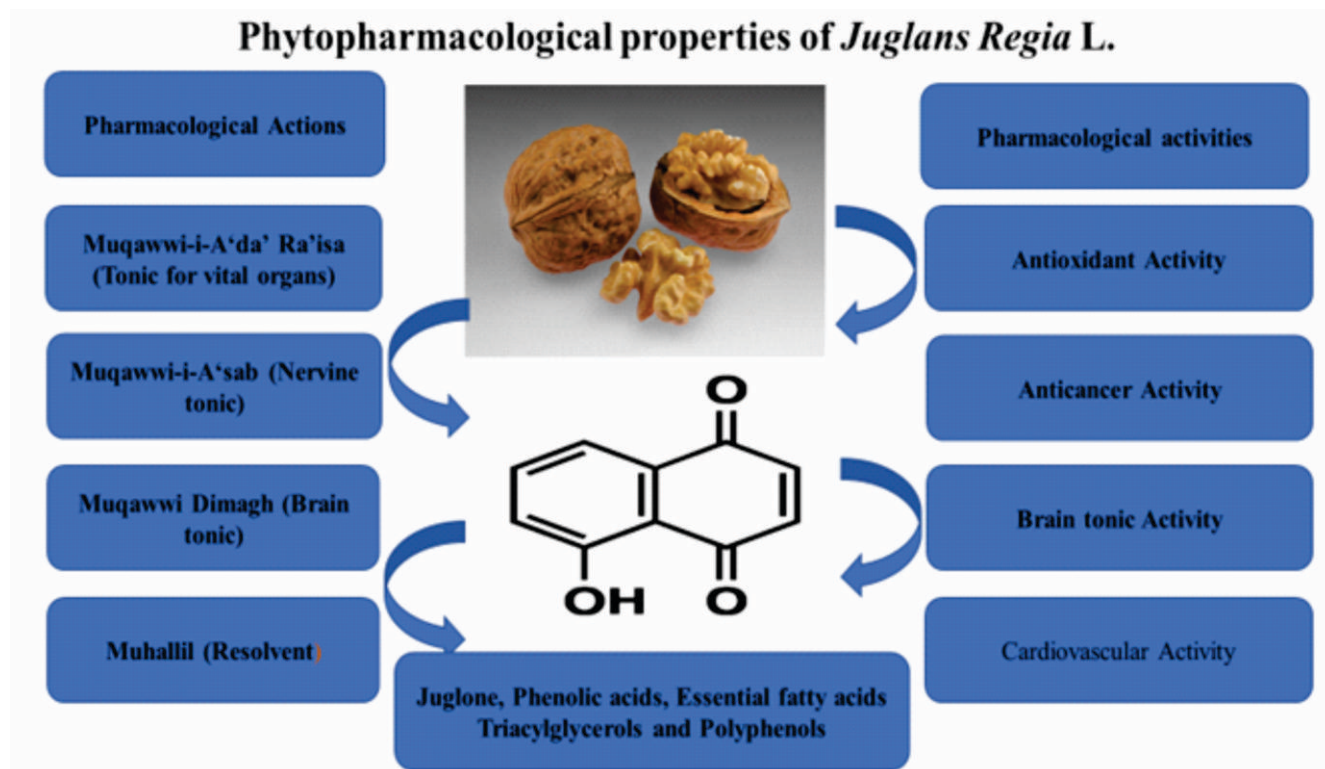


Fig. 1: Phytopharmacological properties of *Juglans Regia* L.

4. Conclusion

Due to their special combination of phytochemicals and bioactive elements, as well as their complex synergy that affects a variety of metabolic pathways, walnut consumption also enhances general health. When it comes to the Unani medical system, walnuts are a great food tonic for the heart, brain, and nerves as well as all other organs since they are the drug that has the pharmacological activity of Muqawwi-i-A'da' Ra'isa, or Torto for Vital Organs. Experimental research in its early stages also indicates that ALA may be neuroprotective, while walnut polyphenols most likely work in concert to

improve brain function. It promotes immunity, fights diabetes, has several pharmacological properties that support the prevention of disease, and include anti-bacterial, anti-diabetic, neuroprotective, cardioprotective, and anti-cancer properties.

Future prospective

To completely utilize every component of the walnut, further extraction techniques will be required in the future. Nevertheless, more investigation is required to assess the long-term effectiveness of walnut eating and the ensuing health benefits. Juglone is regarded as a potent

anti-cancer substance that, with further study, might be useful against the majority of cancers that occur often. The bioactive qualities of walnut polyphenols are nevertheless supported by the data currently available, and further research on this topic is warranted.

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Conflicts of interest

There are no conflicts of interest.

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