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Review

Global Perspectives on the Medicinal Implications of Green Walnut and Its Benefits: A Comprehensive Review

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Abstract: Green walnuts have been valued for their health and medicinal effects for many years. Green walnuts have several bioactive metabolites, including polyphenols, flavonoids, and tannins, that have antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. With previous records of increased inclination towards natural or botanical sources of therapeutics, green walnuts have regained the uniqueness of therapeutic prominence globally. This comprehensive review provides a deep understanding of the use of green walnut (*Juglans regia L.*) around the globe and shows its potential pharmacological benefits. It explores the different therapeutic and medicinal uses of green walnuts, including their historical use in traditional medicine throughout different continents and regions, including Asia, Europe, America, Africa, and the Middle East. This review also provides the substantial studies conducted on green walnuts, which investigate the bioactive substances found in various parts of the walnut tree, including the kernel, shell, leaves, shoots, bark, and roots, indulging in their health advantages. It also diversifies the antibacterial, antioxidant, anti-inflammatory, cardiovascular, and antihypertensive activities of the green walnut, which clearly shows the prospective use of the walnut in nutraceutical and medicinal applications. This review continues by emphasizing the necessity for further research to focus on and attract global researchers to aim for a detailed understanding of the pharmacological implications of green walnuts and enhance their use in traditional and modern medicine.

Keywords: medicinal applications; antioxidants; phytonutrients; bioactivities; disease prevention

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1. Introduction

Medicinal plants have a significant role in providing healthcare and welfare services to humans. Walnuts, scientifically known as *J. regia L.*, have a long history of being utilized for their medicinal properties to treat various ailments. The plant components mentioned possess phytochemicals that have medicinal characteristics, including flavonoids, alkaloids, and polyphenolic compounds. Ayurveda and other medical fields utilize plant parts extensively. Due to their natural origins, high phytochemical content, and absence of negative health effects when compared to contemporary treatments, walnut trees are becoming

more and more popular worldwide [1]. Because of their various medicinal properties, these plants are widely used in homoeopathic, allopathic, and ayurvedic systems. Many parts of the plant, including the root, bark, fruit, flower, seed, leaves, stem, and their derivatives, exhibit biological activity. The plant has vital constituents such as vitamins, minerals, enzymes, and trace elements that are necessary for pharmaceutical formulations [2].

There are many varieties of walnuts that can be found all over the world, such as the butter or white walnut (*J. cinerea*), English or Persian walnut (*J. regia L.*), black walnut (*J. nigra*), Arizona black walnut *(J. major*), and California black walnut (*J. californica*). Andean walnuts are also available. These species exhibit variations in medicinal value due to diverse phytochemical compositions. Nutrient values and content of phytochemicals are influenced by genotypes, cultivar, ecology, and nature of the soil. Different parts of walnuts exhibit diverse compositions and health benefits and are utilized for medicinal purposes. English and Persian walnuts are common names for Juglans regia L., a member of the Juglandaceae family. It may be accessed easily in China, the US, Australia, New Zealand, Turkey, India, Tajikistan, Kyrgyzstan, Western Asia, and Southern Europe [3]. The United States is the second-largest producer of walnuts in the world; the only nation that produces more walnuts than the US is China [4]. The lifetime of this plant is 100–200 years, with some species reaching 1000 years [5]. Wild populations of *J. regia* have been found in the Caucasus, Middle East, East and South Asia, and temperate and semi-arid mountainous regions of Central Asia. The remarkable morphological and physiological diversity of these woods, along with the presence of many wild relatives of cultivated species, underscore their significance as a hotspot for global biodiversity.

Walnut trees (*Juglans regia*) are large and deciduous and can reach heights of more than 20 to 30 metres. Young trees have smooth, grey bark, but as the tree ages, its bark fissures. The pinnate, alternating leaves are 20–45 cm long and have five to seven leaflets each. Despite being monoecious, the male flowers release their pollen before the female flowers open, which leads to inadequate fruit-setting. Male flowers are produced as catkins on twigs from the previous season, while female flowers are produced in late spring as pistillate spikes of two to five blooms at the tips of the stems from the current season [6].

The fruit might be characterized as dry drupes or nuts. The seed is big, has two cotyledons, and has a thin shell called a pellicle covering it. The five-centimetre-long fruit of *Juglans regia* has a firm, four-lobed endocarp and a leathery, wrinkled exocarp. Green walnut fruits are found in clusters on the tree. Seeds are edible in the nature. The round nuts are between 1.5 and 2 inches in diameter [7]. Oval-shaped green walnut fruits have a firm, lime-green skin flecked with small white spots. The walnut is undeveloped and white beneath the skin, with a gelatinous, sticky, syrupy consistency. Walnut trees are capable of surviving temperatures as low as −30 °C during the hibernation season; the variety of green walnut Yuanlin from China can especially adapt to low temperatures [8]. A walnut tree's maturity depends on several variables, including its species, race, climate, and growing location [9]. Green walnuts, or unripe walnuts, refer to the premature, not yet fully ripened fruits of the walnut tree. They are highly valued for their distinctive taste and scent, characterized by a combination of spiced-citrus and bitter elements. Green walnuts have been utilized in traditional medicine for several purposes. A long history of medical use has been documented for the walnut tree and its many parts, including as the leaves, green husk, and bark.

Green walnuts are traditionally used in alternative medicine in the treatment of diabetes, cancer, inflammation, and cardiovascular disorders [8]. They are commonly appreciated for their antioxidant, anti-inflammatory, and antibacterial properties [9]. Various civilizations have utilized unripe walnuts in treatments for a large part of their history. Walnut leaves have also been utilized to improve regulation over diabetes and decrease blood glucose levels. The green husk was considered for combatant action against distinctive ailments, including cancer, bacterial infections, inflammation, and reducing pain. The historical usage of green walnuts in medicines is indicative of the numerous therapeutic effects of walnut trees and their parts [10]. The current review article aims to comprehen-

sively explore medicinal uses of green walnuts globally and highlights their incorporation as essential ingredients in modern medical therapy with varied qualities and therapeutic characteristics. The attainable people's point of view across the globe on the use of green walnuts is also another objective. This review also elaborates on the types of scientific data surrounding the traditional use of green walnuts to explore their phytochemicals, pharmacological activities, and biological significances following extraction and the use of various models. Moreover, the current study can review the recent technology, challenge, and prospect of green walnut utilization.

2. Use of Green Walnut at a Global Perspective

The pharmacological features of green walnuts allow them to be included in the list of natural methods of treatment and be actively used in traditional medicine. In particular, the walnut has been given special attention by the United Nations Food and Agriculture Organization as a priority plant thanks to its unique health benefits and nutritional value, underlining its importance for human nutrition [10]. *J. regia L.* also possesses pharmacological characteristics in all its different parts, including the leaves, bark, green husk, shell, seed, and fruit [11]. *J. regia* L. (green walnut) is also rich in monounsaturated fatty acids, omega-3 fatty acids, arachidonic acids, and vitamin E [12]. Several chemical compounds, such as ascorbic acid, gallic acid, terpenoids, polyphenols, quercetin, and sitosterol, are found in it. Anti-inflammatory, diuretic, anticancer, laxatives, anti-diabetic, antimutagenic, antifungal, antioxidant, antiseptic, antibacterial, antiallergic, astringent, and antiulcer properties are all attributed to the green walnut [13,14].

Since ancient times, people have consumed green walnuts, which originate in many parts of the world. Green walnuts are widely available in France, Italy, and Turkey, where they form an essential component of many regional cuisines. These young walnuts are highly prized for their unique flavour and adaptability, and they are integral to the region's culinary legacy. Green walnuts are becoming more and more well-known around the world.

2.1. Asia

Traditional medicine in Asia, specifically in China [15] and India, has long recognized the therapeutic, anticancer, antioxidant, and other beneficial properties of green walnuts. Juglone, a bioactive compound discovered in the green husk, has garnered attention in recent pharmacological investigations owing to its potential antitumor properties [9,12,13]. Green walnuts have been utilized in these areas due to their many health advantages, such as promoting joint health, boosting the immune system, and treating skin conditions. Recent scientific study has confirmed the validity of these traditional methods [1]. Juglone at high concentrations has the potential to induce hyperthermia, excessive impairment of ATP production, and fatality; conversely, low doses may have advantageous effects on health [16].

2.2. Europe

Green walnuts have also been utilized extensively in European countries, particularly Italy and France, for culinary and medicinal purposes, as exemplified by the Italian digestive liquor Nocino [17]. French medicine attributes to green walnut husks the capacity to purify the blood and address microbial and skin-related concerns. This is consistent with the acknowledged existence of bioactive constituents such as flavonoids and polyphenols, which are responsible for the therapeutic attributes of green walnuts [1,18].

2.3. America

The medicinal properties of green walnuts have been acknowledged by traditional medicine in the Americas, with a multitude of documented applications spanning both North and South America. Historically, the immature hulls have been utilized in North America to treat skin conditions and aid in detoxification. Recent studies have confirmed

that these components possess antioxidant and antibacterial properties. Recent research confirming the anticancer properties of green walnut hulls has provided similar support for the traditional uses of these materials in South America [7,19,20].

2.4. Africa and Middle East

Historical applications of green walnuts and their constituents in Africa and the Middle East have been for their antibacterial, anti-inflammatory, and antitumor qualities, as in Nigeria and the wider Middle Eastern areas. The medicinal uses of the African walnut and the green kernels of the Persian walnut are renowned for their antioxidative properties. Contemporary scientific inquiry substantiates these time-honoured applications, with an emphasis on their anti-gastric cancer properties, thereby furnishing these antiquated practices with a contemporary scientific framework [15,21].

3. Literature Review Methodology

A diverse array of the scientific literature is within the domain of science and is archived in numerous databases, including Google Scholar, PubMed, Scopus, and Web of Science (WoS). The authors of this review opted to utilize Web of Science due to its status as an ancient, authoritative, and extensively utilized database that encompasses citations and research publications from around the globe, including information from thousands of journals [22]. Indeed, as a prominent literature archive and data source, WoS comprises peer-reviewed articles. Its interface is straightforward and intuitive, facilitating the process of conducting bibliographic reviews of the literature and visualizing data through applications such as VOS viewer. The authors used the following search words in WoS: ("green walnut" OR "unripe walnut" OR "Juglans regia" OR "walnut extract" OR "walnut oil") AND (medicinal OR pharmaceutical OR therapeutic OR "health benefits") AND (antioxidant* OR anti-inflammatory OR nutraceutical* OR "natural products"). Then, after obtaining the search results, they were analysed using VOS Viewer software (Version 1.5.5), developed by Liden University, Netherlands [23]. The results, as shown in Figure 1, were obtained from the top keywords used, i.e., green walnut, walnut, its applications, bioactive compounds, its properties and characterization, walnut husk, etc., using Vos viewer software (Version-1.6.20 for iOS).

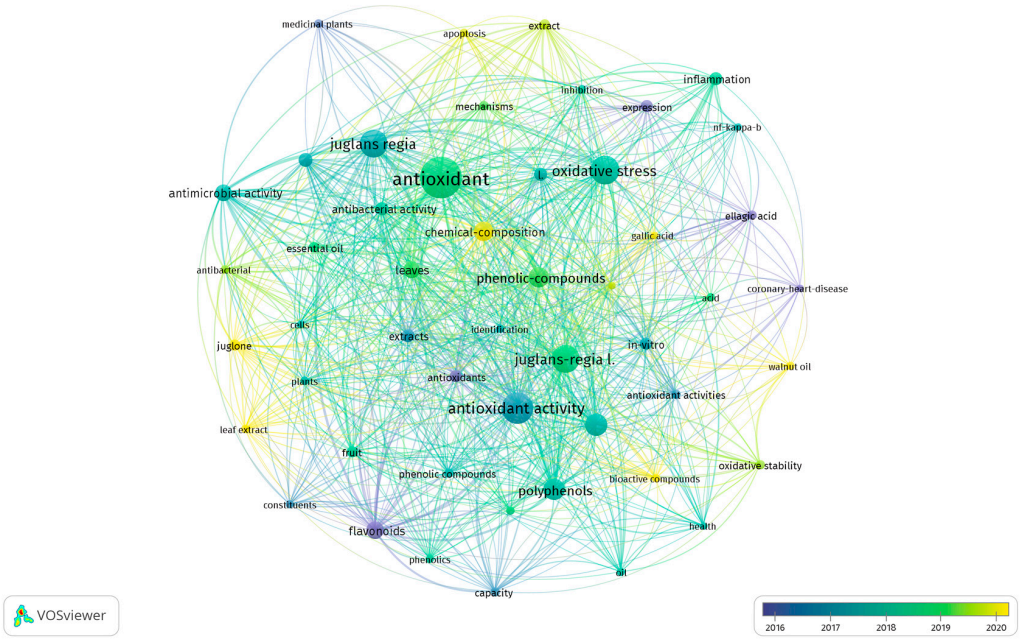


Figure 1. Top keywords used for green walnuts around the globe.

4. Nutritional Composition of Green Walnut

Green walnuts are rich in vitamins C, E, K, and folic acid. Minerals like potassium, magnesium, copper, selenium, and iron are present in green walnut. Green walnuts are a rich source of fats and contain omega-3 fatty acids (alpha-linolenic acid), omega-6 fatty acids (linoleic acid), and monounsaturated fats, as shown in Table 1.

Table 1. Detailed information about the nutritional composition of walnut.

Nutritional Information	Content (per 100 g)	Reference
Protein (g)	14.60	[24,25]
Carbohydrates (g)	10.30	
Fat (g)	64.5 g/100 g	
Total MUFA (g) *	15.28 g/100 g lipid	
Total PUFA (g) *	72.96 g/100 g lipid	
Linoleic acid (C18:2n6) (g)	59.79/100 g lipid	
Alpha-linolenic acid (C18:3n3) (g)	13.17/100 g lipid	
Vitamins A	0.036	
Vitamins B1	0.26	
Vitamins B2	0.15	
Niacin	1.13	
Vitamins C	1.3	
Vitamin B6	0.54	
Vitamins E	43.21	
K (mg)	441.00	
P (mg)	346.00	
Mn (mg)	3.80	
Zn (mg)	3.09	
Cu (mg)	1.50	
Mg (mg)	158.00	
Ca (mg)	98.00	
Se (mg)	4.62	
Ai (mg)	0.58	
Na (mg)	2.00	
Fe (mg)	2.90	
Dietary fibre content	9.79 g/100 g	[26]

* MUFA—Monounsaturated fatty acid. * PUFA—Polyunsaturated fatty acid.

Walnuts are a rich source of protein, with a protein content ranging from 13.6 to 18.1 g per 100 g of dry matter [27]. In the amino acid profile of walnut, arginine content is high and lysine content is low, which may help to prevent platelet adhesion and aggregation [28,29]. A protein's low lysine/arginine ratio can also help to prevent the development of atherosclerosis. About 65% of the calories and energy in walnuts come from fat. Triacylglycerols make up most of the compounds in walnut oil, with linoleic acid being the most common omega-6 fatty acid. Alpha-linolenic acid (ALA), a healthy omega-3 fatty acid, is also abundant in walnuts and makes up 8–14% of their fat composition. It is believed that ALA helps reduce inflammation, improve blood lipid composition, and strengthen the heart. Long-chain omega-3 fatty acids EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) are derived from ALA and are also associated with several

health benefits [30]. Green walnuts are a good source of dietary fibre, and it contains 3.1 to 5.2 g/100 g dietary fibre on a dry matter basis. Fibre acts as a nutraceutical for coronary heart diseases, diabetes, and gut health [31,32]. Walnuts are an excellent source of several vitamins and minerals. Compared to other nuts, walnuts have a higher amount of gamma tocopherol, a unique form of vitamin E. It plays a crucial role in preventing the oxidation of fats in lipid membranes because of its potent antioxidant properties [33]. Walnuts contain vitamin B6, which strengthens the immune system and supports neurological health. This vitamin aids in preventing the deficiency of microcytic anaemia. Folic acid, often known as vitamin B9, is found in walnuts and is essential for many biological functions. Deficiencies of folic acid during pregnancy may cause birth defects [34]. Numerous minerals, including magnesium, phosphorus, manganese, zinc, copper, selenium, calcium, and iron, can be found in green walnuts and their husks [35]. A body's ability to maintain a proper electrolyte balance depends on these elements [36]. Copper supports the health of the heart. It also promotes bone, neurological, and immune system health. Iron is a necessary mineral since it is a component of myoglobin, haemoglobin, and many other enzymes. As the main component of bones, calcium aids in the growth of teeth. Zinc is a necessary element for all living things, including people, animals, and plants. It is a component of enzymes involved in most key metabolic pathways. These minerals are essential for maintaining the health of the kidney, heart, brain, muscular tissues, and other vital human organs [37].

Green walnuts are unripe walnuts and harvesting begins in June to mid-July. This is when the nuts are still unripe and have a bright green colour, and the shell has not yet hardened. Green walnuts have the highest nutritional value when they are harvested in mid-June.

5. Pharmacological Properties and Bioactive Compounds

Green walnuts are unripe walnuts that contain a unique nutritional profile and bioactive compounds compared to mature walnuts. They are rich in biologically active substances like polyphenols, flavonoids, steroids, phospholipids, triterpenes, kinins, fatty acids, tannins, gallic acid, and ellagic acid. It is also a rich source of antioxidants such as ellagic acid, quercetin, juglone, and polyphenols. Green walnut fruit along with the different tree parts offer several health benefits, including antioxidant properties, which combat free radicals and reduce oxidative stress, and anti-inflammatory effects, which reduce inflammation and improve immune function; additionally, they promote brain health by improving memory, learning abilities, and protect against age-related cognitive decline; heart health, reducing the risk of heart disease; and gut health by supporting a healthy gut microbiota. They are also a major source of medicinal compounds and are used extensively in traditional medicine. Because of all these qualities, walnuts are now a valuable commercial product in the food and medicinal industries. Green walnut contains α tocopherol, a form of vitamin E in a highly concentrated form [38]. Green husks of walnuts have strong antioxidant properties and are used as a source of natural antioxidant [39]. The extract of green husk and powder are used as a natural additive and medicinal component [40]. Essential fatty acids, such as linoleic acid, which is abundant in walnuts, can reduce the risk of cardiovascular illnesses by raising HDL and lowering LDL levels [30]. Walnuts also contain flavonoids and ellagic acid, which can influence blood cholesterol levels and some of which have cardioprotective qualities [27].

6. Bioactive Components from Different Plant Parts of *Juglans regia*

6.1. Husk

The husk of green walnuts contains a variety of bioactive compounds such as juglone, tannins, flavonoid, phenolic acids, and vitamin C [41]. Juglone has antioxidant, anti-inflammatory, and potential anticancer properties. Tannins possess both antioxidant and anti-inflammatory characteristics. Flavonoids, which are antioxidants, have the potential to provide protection against chronic diseases [42]. Phenolic acids have antioxidant effects as

well. Green walnuts are a rich source of vitamin C, which aids in immunological function and the production of collagen [43], as shown in Table 2 and Figure 2A–C.

6.2. Kernel

Green walnut kernels are high in protein, fibre, omega-3 fatty acids, vitamin E, phytosterols, and polyphenols, among other nutrients and bioactive substances [44]. Healthy fats such as omega-3 fatty acids are good for heart health and brain function. An excellent supply of necessary amino acids is protein. In addition to improving digestive health, fibre may also help reduce cholesterol [45]. As an antioxidant, vitamin E (tocopherol) shields cells from harm from free radicals. It has been demonstrated that phytosterols can help decrease cholesterol levels. Walnut polyphenols provide anti-inflammatory and antioxidant properties [46].

6.3. Shell

Some bioactive substances, including tannins, phenolic compounds, pyroligneous acids, naphthoquinones, and tannins, are found in walnut shells [47]. Naphthoquinones possess antioxidant properties. The astringent and antioxidant qualities of tannins are found in the shell. The walnut's antioxidant potential is partly attributed to phenolic chemicals. The anti-inflammatory, anticancer, and antioxidant properties of pyroligneous acids are enhanced [48], as shown in Figure 2A–C.

6.4. Leaves

The pharmacological and therapeutic properties of the phenolic compounds present in walnut leaves make them particularly important [49]. They are widely used in conventional medical practices to treat a wide range of ailments, such as haemorrhoids and venous insufficiency. Extracts from walnut leaves have keratolytic, hypotensive, antifungal, relaxing, and anti-scrofulous properties [50]. Portugal and other European nations often employ dried leaves as a medicinal source.

6.5. Shoot

The health advantages of walnut trees are partly attributed to the bioactive components found in their shoots. The abundant polyphenolic chemicals found in the shoots have been connected to anti-inflammatory, anticancer, and antioxidant effects [51]. More specifically, it has been discovered that immature walnut shoots contain flavonoids, quinones, and phenolic acids. It has been demonstrated that these substances have antioxidant capacity in addition to other health-promoting qualities. Shoots from walnut trees are used to treat a number of illnesses and conditions, including diabetes, cancer, inflammation, and cardiovascular issues [52], as shown in Table 2.

6.6. Bark

Numerous bioactive substances, such as polyphenolic compounds, flavonoids, and alkaloids, have been shown to have therapeutic benefits when found in walnut bark [53]. The bark has long been used to treat skin disorders, liver stimulation, constipation, and poor digestion [54]. Antioxidant, antibacterial, antiviral, anticancer, anti-inflammatory, and cognitive-enhancing qualities have all been connected to these bioactive substances [55]. Bark is also utilized in dental products to enhance brush preparation and dental hygiene. Walnut bark extract has been used as a natural hair dyeing agent and antimicrobial agent for modern cosmetic products [56].

6.7. Root

Walnut tree roots contain bioactive components that contribute to various health benefits. Its roots have been used in traditional medicine and is rich in phytochemicals such as alkaloids, flavonoids, and polyphenolic compounds [57]. The walnut root has antioxidant properties and could be a potential source of bioactive compounds. These

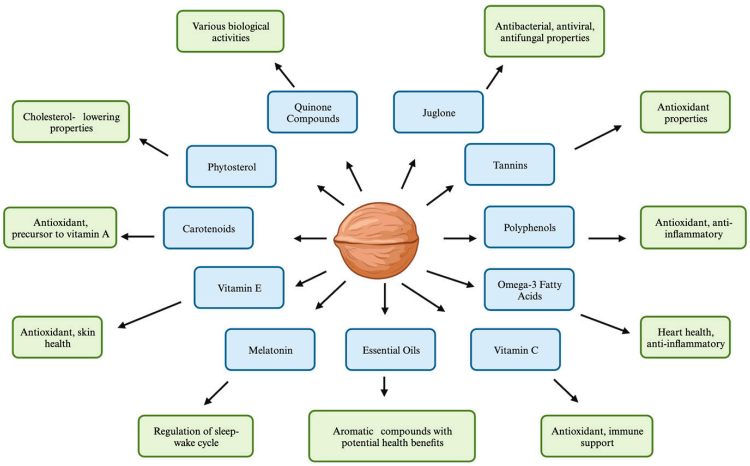
bioactive compounds have potential antifungal and antibacterial properties [58], as shown in Figure 2A–C and Table 2.

Table 2. Medicinal uses of green walnut plant's different parts.

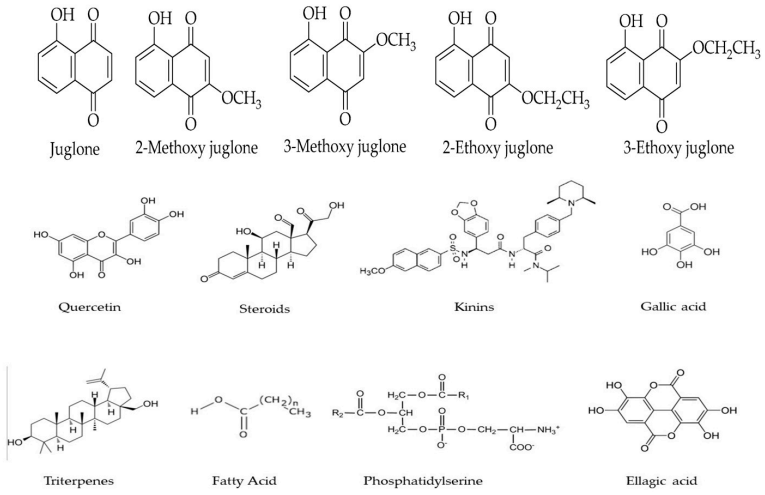
Parts of Green Walnut	Name of Bioactive Compounds	Medicinal Uses	Experiment-Conducted Country, Doses	References
Leaves	Juglone, galactosidase, arabinoside, xyloside, rhamnoside, 1,4-naphthoquinone, juglone phenolic acids, tannins, essential fatty acids, ascorbic acid, flavonoids, caffeic acid, para-coumaric acid, hydrojuglone-β-D-glucopyranoside, hydrojuglone rutinoside, hydrojuglone rhamnoside, hydrojuglone pentoside, hydrojuglone derivative 1 and 2, hydrojuglone derivative pentoside 1 and 2, hydrojuglone hexoside derivative, hydrojuglone dihexoside derivative, 5-hydroxy-2,3-dihydro-1,4-naphthalenedione, dihydroxytetralone hexoside	Anti-diabetic effect, anticancer effect, hepato-protective activity and anti-ageing activity, antioxidant activity, lipid-lowering effect, antihypertensive effect, antimicrobial effects, gastroprotective activity, hypercholesteraemic activity	In the regions of Europe, Asia, Iran and United states, studies were conducted on the identification of various bioactive compounds from the walnut tree leaves and its application in the food and medical fields through several clinical trials. 400 PPM leaf extracts had antioxidant activities.	[59–64]
Root	Polyphenolic compounds alkaloids, 1,4-naphthoquinone, juglone, α-hydrojuglone, flavonoids, hydrojuglone derivative 1, hydrojuglone derivative 5, hydrojuglone derivative rhamnoside, dihydroxytetralone hexoside	Hair fall, dandruff, skin disorders	In China and India, research was carried out on the extraction of bioactive compounds from the roots of the walnut tree and identified its various applications in the medical field. Addition of tender roots in mustard oil for 2–3 months and its application on hair to stop hair fall and dandruff.	[57,58,63–66]
Husk	Flavonoid, phenolic acids, vitamin C, 1,4-naphthoquinone, juglone, tannins, citric acid, malic acid, juglone, polyphenols, α-hydrojuglone, hydrojuglone-β-D-glucopyranoside, hydrojuglone rutinoside, hydrojuglone rhamnoside, hydrojuglone pentoside, hydrojuglone derivative 5, hydrojuglone derivative pentoside 1,2 and 3, hydrojuglone derivative rhamnoside, hydrojuglone hexoside derivative, bisjuglone, juglanin b, p-hydroxymetoxybenzobijuglone, regiolone, 5-hydroxy-2,3-dihydro-1,4-naphthalenedione, 4,5,8-trihydroxynaphthalene-5-D-glucopyranoside, 1,4,8-trihydroxynaphthalene-1-D-glucopyranoside, dihydroxytetralone hexoside, dihydroxytetralone galloyl hexoside, trihydroxytetralone derivative	Liver- and kidney-protective, antioxidant, anti-inflammatory, and anticancer properties and improves immune function	Experiments on the determination of bioactive compounds from green walnut husks were carried out in Hungary and the United States. Clinical trials were conducted to evaluate the application of husks in various medical conditions. 1.25 to 5 mg/mL of husk extract presented antimicrobial activity.	[43,63,64,67,68]
Shell	Pyroligneous acids, juglone, tannins, phenolic compounds, dihydroxytetralone hexoside	Antioxidant, anticancer, and anti-inflammatory properties	In Serbia, an experiment was carried out on the determination of bioactive compounds and production of green walnut liquor.	[63,64,69–72]
Bark	Flavonoids, polyphenols, 1,4-naphthoquinone, juglone, α-hydrojuglone, hydrojuglone-β-D-glucopyranoside, hydrojuglone rutinoside, hydrojuglone rhamnoside, hydrojuglone pentoside, hydrojuglone derivative 1, 2, 3, 4, 5, and 6, hydrojuglone derivative pentoside 1, 2, and 3, hydrojuglone derivative rhamnoside, dihydroxytetralone hexoside, procyanidin dimer 2 (+)catechin, ellagic acid derivative	Prevents tooth ache and tooth decay, has antimicrobial activity, antioxidant activity, antifungal activity, platelet aggregation, and is antiseptic	Study regarding extraction of bioactive compounds from the walnut tree bark and its assessment conducted in Pakistan. Dried bark twigs used as toothbrush.	[55,63–65,73–75]

Table 2. *Cont.*

Parts of Green Walnut	Name of Bioactive Compounds	Medicinal Uses	Experiment-Conducted Country, Doses	References
Kernel	Ellagitannin, pedunculagin, hydrojuglone-β-D-glucopyranoside	Hypolipidemic effect, antioxidant activity, antibacterial properties, antiproliferative, chemo-preventive properties	In Hungary and parts of Africa, experiments were conducted on the exploration of the therapeutic potential and molecular mechanisms of the bioactive compounds present in green walnut kernels. With several dosages, clinical studies were carried out for medicinal and food purposes. 5 g of fruit kernel and its consumption in 500 mL of boiled milk was found to be a remedy for constipation and as a memory booster.	[24,44,46,63,64,76]

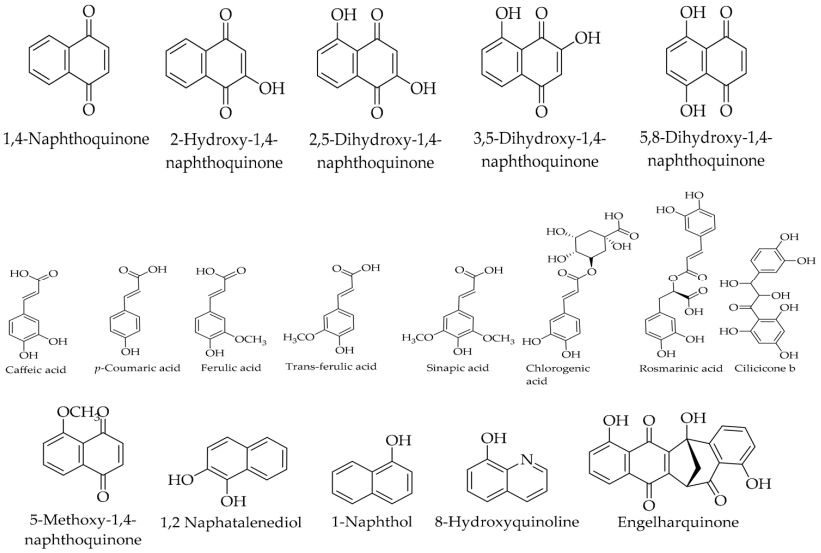


(**A**)



(**B**)

Figure 2. *Cont.*



(**C**)

Figure 2. (**A**) Phytonutrient of green walnut and their functional properties; (**B**) structure of available bioactive compounds in green walnut; (**C**) structure of available bioactive compounds in green walnut.

7. Health Benefits

There are many phenolic compounds with antioxidant properties found in walnuts. Because of its high antioxidant content and nutritional value, Persian walnuts are vital to human nutrition [77]. When compared to other nuts and seeds, it contains the highest concentration of antioxidants [78]. Using walnuts and their derivatives can help reduce the risk of developing certain diseases, such as cancer, heart problems, and degenerative diseases. A medicinal plant, walnut trees are used to cure diabetes with their roots; fever, rheumatic pain, and skin disorders with their leaves; and malaria and rheumatic pain with their flowers [79]. Because of its high phenolic content, walnut extract has anti-inflammatory and anticancer potential [80]. It also functions as a blood purifier and has antiparasitic and anti-diarrheal properties [81]. Multiple studies have been conducted (as shown below in Table 3) on the different polyphenols and their bioactivities. The different available phytonutrients in green walnuts are shown in (Figure 2A)

Table 3. Detailed studies about polyphenols and their bioactivities.

Bioactivities on Human Health	Bioactive Compounds	Description	References
Blood sugar level control	Dietary fats Walnut kernels with polyphenolic extracts	Helps to improve the health level of patients with type 2 diabetes and reduces insulin levels. Also helps to decrease blood glucose levels. Reduces the total cholesterol and triglycerides.	[82–85]

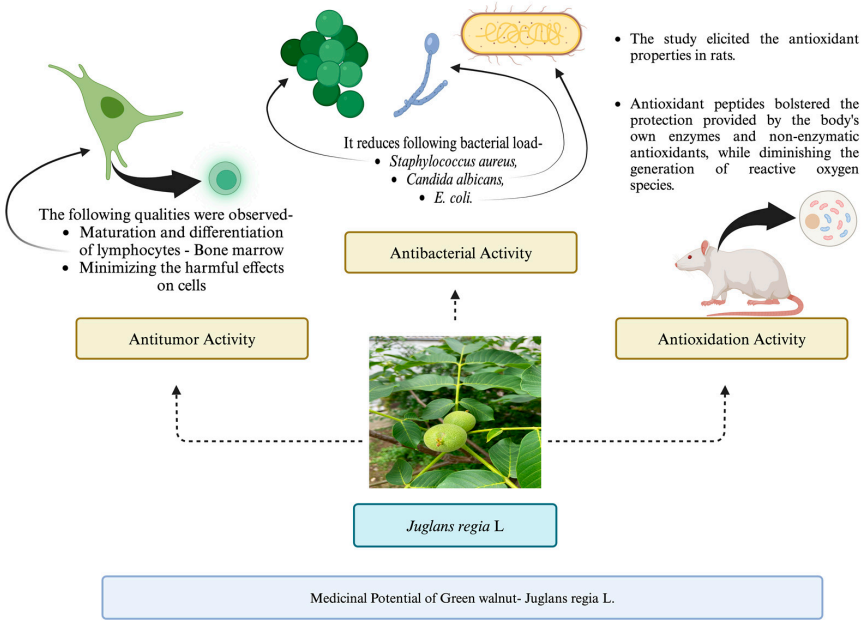
Table 3. *Cont.*

Bioactivities on Human Health	Bioactive Compounds	Description	References
Anticancer	Juglone Walnut polyphenol extracts	Triggers cell cycle arrest and programmed cell death (apoptosis) in human endometrial cancer cells. Suppresses the growth of Caco-2, MCF-7, and other cell types. Decreases the rate of prostate tumour growth by 30% to 40%. Decreases the likelihood of developing breast cancer; slows down the rate at which tumours grow.	[86–89]
Antioxidation	Ellagitannin-derived Walnut polyphenol extracts	Controls the activity of the enzyme. Contains the antioxidant activity of the scavenging ability for DPPH and $ABTS^{+}$. Contains chemical substances that decrease the number of electrons in a reaction, substances that remove unstable molecules with unpaired electrons, and substances that supply hydrogen atoms. Enhances blood lipid and endothelial function.	[90–93]
Gut health	Walnut polyphenol extracts containing omega-3 and omega-6 fatty acids	Controls the gut microbiome. Immunomodulation refers to the process of modifying or regulating the immune system. Enhances the composition of gut bacteria and promotes the production of secondary bile acids; decreases the concentration of LDL cholesterol.	[94,95]
Cardiovascular activity	Ellagic acid Ellagitannin Walnut kernels	Facilitates the initiation of neurodegenerative disorders. Reduces the likelihood of developing cardiovascular diseases and improves blood lipid levels. The enhancement of the defense mechanism of HDL cholesterol and antioxidants, together with the reduction in total cholesterol and LDL, effectively averts the occurrence of cardiovascular illnesses and alleviates the irritation.	[96–101]

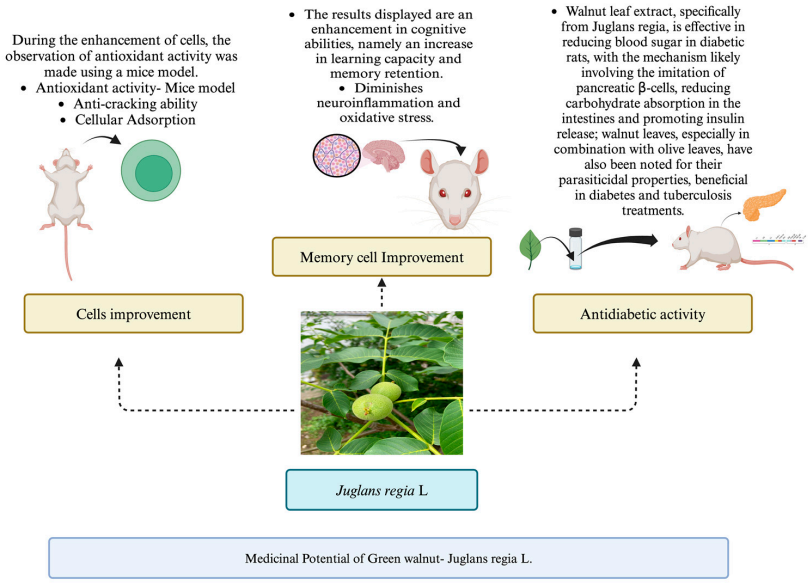
8. Memory Cell Improvement

Research has indicated that green walnuts exhibit anti-inflammatory properties, modulate the cholinergic system, reduce oxidative stress, and promote autophagy. The symptoms of Parkinson's disease, Alzheimer's disease, and cognitive impairment are all positively impacted by these actions [102]. Green walnut has been shown to mitigate scopolamine-induced memory impairment in mice by modifying the cholinergic system and reducing oxidative stress. The application of WMBP demonstrated this impact. Furthermore, it was discovered that memory impairment may be effectively improved by two neuroprotective

peptides, FY and SGFDAE [103]. Furthermore, it was found that three peptides (GGW, VYY, and LLPF) generated from WM demonstrated strong neuroprotective effects on PC12 cells treated with glutamate. These peptides damaged the integrity of the mitochondrial membrane, prevented Ca^{2+} ions from entering, and controlled the synthesis of proteins linked to programmed cell death (apoptosis). Furthermore, in PC12 cells treated with glutamate, three peptides (GGW, VYY, and LLPF) generated from WM were found to exhibit strong neuroprotective effects. The peptides caused damage to the mitochondrial membrane, prevented Ca^{2+} ions from entering, and controlled the synthesis of proteins linked to programmed cell death [104]. Later, it was shown that WMBP might have a neuroprotective effect on mice against the neurotoxicity caused by D-galactose and aluminium chloride. The results demonstrated that the WMBP treatment enhanced cognitive abilities in the mice by decreasing oxidative stress and correcting cholinergic impairment [105]. As shown in (Figure 3B).

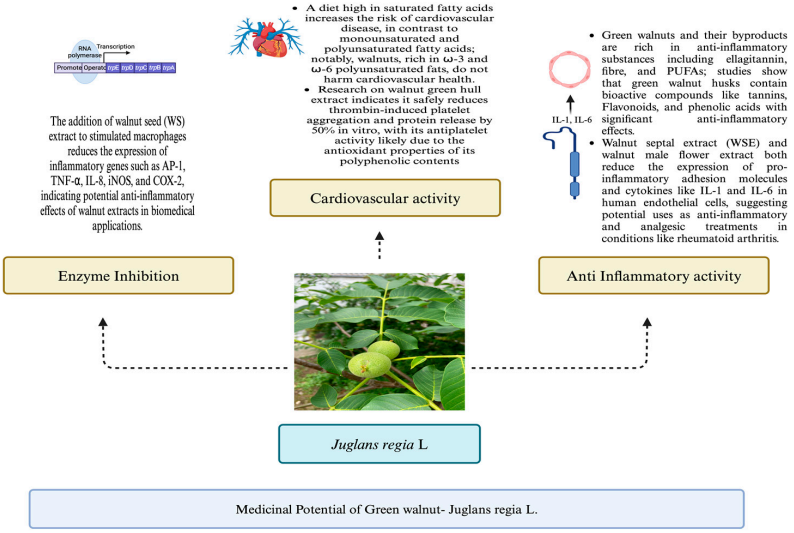


(**A**)



(**B**)

Figure 3. *Cont.*



(**C**)

Figure 3. (**A**–**C**) Medicinal potentials of *J. regia* L.

9. Antimicrobial, Antifungal Activity, and Antibacterial Activity

Juglans regia possesses both antifungal and antibacterial properties [106]. Methanolic extracts have been shown in studies to be beneficial in treating oral candidiasis. Additionally, at concentrations of 0.1 mg/mL, green walnut extracts have inhibitory effect against strains of fungi, bacteria, and Gram-positive and -negative bacteria. Dental plaque germs were shown to be susceptible to the antibacterial activity of an ethanol extract from walnut leaves, with *Streptococcus salivarius* and *sanguinis* showing the greatest susceptibility [107]. The antibacterial activity of the hydro-alcoholic extract of walnut stem bark against bacterial isolates from mastitis milk was also studied in vitro. Certain microorganisms were suppressed by the hydro-alcoholic extract [108]. The compounds found in green walnut husk extracts, including catechin, taxifolin, phenolic acids, salicylate glucuronide, and quercetin isomers, as well as other components including tocopherols, sterols, and fatty acids, are responsible for the extracts' antibacterial activity [109].

Green walnuts have a plentiful number of antibacterial compounds. It was reported that the most significant levels of antioxidant and antibacterial activity were discovered in fully developed green walnut husks with exposed shells. Green walnut husks in varied stages, including both open and closed, exhibited diverse antioxidant and antibacterial properties. Regardless of the state of the green walnut husk, extracts effectively inhibited the growth of Gram (-) negative bacteria such as *Escherichia coli* [110] (Figure 3A). In addition, a limited number of research studies have conducted a comparison between the impacts of clotrimazole and green walnut extract on *Candida albicans* in female rats, respectively. The results showed that female rats saw a considerable reduction in the growth of *Candida albicans* following one week of therapy with the vaginal cream that was prepared. Nevertheless, the utilization of nanotechnology in our everyday existence is becoming increasingly prevalent [111]. Researchers produced hydrothermal charcoal by utilizing walnut shells to battle *Pseudomonas* species, *Candida albicans*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*. Researchers found that the usage of walnut shell hydrothermal charcoal can lead to the destruction of cell structures in these bacteria, with *C. parapsilosis* exhibiting the highest level of inhibition at 96.67%. Thus, walnut shell hydrothermal charcoal serves as a cost-effective, safer, and more environmentally friendly alternative to chemical disinfectants [112].

10. Antitumor Activity

Walnut contains active plant components such as quinones, polyphenols, essential fatty acids, and proteins; these phytochemicals have pharmacological activity in treating

chronic illnesses, including cancer. Green walnut and its extracts have shown antitumor activity against glioblastoma and gastric cancer cells, among other types of cancer cells [113]. The extract from walnut possesses anti-inflammatory and anticancer qualities. Traditional medical practices include the use of walnut leaves and green walnut extract to heal burns, gastrointestinal issues, and skin irritations [114]. Shown in Figure 3. It has been discovered that different human cancer cells are vulnerable to the cytotoxic effects of walnut root chloroform extract. Eating a diet high in polyphenols can lower one's risk of cancer. Green walnut husk extracts are thought to have antitumour properties primarily because they induce apoptosis and decrease proliferation, migration, and invasion [115]. By upregulating gene expression, extracts of walnut green husk and root bark have been shown to induce apoptosis in prostate and breast cancer cells. Anticancer drugs can also be produced from walnut green husks. Multiple studies have demonstrated the antitumour properties of green walnut husk extract and nanotechnology. Green synthetic silver nanoparticles (Ag-NPs) were found to greatly enhance the antioxidant properties and cytotoxicity against cancer cell types. The temperature at which Ag-NPs were prepared using WGH extract was discovered to be a critical factor by the researchers. Furthermore, "Ag-NPs" had minimal negative effects on both normal and malignant cells at concentrations below 250 µg/mL. Their toxicity varies with dosage, which is a feature that makes them appropriate for a range of medical uses [116]. Studies have investigated how WSP extract affects leukopenia brought on by radiation and/or chemotherapy for cancer. According to the findings, the WSP extract caused leukopenia in mice and promoted bone marrow development, differentiation, and proliferation [117]. Prior research has examined the effects of WSP extract on leukopenia resulting from cancer treatment with radiation or chemotherapy. The results showed that the WSP extract enhanced bone marrow growth, differentiation, and proliferation in mice while also causing leukopenia [118] (Figure 3A). They also looked at how the WSP extract affected glioblastoma.

The WSP extract, according to the researchers, had a pro-apoptotic effect on glioblastoma, which decreased the tumour's migration and multiplication. This outcome offered a cutting-edge approach to tumour treatment.

11. Cell Improvement

A study has investigated the effects of WSP extract on the functional characteristics of erythrocytes during the administration of cyclophosphamide, a cytotoxic medication. As shown in Figure 3B, the researchers found that the WSP extract improved red blood cells' capacity to take in oxygen and strengthened their resistance to lysis. Overall, there are a lot of possible uses for the bioactive ingredients in walnut by-products. While there has been substantial research on the bioactive and chemical content of walnut by-products, our understanding of their modes of action and pharmacological toxicity is currently restricted. Thus, future research should prioritize the safety verification of walnut by-products and place greater emphasis on collecting data regarding the digestion, absorption, and metabolism of walnut by-products through clinical experiments [119]. Additionally, it is crucial to investigate the molecular mechanisms underlying the antioxidant, antimicrobial, anticancer, and cell activity enhancement properties of various walnut by-product extracts. If necessary, these investigations should be conducted at the cellular and genetic levels. In addition, it is critical to consider new methods for maintaining the synergistic efficacy of bioactive substances. This involves controlling the slow re-release of bioactive components and improving absorption using microencapsulation and nanoencapsulation techniques. Toxicological effects, bioavailability, and bioactivity of these extracts should be further investigated. This will help determine how they interact with other components in food and organs in the body, ensuring their safety and reliability for human consumption (Figure 3B).

12. Anti-Diabetic Activity

Ayurvedic studies suggest that over 1200 medicinal herbs have potential benefits in the treatment of diabetes and its associated complications. Green walnut and its extracts have demonstrated anti-diabetic benefits through several techniques. Walnut extract hydrosol has been shown to cause elevated insulin levels and reduced blood glucose levels in individuals diagnosed with type 2 diabetes. The hydroalcoholic extract of *J. regia* leaves, which contains green walnut leaves, reduces blood sugar levels in diabetic rats. Recent findings indicate that walnut leaf extract enhances glucose absorption in laboratory conditions and suppresses the activity of PTP1B, an enzyme responsible for regulating insulin signalling in a negative manner [73]. Treatments for diabetes and tuberculosis have been proven to be successful with walnut leaves because they contain a toxin that destroys parasites. Diabetics' blood glucose levels can be lowered by infusing walnut leaves either by themselves or in conjunction with olive leaves. The reason for this decline is pancreatic β-cells, which imitate the functions of β-cells by blocking the small intestine's ability to absorb carbohydrates and release more insulin. Furthermore, the protective effects of polyunsaturated fatty acids (PUFAs) obtained from walnut oil against gestational diabetes mellitus (GDM) have been shown to enhance oxidative stress, lipid metabolism, pregnancy outcomes, and glucose metabolism [120]. Through a variety of mechanisms, including by raising insulin levels, blocking PTP1B, and enhancing glucose metabolism and lipid profiles in animal models, green walnut and its extracts have shown anti-diabetic benefits as shown in (Figure 3C).

13. Enzyme Inhibition

Multiple investigations have revealed that the by-products of walnuts possess powerful enzyme inhibitory properties. One study examined the impact of walnut seed extract, both with and without the shell, on rats. Researchers found that extracts from roasted walnuts in their shells were more effective in inhibiting the formation of ACE, phosphodiesterase-5, arginase, and acetylcholinesterase [121]. A small group of researchers noted that the inclusion of WS extract in LPS-stimulated macrophages resulted in a decrease in the production of AP-1, TNF-α, IL-8, iNOS, and COX-2 genes [122]. ACE, which stands for angiotensin-converting enzyme, is a key enzyme involved in regulating blood pressure. ACE inhibitory peptides could regulate the activity of ACE. All ACE inhibitors effectively prevent the conversion of angiotensin I to angiotensin II, and their physiological and therapeutic effects are similar. Walnut extract is a commonly used source of ACE inhibitory peptides. Research is currently underway to discover further benefits of green walnut extract as enzymatic inhibitors (Figure 3C).

14. Antioxidant Activity

Walnuts are a nutritious food that are high in polyphenolics with potent antioxidant properties and fatty fractions containing alpha-linolenic acid. They may also aid in lowering oxidative stress because they are strong free radical scavengers. Walnut kernels, which are high in nutrients, are abundant in minerals and vitamins, such as vitamin E, phenolic compounds, and other phytochemicals. Walnut leaf methanolic extract contains anticancer and antioxidant qualities and is not harmful to healthy liver cells [123]. Because of their many health advantages, natural chemicals like antioxidants from walnut by-products are becoming more and more significant. A range of phenolic compounds, such as flavonoids, lignans, naphthoquinones, and phenolic acids, are found in walnut fruits. By preventing DNA binding proteins, halting mitochondrial ATP generation, generating reactive oxygen species, and triggering apoptosis, phenolic substances could eradicate cancer cells [124]. The juglone's (naphthoquinone) is mainly found in the green walnut husks. Protocatechuic, gallic, sinapic, ellagic, and chlorogenic acids also have antioxidant properties (Figure 3A).

15. Anti-Inflammatory Activity

Green walnuts and their by-products, including the husk and septum (inside shell), provide anti-inflammatory bioactive substances. The anti-inflammatory properties of walnuts are attributed to their abundance of antioxidant polyphenols, such as ellagitannins, fibre, and polyunsaturated fatty acids (PUFAs). Numerous bioactive substances found in green walnut husks, including tannins, flavonoids, and phenolic acids, have been demonstrated to have anti-inflammatory properties [125] (Figure 3C). According to a study on walnut septal extract (WSE), pro-inflammatory adhesion molecules were expressed less frequently in isolated human endothelial cells, and pro-inflammatory cytokines, such as IL-1 and IL-6, were released less frequently. Another study found that in isolated human endothelial cells, a methanolic extract of walnut male flowers suppressed the production of pro-inflammatory adhesion molecules and the release of pro-inflammatory cytokines, such as IL-1 and IL-6. The extracts show potential as an anti-inflammatory and analgesic for diseases such as rheumatoid arthritis [61].

16. Cardiovascular Activity

Cardiovascular disease risk is increased by consuming a high dose of saturated fatty acids relative to monounsaturated and polyunsaturated fatty acids. ω-3 and ω-6 polyunsaturated fats, which are abundant in walnuts, have been shown to have no detrimental impact on cardiovascular health [126]. Walnut green hull extract was found to have no adverse effects and to lower by 50% the thrombin-induced platelet aggregation and protein release in in vitro research. This shows that the antiplatelet activity of walnut green hull extract may be attributed to the antioxidant qualities of the polyphenolic components [42] (Figure 3C).

17. Antihypertension Activity

Hypertension is a common cardiovascular disorder that presents a substantial threat to human well-being [127]. ACE, or angiotensin-converting enzyme, plays a vital role in the regulation of blood pressure. Its activity, which is essential for this process, can be modified by peptides that block ACE. ACE inhibitors effectively limit the conversion of angiotensin I to angiotensin II, leading to similar therapeutic and physiological effects. WM is a prevalent origin of ACE inhibitory peptides. A study discovered that WM protein hydrolysate demonstrated strong ACE inhibitory activity and stability, resulting in a significant reduction in systolic blood pressure in hypertensive mice [128]. In addition, another study employed alcalase and trypsin enzymes to carry out the hydrolysis of WM. The hydrolysate exhibited notable ACE inhibitory activity and demonstrated low IC50 values. This is shown in Figure 4.

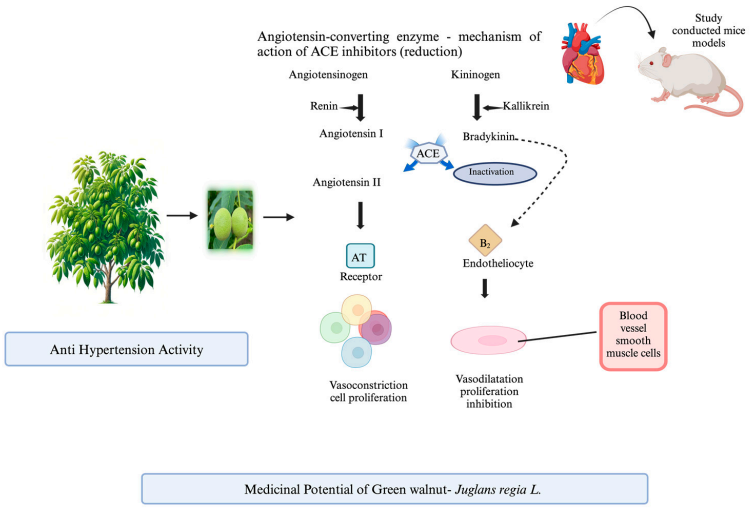


Figure 4. Study of antihypertension activity conducted on mice models.

18. Traditional vs. Modern Medicine

Traditional medicine, which has historically supplied a substantial proportion of the world's population with primary healthcare, has heavily depended on the availability and indigenous expertise of herbal remedies, where walnuts and other similar plants have been pivotal [129]. Walnuts, which are highly regarded globally for their medicinal properties and nutritional value, have been cultivated extensively in numerous cultures. The applications of walnuts, which have been influenced by centuries of cultural history, frequently deviate from the traditional uses validated by contemporary scientific research. Recent research has specifically examined the chemical and phytochemical characteristics of walnuts, emphasizing their potential as functional foods that offer a range of health advantages, such as the prevention of diseases and the promotion of overall health [130]. Modern medicine investigates the active compounds present in walnuts and assesses them using stringent scientific procedures. This results in a knowledge of their health benefits that is grounded in empirical evidence and has the potential to validate or enhance traditional practices.

19. Walnut Application in the Pharmaceutical Industry

Walnuts have long been utilized in traditional medicine, and because of their possible health advantages, their use in modern medications has grown. Walnuts boost healthy cholesterol levels and offer protection against cardiovascular diseases, according to research [131]. Additionally, they might delay or prevent the beginning of serious conditions including Alzheimer's and Parkinson's. Additionally, walnuts help with blood circulation, sleep issues, and the human digestive system [132]. They have been used as a diuretic, a weight gain help, a pregnant nausea reliever, and a relaxant. Because of their pharmacological qualities, which include vasoconstrictor, hypoglycaemic, antifungal, anti-wart, diarrhoea-suppressing, and skin-cleaning capabilities, walnut leaves and shells have been utilized in complementary and alternative medicine [133]. Additionally, wounds, eczema, bee stings, inflammatory skin diseases, ulcers, and more have been treated using walnut leaves [11].

20. Walnut Application in Food Industry as a Nutraceutical

Walnut husk extract is used in food products to extend shelf life and preserve processed products [134]. Walnut husk extract was added to ketchup to increase its antibacterial properties and to prevent oxidation in sunflower extract [135]. Porridge made from walnut leaves can treat wounds, swollen glands, and acne. Various value-added products are prepared from the green walnut husk extract and fruit such as beverages, bakery, confectionery, and traditional dishes.

21. Contemporary Research

Recent research has shown that walnut husk has medicinal properties that could be used as treatments for various illnesses. Walnut husk has been found to be helpful against malignant cells, with the human gastric cell line showing reduced cancer cell proliferation when treated with walnut husk extract [115]. The cytotoxic potential of naphthoquinones and its derivatives against human cancer cells was studied. The HepG-2 hepatoma cell line has been used to demonstrate the inhibitory impact of oleanolic acid isolated from walnut husk on human cancer cell lines [136].

22. Regulatory Approvals and Adverse Health Effects

Regarding the regulatory approval of green walnuts for human sustenance, such as FDA approval or endorsements from international regulatory agencies, the search results were devoid of pertinent information. Discussions pertaining to walnuts, including green walnuts, generally revolve around their nutritional benefits, culinary uses, and the extraction of compounds for scientific inquiry (e.g., the antibacterial properties exhibited by walnut green husks) [137,138]. Juglone, when present in high concentrations, can

potentially cause hyperthermia, a significant impairment of ATP production, and fatality. On the other hand, minimal quantities of juglone may yield beneficial outcomes for human health [16]. Within the regulatory framework of food safety, the FDA's Produce Safety Rule establishes science-based minimum criteria for producing, harvesting, packaging, and storing food for human consumption [139]. While green walnuts are not explicitly referenced, this implies that they would be considered safe for ingestion if they met these general safety standards. To acquire an unequivocal response concerning green walnuts, it is imperative to initiate direct communication with regulatory agencies or consult the pertinent regulations that govern almonds and associated merchandise.

23. Challenges and Future Directions

It may be stated that for the green walnut treatment to be effective and reliable, an extraction method must be standardized. In addition, clinical analysis should be conducted to validate safety and efficiency. To prevent the unnecessary adverse effects of green walnut treatment and optimize the application of it in modern medicine, it is also essential to establish a better understanding of all active ingredients and the ways in which they operate. Furthermore, it seems necessary to define how traditional green walnut treatment could be combined properly with modern medications to complement treatment. Green walnut has a positive clinical use in many areas, covering skin wellness, wound healing, anticancer, antibacterial, antioxidant, or anti-inflammatory properties. However, long, and accurate medical trials are required to prove the safety and efficiency of green walnuts.

24. Conclusions

Almost every component of the walnut plant, including the bark, kernel, fruit, leaves, green husk, blossom, and root, has a variety of therapeutic uses. The available data recommend extensive research conducted on the ethnopharmacological effects of walnut. The wide range of ethnopharmacological activities makes the walnut a promising medicinal plant with high effectiveness. In addition to offering basic nutritional functions, walnuts serve as an excellent choice for their physiological benefits on human hosts due to their plethora of phytochemicals, fat-soluble bioactive compounds, nutrients, and non-nutrient antioxidants, which make them a good choice as food additives and heart-healthy snacks. It is important to conduct further research in every continent since different varieties of green walnuts possess different qualities and health benefits in terms of medicinal uses.

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Abbreviations

WGH	Walnut green husk
WSP	Walnut septum
WMBP	Walnut meal bioactive peptide
WM	Walnut meal
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
MUFA	Monounsaturated fatty acid
PUFA	Polyunsaturated fatty acid

References

1. Sharma, M.; Sharma, M.; Sharma, M. A comprehensive review on ethnobotanical, medicinal and nutritional potential of walnut (*Juglans regia* L.). *Proc. Indian Natl. Sci. Acad. Part A Phys. Sci.* **2022**, *88*, 601–616. [CrossRef]
2. Verma, G.; Sharma, V. A Scientific Update on Juglans Regia Linn. *Asian J. Pharm. Res. Dev.* **2020**, *8*, 166–175. [CrossRef]
3. Ghasemi, M.; Arzani, K.; Hassani, D. Evaluation and identification of walnut (*Juglans regia* L.) genotypes in Markazi province of Iran. *Crop Breed. J.* **2012**, *2*, 119–124.
4. Wu, S.; Ni, Z.; Wang, R.; Zhao, B.; Han, Y.; Zheng, Y.; Liu, F.; Gong, Y.; Tang, F.; Liu, Y. The effects of cultivar and climate zone on phytochemical components of walnut (*Juglans regia* L.). *Food Energy Secur.* **2020**, *9*, e196. [CrossRef]
5. de Rigo, D.; Enescu, C.M.; Durrant, T.H.; Tinner, W.; Caudullo, G. *Juglans regia in Europe: Distribution, Habitat, Usage and Threats*; Publication Office of the European Union: Luxembourg, 2016.
6. Habibi, A.; Hamedpour-Darabi, M.; Vahdati, K. Local cultural values of Persian walnut in Iran. In *The Cultural Value of Trees*; Routledge: London, UK, 2022; pp. 162–173.
7. Hajipuor, S.; Alinia-Ahandani, E.; Selamoglu, Z. A Closer Look at Some Medical Use of Green Persian Walnut Shell. *Eurasian J. Med. Biol. Sci.* **2022**, 17.
8. Zhang, R.; Liu, B.; Xin, G.; Zhang, X.; Li, J.; Wang, Y. Evaluation of Cold Tolerance of Seven Walnut Varieties. *Cryoletters* **2022**, *43*, 74–82. [CrossRef] [PubMed]
9. Aryapak, S.; Ziarati, P. Nutritive value of Persian walnut (*Juglans regia* L.) Orchards. *Am. Eurasian J. Agric. Environ. Sci.* **2014**, *14*, 1228–1235.
10. Gandev, S. Budding and grafting of the walnut (*Juglans regia* L.) and their effectiveness in Bulgaria. *Bulg. J. Agric. Sci.* **2007**, *13*, 683.
11. Milind, P.; Deepa, K. Walnut: Not a hard nut to crack. *Int. Res. J. Pharm.* **2011**, *2*, 8–17.
12. Şen, S.M.; Karadeniz, T. The nutritional value of walnut. *J. Hyg. Eng. Des.* **2015**, *11*, 68–71.
13. Pan, Z.; Zhang, R.; Zicari, S. *Integrated Processing Technologies for Food and Agricultural by-Products*; Academic Press: Cambridge, MA, USA, 2019.
14. Berkey, C.S.; Tamimi, R.M.; Willett, W.C.; Rosner, B.; Hickey, M.; Toriola, A.T.; Frazier, A.L.; Colditz, G.A. Adolescent alcohol, nuts, and fiber: Combined effects on benign breast disease risk in young women. *NPJ Breast Cancer* **2020**, *6*, 61. [CrossRef] [PubMed]
15. Park, G.; Jang, D.S.; Oh, M.S. Juglans mandshurica leaf extract protects skin fibroblasts from damage by regulating the oxidative defense system. *Biochem. Biophys. Res. Commun.* **2012**, *421*, 343–348. [CrossRef] [PubMed]
16. Saling, S.C.; Comar, J.F.; Mito, M.S.; Peralta, R.M.; Bracht, A. Actions of juglone on energy metabolism in the rat liver. *Toxicol. Appl. Pharmacol.* **2011**, *257*, 319–327. [CrossRef] [PubMed]
17. Stampar, F.; Solar, A.; Hudina, M.; Veberic, R.; Colaric, M. Traditional walnut liqueur—Cocktail of phenolics. *Food Chem.* **2006**, *95*, 627–631. [CrossRef]
18. Pycia, K.; Kapusta, I.; Jaworska, G.; Jankowska, A. Antioxidant properties, profile of polyphenolic compounds and tocopherol content in various walnut (*Juglans regia* L.) varieties. *Eur. Food Res. Technol.* **2019**, *245*, 607–616. [CrossRef]
19. Chudhary, Z.; Khera, R.A.; Hanif, M.A.; Ayub, M.A.; Hamrouni, L. Walnut. In *Medicinal Plants of South Asia*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 671–684.
20. Zhao, P.; Zhou, H.-J.; Potter, D.; Hu, Y.-H.; Feng, X.-J.; Dang, M.; Feng, L.; Zulfiqar, S.; Liu, W.-Z.; Zhao, G.-F.; et al. Population genetics, phylogenomics and hybrid speciation of Juglans in China determined from whole chloroplast genomes, transcriptomes, and genotyping-by-sequencing (GBS). *Mol. Phylogenetics Evol.* **2018**, *126*, 250–265. [CrossRef] [PubMed]
21. Kithi, L.; Lengyel-Kónya, É.; Berki, M.; Bujdosó, G. Role of the green husks of persian walnut (*Juglans regia* L.)—A Review. *Horticulturae* **2023**, *9*, 782. [CrossRef]
22. Birkle, C.; Pendlebury, D.A.; Schnell, J.; Adams, J. Web of Science as a data source for research on scientific and scholarly activity. *Quant. Sci. Stud.* **2020**, *1*, 363–376. [CrossRef]
23. Van Eck, N.J.; Waltman, L. Citation-based clustering of publications using CitNetExplorer and VOSviewer. *Scientometrics* **2017**, *111*, 1053–1070. [CrossRef]
24. Martínez, M.L.; Labuckas, D.O.; Lamarque, A.L.; Maestri, D.M. Walnut (*Juglans regia* L.): Genetic resources, chemistry, by-products. *J. Sci. Food Agric.* **2010**, *90*, 1959–1967. [CrossRef]

25. Atanasov, A.G.; Sabharanjak, S.M.; Zengin, G.; Mollica, A.; Szostak, A.; Simirgiotis, M.; Huminiecki, Ł.; Horbanczuk, O.K.; Nabavi, S.M.; Mocan, A. Pecan nuts: A review of reported bioactivities and health effects. *Trends Food Sci. Technol.* **2018**, *71*, 246–257. [CrossRef]
26. Feldman, E.B. The scientific evidence for a beneficial health relationship between walnuts and coronary heart disease. *J. Nutr.* **2002**, *132*, 1062S–1101S. [CrossRef] [PubMed]
27. Savage, G.P. Chemical composition of walnuts (*Juglans regia* L.) grown in New Zealand. *Plant Foods Hum. Nutr.* **2001**, *56*, 75–82. [CrossRef] [PubMed]
28. Ruggeri, S.; Cappelloni, M.; Gambelli, L.; Nicoli, S.; Carnovale, E. Chemical composition and nutritive value of nuts grown in Italy. *Ital. J. Food Sci.* **1998**, *10*, 243–252.
29. Lavedrine, F.; Zmirou, D.; Ravel, A.; Balducci, F.; Alary, J. Blood cholesterol and walnut consumption: A cross-sectional survey in France. *Prev. Med.* **1999**, *28*, 333–339. [CrossRef] [PubMed]
30. Amaral, J.S.; Casal, S.; Pereira, J.A.; Seabra, R.M.; Oliveira, B.P.P. Determination of sterol and fatty acid compo- sitions, oxidative stability, and nutritional value of six wal- nut (*Juglans regia* L.) cultivars grown in Portugal. *J. Agric. Food Chem.* **2003**, *51*, 7698–7702. [CrossRef] [PubMed]
31. Sabate, J.; Fraser, G.E.; Burke, K.; Knutsen, S.F.; Bennett, H.; Lindsted, K.D. Effects of walnuts on serum lipid levels and blood pressure in normal men. *N. Engl. J. Med.* **1993**, *328*, 603–607. [CrossRef] [PubMed]
32. Bolling, B.W.; Chen, C.-Y.O.; McKay, D.L.; Blumberg, J.B. Tree nut phytochemicals: Composition, antioxidant capacity, bioactivity, impact factors. A systematic review of almonds, Brazils, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios and walnuts. *Nutr. Res. Rev.* **2011**, *24*, 244–275. [CrossRef] [PubMed]
33. Anwar, F.; Qadir, R.; Abbas, A. *Cold Pressed Walnut (Juglans regia L.) Oil, in Cold Pressed Oils*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 491–495.
34. Ozcan, M.M. Some nutritional characteristics of fruit and oil of walnut (*Juglans regia* L.) growing in Turkey. *Iranian J. Chem. Chem. Eng. Int. Engl. Ed.* **2009**, *28*, 57–62.
35. Siahnouri, Z.; Sadeghian, M.; Salehisormghi, M.; Qomi, M. Determination of Iranian walnut and pistachio mineral contents. *J. Basic Appl. Sci. Res.* **2013**, *3*, 217–220.
36. Alaviani, S.; Mahmoudyar, F.; Miraftabi, S.F.; Salehisormghi, M.H.; Qomi, M. Determination of Iranian Almond, Peanut and Hazelnut Mineral Contents. *J. Basic Appl. Chem.* **2012**, *2*, 50–54.
37. Özkutlu, F.; Doğru, Y.Z.; Özenç, N.; Yazici, G.; Turan, M.; Akçay, F. The importance of Turkish hazelnut trace and heavy metal contents for human nutrition. *J. Soil Sci. Environ. Manag.* **2011**, *2*, 25–33.
38. Li, W.; Li, D.-Y.; Wang, H.-D.; Zheng, Z.-J.; Hu, J.; Li, Z.-Z. *Juglans regia* hexane extract exerts antitumor effect, apoptosis induction and cell circle arrest in prostate cancer cells in vitro. *Trop. J. Pharm. Res.* **2015**, *14*, 399–405. [CrossRef]
39. Noshirvani, N.; Fasihi, H.; Moradipayam, A. Study on the Antioxidant Effects of Extract and Powder of Green Walnut Hulls on the Oxidation of Sunflower Oil. *Iran. J. Nutr. Sci. Food Technol.* **2015**, *10*, 79–90.
40. Salejda, A.M.; Janiewicz, U.; Korzeniowska, M.; Kolniak-Ostek, J.; Krasnowska, G. Effect of walnut green husk addition on some quality properties of cooked sausages. *LWT-Food Sci. Technol.* **2016**, *65*, 751–757. [CrossRef]
41. Oliveira, I.; Sousa, A.; Ferreira, I.C.; Bento, A.; Estevinho, L.; Pereira, J.A. Total phenols, antioxidant potential and antimicrobial activity of walnut (*Juglans regia* L.) green husks. *Food Chem. Toxicol.* **2008**, *46*, 2326–2331. [CrossRef] [PubMed]
42. Meshkini, A.; Tahmasbi, M. Anti-platelet aggregation activity of walnut hull extract via suppression of ROS generation and caspase activation. *J. Acupunct. Meridian Stud.* **2017**, *10*, 193–203. [CrossRef] [PubMed]
43. Fernández-Agulló, A.; Pereira, E.; Freire, M.S.; Valentao, P.; Andrade, P.B.; González-Álvarez, J.; Pereira, J.A. Influence of solvent on the antioxidant and antimicrobial properties of walnut (*Juglans regia* L.) green husk extracts. *Ind. Crops Prod.* **2013**, *42*, 126–132. [CrossRef]
44. Greve, L.C.; McGranahan, G.; Hasey, J.; Snyder, R.; Kelly, K.; Goldhamer, D.; Labavitch, J.M. Variation in polyunsaturated fatty acids composition of Persian walnut. *J. Am. Soc. Hortic. Sci.* **1992**, *117*, 518–522. [CrossRef]
45. Elmadfa, I.; Kornsteiner, M. Dietary fat intake–A global perspective. *Ann. Nutr. Metab.* **2009**, *54* (Suppl. S1), 8–14. [CrossRef]
46. Moghaddam, P.Z.; Mohammadi, A.; Feyzi, P.; Alesheikh, P. In vitro antioxidant and antibacterial activity of various extracts from exocarps and endocarps of walnut. *Pak. J. Pharm. Sci.* **2017**, *30*, 1725–1731. [PubMed]
47. Jahanban-Esfahlan, A.; Amarowicz, R. Walnut (*Juglans regia* L.) shell pyroligneous acid: Chemical constituents and functional applications. *RSC Adv.* **2018**, *8*, 22376–22391. [CrossRef] [PubMed]
48. Zhai, M.; Shi, G.; Wang, Y.; Mao, G.; Wang, D.; Wang, Z. Chemical compositions and biological activities of pyroligneous acids from walnut shell. *BioResources* **2015**, *10*, 1715–1729. [CrossRef]
49. Nour, V.; Trandafir, I.; Cosmulescu, S. Optimization of ultrasound-assisted hydroalcoholic extraction of phenolic compounds from walnut leaves using response surface methodology. *Pharm. Biol.* **2016**, *54*, 2176–2187. [CrossRef] [PubMed]
50. Qa'Dan, F.; Thewaini, A.-J.; Ali, D.A.; Afifi, R.; Elkhawad, A.; Matalka, K.Z. The antimicrobial activities of *Psidium guajava* and *Juglans regia* leaf extracts to acne-developing organisms. *Am. J. Chin. Med.* **2005**, *33*, 197–204. [CrossRef] [PubMed]
51. Solar, A.; Colarič, M.; Usenik, V.; Stampar, F. Seasonal variations of selected flavonoids, phenolic acids and quinones in annual shoots of common walnut (*Juglans regia* L.). *Plant Sci.* **2006**, *170*, 453–461. [CrossRef]

52. Cheniany, M.; Ebrahimzadeh, H.; Vahdati, K.; Preece, J.E.; Masoudinejad, A.; Mirmasoumi, M. Content of different groups of phenolic compounds in microshoots of *Juglans regia* cultivars and studies on antioxidant activity. *Acta Physiol. Plant.* **2013**, *35*, 443–450. [CrossRef]
53. Taha, N.A.; Al-wadaan, M.A. Utility and importance of walnut, *Juglans regia* Linn: A. *Afr. J. Microbiol. Res.* **2011**, *5*, 5796–5805.
54. Thakur, A. Juglone: A therapeutic phytochemical from *Juglans regia* L. *J. Med. Plants Res.* **2011**, *5*, 5324–5330.
55. Bhatia, K.; Rahman, S.; Ali, M.; Raisuddin, S. In vitro antioxidant activity of *Juglans regia* L. bark extract and its protective effect on cyclophosphamide-induced urotoxicity in mice. *Redox Rep.* **2006**, *11*, 273–279. [CrossRef]
56. NirmlaDevi, T.; Apraj, V.; Bhagwat, A.; Mallya, R.; Sawant, L.; Pandita, N. Pharmacognostic and phytochemical investigation of *Juglans regia* Linn. bark. *Pharmacogn. J.* **2011**, *3*, 39–43. [CrossRef]
57. Raja, V.; Ahmad, S.I.; Irshad, M.; Wani, W.A.; Siddiqi, W.A.; Shreaz, S. Anticandidal activity of ethanolic root extract of *Juglans regia* (L.): Effect on growth, cell morphology, and key virulence factors. *J. De Mycol. Médicale* **2017**, *27*, 476–486. [CrossRef] [PubMed]
58. Allaie, A.H.; Singh, R.; Ganaie, A.A.; Mishra, R.P.; Ali, S. Phytochemically analyzed *Juglans regia* root extracts and their bactericidal facets against some urinary tract infection causing bacteria. *Int. J. Biol. Med. Res.* **2018**, *9*, 6304–6308.
59. Rahimipanah, M.; Hamedi, M.; Mirzapour, M. Antioxidant activity and phenolic contents of Persian walnut (*Juglans regia* L.) green husk extract. *Afr. J. Food Sci. Technol* **2010**, *1*, 105–111.
60. Al-Snai, A. Iraqi medicinal plants with antifungal effect—A review. *IOSR J. Pharm.* **2019**, *9*, 16–56.
61. Verma, R.S.; Padalia, R.C.; Chauhan, A.; Thul, S.T. Phytochemical analysis of the leaf volatile oil of walnut tree (*Juglans regia* L.) from western Himalaya. *Ind. Crops Prod.* **2013**, *42*, 195–201. [CrossRef]
62. Noumi, E.; Snoussi, M.; Trabelsi, N.; Hajlaoui, H.; Ksouri, R.; Valentin, E.; Bakhrouf, A. Antibacterial, anticandidal and antioxidant activities of Salvadora persica and *Juglans regia* L. extracts. *J. Med. Plants Res.* **2011**, *5*, 4138–4146.
63. Medic, A.; Hudina, M.; Jakopic, J.; Veberic, R. Is juglone really the only allelochemical in *J. regia* affecting plant growth and seed germination? In Proceedings of the XXXI International Horticultural Congress (IHC2022): International Symposium on Quality Seeds and Transplants for Horticultural 1365, Angers, France, 14–20 August 2022.
64. Medic, A.; Jakopic, J.; Solar, A.; Hudina, M.; Veberic, R. Walnut (*J. regia*) agro-residues as a rich source of phenolic compounds. *Biology* **2021**, *10*, 535. [CrossRef] [PubMed]
65. Hasan, T.N.; Grace, B.L.; Shafi, G.; Al-Hazzani, A.A.; Alshatwi, A.A. Anti-proliferative effects of organic extracts from root bark of *Juglans regia* L. (RBJR) on MDA-MB-231 human breast cancer cells: Role of Bcl-2/Bax, caspases and Tp53. *Asian Pac. J. Cancer Prev.* **2011**, *12*, 525–530.
66. Gupta, A.; Behl, T.; Panichayupakaranan, P. Review of phytochem- istry and pharmacology profile of *Juglans regia*. *Obes. Med.* **2019**, *16*, 100142. [CrossRef]
67. Anderson, K.J.; Teuber, S.S.; Gobeille, A.; Cremin, P.; Waterhouse, A.L.; Steinberg, F.M. Walnut Polyphenolics Inhibit In Vitro Human Plasma and LDL Oxidation. *J. Nutr.* **2001**, *131*, 2837–2842. [CrossRef] [PubMed]
68. Rahimi, P.; Kabiri, N.; Asgary, S.; Setorki, M. Anti-diabetic effects of walnut oil on alloxan-induced diabetic rats. *Afr. J. Pharm. Pharmacol.* **2011**, *5*, 2655–2661.
69. Kazemipour, M.; Ansari, M.; Tajrobehkar, S.; Majdzadeh, M.; Kermani, H.R. Removal of lead, cadmium, zinc, and copper from industrial wastewater by carbon developed from walnut, hazelnut, almond, pistachio shell, and apricot stone. *J. Hazard. Mater.* **2008**, *150*, 322–327. [CrossRef] [PubMed]
70. Sial, T.A.; Shaheen, S.M.; Lan, Z.; Korai, P.K.; Ghani, M.I.; Khan, M.N.; Syed, A.-u.-A.; Ali, M.N.A.; Rajpar, I.; Memon, M.; et al. Addition of walnut shells biochar to alkaline arable soil caused contradictory effects on CO_2 and N_2O emissions, nutrients availability, and enzymes activity. *Chemosphere* **2022**, *293*, 133476. [CrossRef] [PubMed]
71. Owens, N.; Lee, D. The use of micro bubble flotation technology in secondary and tertiary produced water treatment—A technical comparison with other separation technologies. In Proceedings of the TUV NEL, 5th Produced Water Workshop, Aberdeen, Scotland, 30–31 May 2007.
72. Jahanban-Esfahlan, A.; Ostadrahimi, A.; Tabibiazar, M.; Amarowicz, R. A Comparative Review on the Extraction, Antioxidant Content and Antioxidant Potential of Different Parts of Walnut (*Juglans regia* L.) Fruit and Tree. *Molecules* **2019**, *24*, 2133. [CrossRef] [PubMed]
73. Mohammadi, J.; Saadipour, K.; Delaviz, H.; Mohammadi, B. Anti-diabetic effects of an alcoholic extract of Juglans regia in an animal model. *Turk. J. Med. Sci.* **2011**, *41*, 685–691. [CrossRef]
74. Ibrar, M.; Hussain, F.; Sultan, A. Ethnobotanical studies on plant resources of Ranyal Hills, District Shangla, Pakistan. *Pak. J. Bot.* **2007**, *39*, 329–337.
75. Zakavi, F.; Hagh, L.G.; Sheikh, A.F.; Daraeighadikolaei, A.; Shooshtari, Z.L. Antibacterial effect of *Juglans regia* bark against oral pathologic bacteria. *Int. J. Dent.* **2013**, *2013*, 854765. [CrossRef] [PubMed]
76. Colaric, M.; Veberic, R.; Solar, A.; Hudina, M.; Stampar, F. Phenolic acids, syringaldehyde, and juglone in fruits of different cultivars of *Juglans regia* L. *J. Agric. Food Chem.* **2005**, *53*, 6390–6396. [CrossRef]
77. Arcan, I.; Yemenicioğlu, A. Antioxidant activity and phenolic content of fresh and dry nuts with or without the seed coat. *J. Food Compos. Anal.* **2009**, *22*, 184–188. [CrossRef]
78. Blomhoff, R.; Carlsen, M.H.; Andersen, L.F.; Jacobs, D.R. Health benefits of nuts: Potential role of antioxidants. *Br. J. Nutr.* **2006**, *96*, S52–S60. [CrossRef] [PubMed]

79. Tsasi, G.; Milošević-Ifantis, T.; Skaltsa, H. Phytochemical study of Juglans regia L. pericarps from Greece with a chemotaxonomic approach. *Chem. Biodivers.* **2016**, *13*, 1636–1640. [CrossRef] [PubMed]
80. Valdebenito, D.; Farías, D.; Oyanedel, E.; Castro, M.; Lampinen, B.; Tixier, A.; Saa, S. The morphology of a Walnut (*Juglans regia* L.) shoot is affected by its position in the canopy and correlated to the number and size of its fruits. *Sci. Hortic.* **2017**, *220*, 303–309. [CrossRef]
81. Tapsell, L.; Batterham, M.; Tan, S.-Y.; Warensjö, E. The effect of a calorie controlled diet containing walnuts on substrate oxidation during 8-hours in a room calorimeter. *J. Am. Coll. Nutr.* **2009**, *28*, 611–617. [CrossRef] [PubMed]
82. Zhao, L.-G.; Zhang, Q.-L.; Liu, X.-L.; Wu, H.; Zheng, J.-L.; Xiang, Y.-B. Dietary protein intake and risk of type 2 diabetes: A dose–response meta-analysis of prospective studies. *Eur. J. Nutr.* **2019**, *58*, 1351–1367. [CrossRef] [PubMed]
83. Fukuda, T.; Ito, H.; Yoshida, T. Antioxidative polyphenols from walnuts (*Juglans regia* L.). *Phytochemistry* **2003**, *63*, 795–801. [CrossRef] [PubMed]
84. Jiang, R.; Manson, J.E.; Stampfer, M.J.; Liu, S.; Willett, W.C.; Hu, F.B. Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA* **2002**, *288*, 2554–2560. [CrossRef]
85. Prokisch, J.; El-Ramady, H.; Daróczi, L.; Nagy, É.; Badgar, K.; Kiss, A.; Shaikh, A.M.; Gilányi, I.; Oláh, C. Functional Yogurt Fortified with Honey Produced by Feeding Bees Natural Plant Extracts for Controlling Human Blood Sugar Level. *Plants* **2022**, *11*, 1391. [CrossRef] [PubMed]
86. Park, J.M.; An, J.M.; Han, Y.M.; Surh, Y.J.; Hwang, S.J.; Kim, S.J.; Hahm, K.B. Walnut polyphenol extracts inhibit Helicobacter pylori-induced STAT3Tyr705 phosphorylation through activation of PPAR-γ and SOCS1 induction. *J. Clin. Biochem. Nutr.* **2020**, *67*, 248–256. [CrossRef]
87. Reiter, R.J.; Tan, D.-X.; Manchester, L.C.; Korkmaz, A.; Fuentes-Broto, L.; Hardman, W.E.; Rosales-Corral, S.A.; Qi, W. A walnut-enriched diet reduces the growth of LNCaP human prostate cancer xenografts in nude mice. *Cancer Investig.* **2013**, *31*, 365–373. [CrossRef]
88. Figueroa, F.; Marhuenda, J.; Zafrilla, P.; Villaño, D.; Martínez-Cachá, A.; Tejada, L.; Cerdá, B.; Mulero, J. High-performance liquid chromatography-diode array detector determination and availability of phenolic compounds in 10 genotypes of walnuts. *Int. J. Food Prop.* **2017**, *20*, 1074–1084. [CrossRef]
89. Zhang, Y.Y.; Zhang, F.; Zhang, Y.S.; Thakur, K.; Zhang, J.-G.; Liu, Y.; Kan, H.; Wei, Z.-J. Mechanism of juglone-induced cell cycle arrest and apoptosis in Ishikawa human endometrial cancer cells. *J. Agric. Food Chem.* **2019**, *67*, 7378–7389. [CrossRef] [PubMed]
90. Adams, L.S.; Zhang, Y.; Seeram, N.P.; Heber, D.; Chen, S. Pomegranate ellagitannin–derived compounds exhibit antiproliferative and antiaromatase activity in breast cancer cells in vitro. *Cancer Prev. Res.* **2010**, *3*, 108–113. [CrossRef] [PubMed]
91. Zhang, Y.-G.; Kan, H.; Chen, S.-X.; Thakur, K.; Wang, S.; Zhang, J.-G.; Shang, Y.-F.; Wei, Z.-J. Comparison of phenolic compounds extracted from *Diaphragma juglandis* fructus, walnut pellicle, and flowers of *Juglans regia* using methanol, ultrasonic wave, and enzyme assisted-extraction. *Food Chem.* **2020**, *321*, 126672. [CrossRef] [PubMed]
92. Khalil, A.A.; Khan, M.R.; Shabbir, M.A. In vitro antioxidant activity and punicalagin content quantification of pomegranate peel obtained as agro-waste after juice extraction. *Pak. J. Agric. Sci.* **2018**, *55*, 197–201.
93. Pandareesh, M.D.; Chauhan, V.; Chauhan, A. Walnut supplementation in the diet reduces oxidative damage and improves antioxidant status in transgenic mouse model of Alzheimer's disease. *J. Alzheimer's Dis.* **2018**, *64*, 1295–1305. [CrossRef] [PubMed]
94. Bober, J.R.; Beisel, C.L.; Nair, N.U. Synthetic biology approaches to engineer probiotics and members of the human microbiota for biomedical applications. *Annu. Rev. Biomed. Eng.* **2018**, *20*, 277–300. [CrossRef] [PubMed]
95. Sethi, V.; Kurtom, S.; Tarique, M.; Lavania, S.; Malchiodi, Z.; Hellmund, L.; Zhang, L.; Sharma, U.; Giri, B.; Garg, B.; et al. Gut microbiota promotes tumor growth in mice by modulating immune response. *Gastroenterology* **2018**, *155*, 33–37.e6. [CrossRef] [PubMed]
96. Badimon, L.; Chagas, P.; Chiva-Blanch, G. Diet and cardiovascular disease: Effects of foods and nutrients in classical and emerging cardiovascular risk factors. *Curr. Med. Chem.* **2019**, *26*, 3639–3651. [CrossRef]
97. Bechthold, A.; Boeing, H.; Schwedhelm, C.; Hoffmann, G.; Knüppel, S.; Iqbal, K.; De Henauw, S.; Michels, N.; Devleesschauwer, B.; Schlesinger, S.; et al. Food groups and risk of coronary heart disease, stroke and heart failure: A systematic review and dose-response meta-analysis of prospective studies. *Crit. Rev. Food Sci. Nutr.* **2019**, *59*, 1071–1090. [CrossRef] [PubMed]
98. Nergiz-Ünal, R.; Kuijpers, M.J.; de Witt, S.M.; Heeneman, S.; Feijge, M.A.; Caraballo, S.C.G.; Biessen, E.A.; Haenen, G.R.; Cosemans, J.M.; Heemskerk, J.W. Atheroprotective effect of dietary walnut intake in ApoE-deficient mice: Involvement of lipids and coagulation factors. *Thromb. Res.* **2013**, *131*, 411–417. [CrossRef] [PubMed]
99. Comstock, S.S.; Gershwin, L.J.; Teuber, S.S. Effect of walnut (*Juglans regia*) polyphenolic compounds on ovalbumin-specific IgE induction in female BALB/c mice. *Ann. N. Y. Acad. Sci.* **2010**, *1190*, 58–69. [CrossRef] [PubMed]
100. Estruch, R.; Ros, E.; Salas-Salvadó, J.; Covas, M.-I.; Corella, D.; Arós, F.; Gómez-Gracia, E.; Ruiz-Gutiérrez, V.; Fiol, M.; Lapetra, J.; et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N. Engl. J. Med.* **2013**, *368*, 1279–1290. [CrossRef] [PubMed]
101. Kurihara, A.; Okamura, T.; Sugiyama, D.; Higashiyama, A.; Watanabe, M.; Okuda, N.; Kadota, A.; Miyagawa, N.; Fujiyoshi, A.; Yoshita, K.; et al. Vegetable protein intake was inversely associated with cardiovascular mortality in a 15-year follow-up study of the general Japanese population. *J. Atheroscler. Thromb.* **2019**, *26*, 198–206. [CrossRef] [PubMed]
102. Tan, B.; Wang, Y.; Zhang, X.; Sun, X. Recent studies on protective effects of walnuts against neuroinflammation. *Nutrients* **2022**, *14*, 4360. [CrossRef] [PubMed]

103. Wang, G.; Zhong, D.; Liu, H.; Yang, T.; Liang, Q.; Wang, J.; Zhang, R.; Zhang, Y. Water soluble dietary fiber from walnut meal as a prebiotic in preventing metabolic syndrome. *J. Funct. Foods* **2021**, *78*, 104358. [CrossRef]
104. Wang, J.; Du, K.; Fang, L.; Liu, C.; Min, W.; Liu, J. Evaluation of the antidiabetic activity of hydrolyzed peptides derived fromJuglans mandshuricaMaxim. fruits in insulin-resistant HepG2 cells and type 2 diabetic mice. *J. Food Biochem.* **2018**, *42*, e12518. [CrossRef]
105. Feng, L.; Wang, X.; Peng, F.; Liao, J.; Nai, Y.; Lei, H.; Li, M.; Xu, H. Walnut protein hydrolysates play a protective role on neurotoxicity induced by d-galactose and aluminum chloride in mice. *Molecules* **2018**, *23*, 2308. [CrossRef] [PubMed]
106. Croitoru, A.; Ficai, D.; Craciun, L.; Ficai, A.; Andronescu, E. Evaluation and exploitation of bioactive compounds of walnut, *Juglans Regia*. *Curr. Pharm. Des.* **2019**, *25*, 119–131. [CrossRef]
107. Chaleshtori, R.S.; Chaleshtori, F.S.; Rafieian, M. Biological characterization of Iranian walnut (*Juglans regia)* leaves. *Turk. J. Biol.* **2011**, *35*, 635–639. [CrossRef]
108. Moori Bakhtiari, N.; Khalafi, E. Antibacterial Activity of the Hydro-Alcoholic Extract of *Juglans regia* L. Stem Bark on Human Bacterial Infection. *Int. Arch. Health Sci.* **2015**, *2*, 139–143.
109. Barekat, S.; Nasirpour, A.; Keramat, J.; Dinari, M.; Meziane-Kaci, M.; Paris, C.; Desobry, S. Phytochemical composition, antimicrobial, anticancer properties, and antioxidant potential of green husk from several walnut varieties (*Juglans regia* L.). *Antioxidants* **2022**, *12*, 52. [CrossRef] [PubMed]
110. Soto-Madrid, D.; Gutiérrez-Cutiño, M.; Pozo-Martínez, J.; Zúñiga-López, M.C.; Olea-Azar, C.; Matiacevich, S. Dependence of the ripeness stage on the antioxidant and antimicrobial properties of walnut (*Juglans regia* L.) green husk extracts from industrial by-products. *Molecules* **2021**, *26*, 2878. [CrossRef] [PubMed]
111. Abedi, P.; Yaralizadeh, M.; Fatahinia, M.; Namjoyan, F.; Nezamivand-Chegini, S.; Yaralizadeh, M. Comparison of the effects of Juglans nigra green husk and clotrimazole on Candida albicans in rats. *Jundishapur J. Microbiol.* **2018**, *11*, e58151. [CrossRef]
112. Yabalak, E.; Eliuz, E.A.E. Green synthesis of walnut shell hydrochar, its antimicrobial activity and mechanism on some pathogens as a natural sanitizer. *Food Chem.* **2022**, *366*, 130608. [CrossRef] [PubMed]
113. Zhang, X.B.; Zou, C.L.; Duan, Y.X.; Wu, F.; Li, G. Activity guided isolation and modification of juglone from *Juglans regia* as potent cytotoxic agent against lung cancer cell lines. *BMC Complement. Altern. Med.* **2015**, *15*, 396. [CrossRef] [PubMed]
114. Alshatwi, A.A.; Hasan, T.N.; Shafi, G.; Syed, N.A.; Al-Assaf, A.H.; Alamri, M.S.; Al-Khalifa, A.S. Validation of the antiproliferative effects of organic extracts from the green husk of *Juglans regia* L. on PC-3 human prostate cancer cells by assessment of apoptosis-related genes. *Evid. Based Complement. Altern. Med.* **2012**, *2012*, 103026. [CrossRef] [PubMed]
115. Zhang, J.; Zhang, J.; Zhao, C.; Sui, H.; Li, C.F.; Zhong, L.; Zhou, Q.; Bai, Y.; An, S.; Du, X.; et al. Green walnut husk extracts Proliferation and Migration in Gastric Cancer. *J. Cancer* **2022**, *13*, 1130. [CrossRef] [PubMed]
116. Izadiyan, Z.; Shameli, K.; Hara, H.; Taib, S.H.M. Cytotoxicity assay of biosynthesis gold nanoparticles mediated by walnut (*Juglans regia*) green husk extract. *J. Mol. Struct.* **2018**, *1151*, 97–105. [CrossRef]
117. Dzidziguri, D.; Rukhadze, M.; Modebadze, I.; Bakuradze, E.; Kurtanidze, M.; Giqoshvili, V. The study of the immune corrective properties of greek walnut (*Juglans regia* L.) septa on the experimental model of leukopenia. *Georgian Med. News* **2016**, *252*, 84–89.
118. Raja, G.; Shaker, I.A.; Sailaja, I.; Swaminathan, R.; Babu, K.S.; Basha, S.S. Nutritional analysis of nuts extract of *Juglans regia* L. *Int. J. Bioassays* **2012**, *1*, 68–73. [CrossRef]
119. Ramishvili, L.; Gordeziani, M.; Tavdishvili, E.; Bedineishvili, N.; Dzidziguri, D.; Kotrikadze, N. The effect of extract of Greek walnut (*Juglans regia* L.) septa on some functional characteristics of erythrocytes. *Georgian Med. News* **2016**, *261*, 51–57.
120. Moravej, H.; Salehi, A.; Razavi, Z.; Moein, M.R.; Etemadfard, H.; Karami, F.; Ghahremani, F. Chemical composition and the effect of walnut hydrosol on glycemic control of patients with type 1 diabetes. *Int. J. Endocrinol. Metab.* **2016**, *14*, e34726. [CrossRef] [PubMed]
121. Ademiluyi, A.O.; Oyeleye, S.I.; Ogunsuyi, O.B.; Oboh, G. Phenolic analysis and erectogenic function of African Walnut (*Tetracarpidium conophorum*) seeds: The impact of the seed shell on biological activity. *J. Food Biochem.* **2019**, *43*, e12815. [CrossRef] [PubMed]
122. Salem, M.A.; Aborehab, N.M.; Al-Karmalawy, A.A.; Fernie, A.R.; Alseekh, S.; Ezzat, S.M. Potential valorization of edible nuts by-products: Exploring the immune-modulatory and antioxidants effects of selected nut shells extracts in relation to their metabolic profiles. *Antioxidants* **2022**, *11*, 462. [CrossRef] [PubMed]
123. Cosmulescu, S.; Trandafir, I. Anti-oxidant activities and total phenolics contents of leaf extracts from 14 cultivars of walnut (*Juglans regia* L.). *J. Hortic. Sci. Biotechnol.* **2012**, *87*, 504–508. [CrossRef]
124. Carey, A.N.; Fisher, D.R.; Joseph, J.A.; Shukitt-Hale, B. The ability of walnut extract and fatty acids to protect against the deleterious effects of oxidative stress and inflammation in hippocampal cells. *Nutr. Neurosci.* **2013**, *16*, 13–20. [CrossRef] [PubMed]
125. Hosseinzadeh, H.; Zarei, H.; Taghiabadi, E. Antinociceptive, anti-inflammatory and acute toxicity effects of *Juglans regia* L. leaves in mice. *Iran. Red Crescent Med. J.* **2011**, *13*, 27. [PubMed]
126. Simopoulos, A.P. The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomed. Pharmacother.* **2002**, *56*, 365–379. [CrossRef]
127. Shukla, P.; Chopada, K.; Sakure, A.; Hati, S. Current Trends and Applications of Food-derived Antihypertensive Peptides for the Management of Cardiovascular Disease. *Protein Pept. Lett.* **2022**, *29*, 408–428. [CrossRef]
128. Wang, F.J.; Yin, X.Y.; Regenstein, J.M.; Wang, J.Z. Separation and purification of angiotensin-I-converting enzyme (ACE) inhibitory peptides from walnuts (*Juglans regia* L.) meal. *Eur. Food Res. Technol.* **2016**, *242*, 911–918. [CrossRef]

129. Mahwasane, S.; Middleton, L.; Boaduo, N. An ethnobotanical survey of indigenous knowledge on medicinal plants used by the traditional healers of the Lwamondo area, Limpopo province, South Africa. *S. Afr. J. Bot.* **2013**, *88*, 69–75. [CrossRef]
130. Bakkalbaşı, E.; Yılmaz, Ö.; Artık, N. Physical properties and chemical composition of some walnut cultivars grown in Turkey. *Akad. Gida* **2010**, *8*, 6–12.
131. Wu, L.; Piotrowski, K.; Rau, T.; Waldmann, E.; Broedl, U.C.; Demmelmair, H.; Koletzko, B.; Stark, R.G.; Nagel, J.M.; Mantzoros, C.S.; et al. Walnut-enriched diet reduces fasting non-HDL-cholesterol and apolipoprotein B in healthy Caucasian subjects: A randomized controlled cross-over clinical trial. *Metabolism* **2014**, *63*, 382–391. [CrossRef] [PubMed]
132. Zibaeenezhad, M.J.; Shamsnia, S.J.; Khorasani, M. Walnut Consum. Hyperlipidemic Patients. *Angiology* **2005**, *56*, 581–583. [CrossRef] [PubMed]
133. Simsek, M. Chemical, mineral, and fatty acid compositions of various types of walnut (*Juglans regia* L.) in Turkey. *Bulg. Chem. Commun.* **2016**, *48*, 66–70.
134. Serrano, A.; Cofrades, S.; Ruiz-Capillas, C.; Olmedilla-Alonso, B.; Herrero-Barbudo, C.; Jiménez-Colmenero, F. Nutritional Profile of Restructured Beef Steak With Added Walnuts. *Meat Sci.* **2005**, *70*, 647–654. [CrossRef] [PubMed]
135. Dehghani, S.; Nouri, M.; Baghi, M. The effect of adding walnut green husk extract on antioxidant and antimicrobial properties of ketchup. *J. Food Bioprocess Eng.* **2019**, *2*, 93–100.
136. Fulin, Y.A.N.; Tiantian, Y.I.N. Chemical constituents and antitumor activities of walnut green husk. *Med. Plant* **2019**, *10*, 17.
137. Ros, E.; Izquierdo-Pulido, M.; Sala-Vila, A. Beneficial effects of walnut consumption on human health: Role of micronutrients. *Curr. Opin. Clin. Nutr. Metab. Care* **2018**, *21*, 498–504. [CrossRef]
138. Sadeghi-Kiakhani, M.; Tehrani-Bagha, A.R.; Gharanjig, K.; Hashemi, E. Use of pomegranate peels and walnut green husks as the green antimicrobial agents to reduce the consumption of inorganic nanoparticles on wool yarns. *J. Clean. Prod.* **2019**, *231*, 1463–1473. [CrossRef]
139. Food and Drug Administration. *Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption: What You Need to Know about the FDA Regulation: Guidance for Industry Small Entity Com-Pliance Guide*; Food and Drug Administration, Ed.; FDA: Silver Spring, MA, USA, 2017.