Section A-Research paper

Walnut Phytochemical and Biological Concerns: Narrative Review

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Abstract:

Background Walnut (Juglans Regia L.) is a nut belonging to the family Juglandaceae. In India, it is commonly known as 'Akhrot'. Walnut roots and leaves are traditionally used to treat diabetes, rheumatic pains, fever, and skin diseases; apart from it also contain several biological reported activities in diseases including cardiovascular dysfunction, cancer metabolic syndrome, and various inflammation-related pathological conditions**.**

Objective: The purpose of this review is to provide important insight into the walnut kernel's nutritional importance, traditional uses, and pharmacological potential in life-threatening diseases and to identify the gap in scientific and potential analytical opportunities for future directions on these herbs.

Method: Related informative data of this review was collected from renowned online databases namely: Science Direct, Research Gate, Scopus, PubMed, and Scientific Information Database.

Results: Omega-3 fatty acids, alpha-linolenic acid, polyphenols, flavonoids, minerals, tannins, monoterpenes, saponins, alkaloids, terpenoids, dietary fibers, and so on were identified from different parts. Moreover, a variety of traditional declarations suggested the

pharmacological utilities, and scientific confirmation of its ethnopharmacological characteristics has been well acknowledged. Reported studies suggest the plant has antidiabetic, antioxidant, antimicrobial, anticancer, anti-hypercholesterolemia, and antihypertensive properties.

Conclusion

This paper draws attention to the use of walnut kernels in a wide array of diseases and provides scientific validation. The presence of active constituents has the potential to cure various medical conditions. Furthermore, it is suggested that the plant brings promising results in reducing the risk of hyperlipidemia, diabetes mellitus, hypertension, cancer, neurodegenerative, and cardiovascular diseases. Therefore, it can be suggested that more emphasis may be laid on clinical trials to be conducted to identify molecules, information pathways, and related genes.

Keywords: Walnut, Antioxidant, Anti-inflammatory, Antidiabetic, Anticancer, Neurodegenerative, Cardioprotective.

1. Introduction:

Walnut (*Juglansregia* L.) is a nut belonging to Juglandaceae family. It is commonly known in India as 'Akhrot,' and is used to treat a variety of ailments. It is one of India's most important nut, exported to 42 countries for a profit of more than $300 million per year [1]. Walnut is single-seeded, rounded stone fruit that grow on the walnut tree. The removal of the husk after complete ripening exposes the wrinkly walnut shells, which is normally contained in two segments commercially (three-segment shells can also form). The husk will become brittle and the shell will become hard as the fruit ripens. The kernel is normally divided into two halves by a partition and is enclosed by the shell. The seed kernels, which are widely sold as shelled walnut, are encased in a brown seed coat that is high in antioxidants. Antioxidants shield the oil-rich seed from oxygen in the air, preventing rancidity [2].

Together the Persians, English, and Black Walnut are the most common walnut species grown for their seed. The English walnut (*J. regia*) comes from Persia, while the black walnut (*J. nigra*) comes from eastern North America [3]. The black walnut has a unique taste but is not commercially grown for production due to its hard shell and poor hulling characteristics [4]. There are numerous walnut species, almost all hybrids of the

English walnut, have been commercially developed. Other plants include *J. californica*, *J. cinerea* (butternut) and *J. major*, the Arizona walnut, California black walnut often used as a rootstock for commercial breeding of *J. regia*. Other sources list *Juglanscalifornica* as a southern California native and *Juglans californicahindsii*, or simply *J. hindsii*, as a northern California native; in at least one case, these are referred to as "geographic variants" rather than subspecies (Botanica) [5].

1.1. Geographical Sources: Jammu and Kashmir, Himachal Pradesh, Uttrakhand, and Arunachal Pradesh are the major producers. Jammu and Kashmir, on the other hand, is the country's leading walnut-growing province, accounting for 82 percent of total area and 92 percent of total production. Anantnag, Pulwama, Kupwara, Budgam, Baramulla, and Srinagar are the most important walnut-growing districts in Kashmir [6], while Doda, Kistwar, Poonch, and Udhampur are important in Jammu, with minor quantities in Rajouri and Kathua, with the productivity of 2.70t/ha, Kullu, Mandi, Shimla, Kinnaur, Sirmour, and Chamba are significant in Himachal Pradesh [7]. In Uttarakhand, the major rising areas are Nainital, Dehradun, Pauri, Tehri, Chamoali, Almora, and Pithoragarh, with a productivity of 1.10t/ha [6]. The major importing countries of walnut for India are Spain, Egypt, Arab Republic, Germany, Netherlands, United Kingdom, France, and Taiwan [8]**.**

1.2. Cultivation and collection: Walnuts are harvested around mid-September. The harvest season usually continues to November. Walnuts are ready to harvest when the green hulls begin to split and nuts naturally drop from the trees [9].

2. Ancient uses:

The whole plant of walnut is enriched with marvelous medicinal values specifically roots are used to cure malnutrition [1], leaves are used to treat rheumatic symptoms, fever, diabetes, and skin diseases, and flowers are used to treat malaria and rheumatic pain in herbal medicine [2]. Monounsaturated fatty acids are abundant in walnuts. Walnut's botanical composition is identical to that of the human brain, so it is classified as a brain nutrient. Many phytochemical compounds can be found in walnut [10]. Walnuts (Juglansregia L.) are rich in antioxidants such as flavonoids, phenolic acid [11] (ellagic acid), melatonin, gamma-tocopherol, and selenium and are a great source of -linolenic acid (plant-based omega-3 fatty acid) [12], [11]. Walnut came in second place among 1,113 separate food products in terms of antioxidant quality. There is a high quality of plant sterols, especially polyphenols, in addition to other constituents [13].

Walnut leaves contain phenolic acids, tannins, essential fatty acids, especially linoleic acid, ascorbic acid, flavonoids, caffeic acid, and paracomaric acid, as well as flavonoids, caffeic acid, and paracomaric acid [14]. The quercetin galactoside and quercetin pantocid derivatives, quercetin arabinoside, quercetin xyloside, and quercetin rhamnoside are the most common flavonoids found in walnut leaves [2]. Epicatechin, syringetin-o-hexoside, myricetin-3-o-glucoside, myricetin-3-o-pantocid, aesculetin, taxifolin-pantocid, jugenol quercetin glucuronide, kaempferolpantocid, and kaempferolrhamnoside are nine of the 17 compounds contained in walnut leaves [15] [16]. The existence of sugars, cardiac glycosides, phenolics, flavonoids, alkaloids, hormones, steroids, and tannin was discovered in rudimentary leaf extracts of J. regia. Phenolic compounds [17] such as 3 and 5-caffeoylquinic acid, 3 and 5-p-coumaroylquinic acid, quercetin 3-galactoside, quercetin 3-pantocide derivatives, quercetin 3-arabinoside, quercetin and quercetin 3-o-xyloside, and quercetin and quercetin 3-rhamonocide have been discovered [18] [19] .

The most important compounds present in walnut leaves and green husks are juglone and phenolic compounds [20].

Walnut bark has been reported to the certain biological properties such as biological certain biological claims to possess the anti-inflammatory [21], blood purifying, anticancer, depurative, diuretic, and laxative activities, apart from it have reported antimicrobial studies [22], antibacterial studies [23]. The combined root and stem bark show anti-helmets, astringent, and detergent properties. The additional effect of dried stem bark as a tooth cleaner or in some countries it is popular as a toothbrush and for makeup purposes as a colorant for coloring the lips, Moreover decoction of bark and leaves are used with alum for staining wool brown [23] [24].

Walnut green husk of walnut fruit contains a rich amount of caffeine, and organic materials such as citric acid, malic acid, phosphate, and calcium oxalate [25]. The two phenolic compounds that have been identified in the extract of the green husks were caffeic acid hexoside I and quercetin-3-O-deoxyhexoside -I[19]. Based on the analytical studies, the main phenolic and flavonoid compounds in walnut hull extract are the identified antioxidants; consisting of chlorogenic acid, caffeic acid, ferulic acid, sinapic acid, gallic acid, ellagic acid, protocatechuic acid, syringic acid, vanillic acid, catechin, epicatechin, myricetin and juglone [17]. In addition to the antioxidant activity, there are several reports related to the anti-inflammatory, anti-cancer, and antimicrobial benefits of walnut hull extract [14, 15],

however, one study is related to the anti-platelet aggregation activity of walnut hull extract via suppression of ROS generation and caspase activation is also reported [26].

3. Chemical composition of walnut:

Table 1:

Energy / Constituents	**Nutritional value per 100 grams**
Carbohydrates	13.71
Starch	0.06
Dietary fiber	6.7
Total Fat	65.21
Saturated fat	6.126
Monounsaturated fat	8.933
Protein	15.23
Energy	2,738 kJ (654 kcal)
Polyunsaturated fat	47.174
Vitamins	**Amount**
Vitamin A equiv.	1 µg
Beta-carotene	12 µg
lutein zeaxanthin	9 µg
Vitamin A	20 IU
Thiamine (B1)	0.341 mg
Riboflavin (B2)	0.15 mg
Niacin (B3)	1.125 mg
Pantothenic acid (B5)	0.570 mg
Vitamin B6	0.537 mg
Folate (B9)	98 µg
Vitamin E	0.7 mg
Vitamin K	2.7 µg
Vitamin B12	0 µg
Vitamin C	1.3 mg
Other constituents	**Amount**
Water	4.07
Trace metals	**Amount**
Potassium	441 mg
Magnesium	158 mg
Calcium	98 mg
Iron	2.91 mg
Sodium	2 mg
Zinc	3.09 mg
Manganese	3.414 mg
Phosphorus	346 mg

µg = micrograms; mg = milligrams; IU = International units. Percentages are roughly approximated using US recommendations for adults (Source: USDA Nutrient Database). These compounds have potential health benefit for: cancers, inflammations, cardiovascular and neurologic illnesses (Table 1) [27] .

Walnut has both saturated and unsaturated fatty acids in small concentrations. In 100 g of walnut, there are 50 grams (47.14) of multi-unsaturated fatty acids, with 40 grams (38.09 g) of Omega 6 (linoleic acid) and 10 grams (9.08 g) of Omega 3 (arachidonic acid) (linolenic acid). In comparison to other hard shell nuts, the ratio of Omega 6 to Omega 3 in walnuts is very poor [28]. Monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) are among the macronutrients found in walnuts (PUFA). Walnut kernels (Juglans regia L.) contain approximately 60% oil, but this varies depending on the growing area, and irrigation intensity [29]. **Figure 1** depicted the supposed action of various constituents of walnut kernels.

Table 2:

Chemical constituents present in green walnut husk along with the retention time

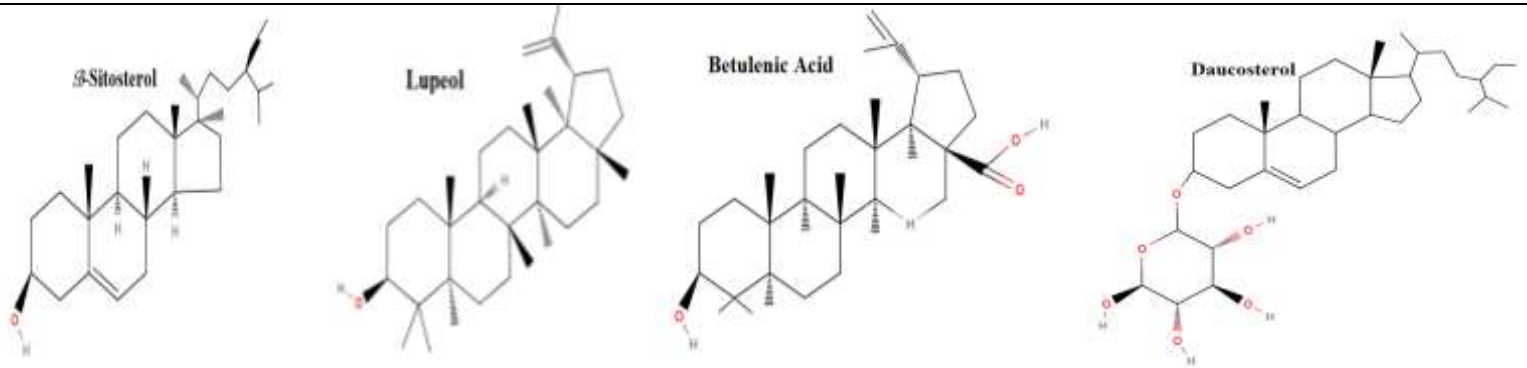
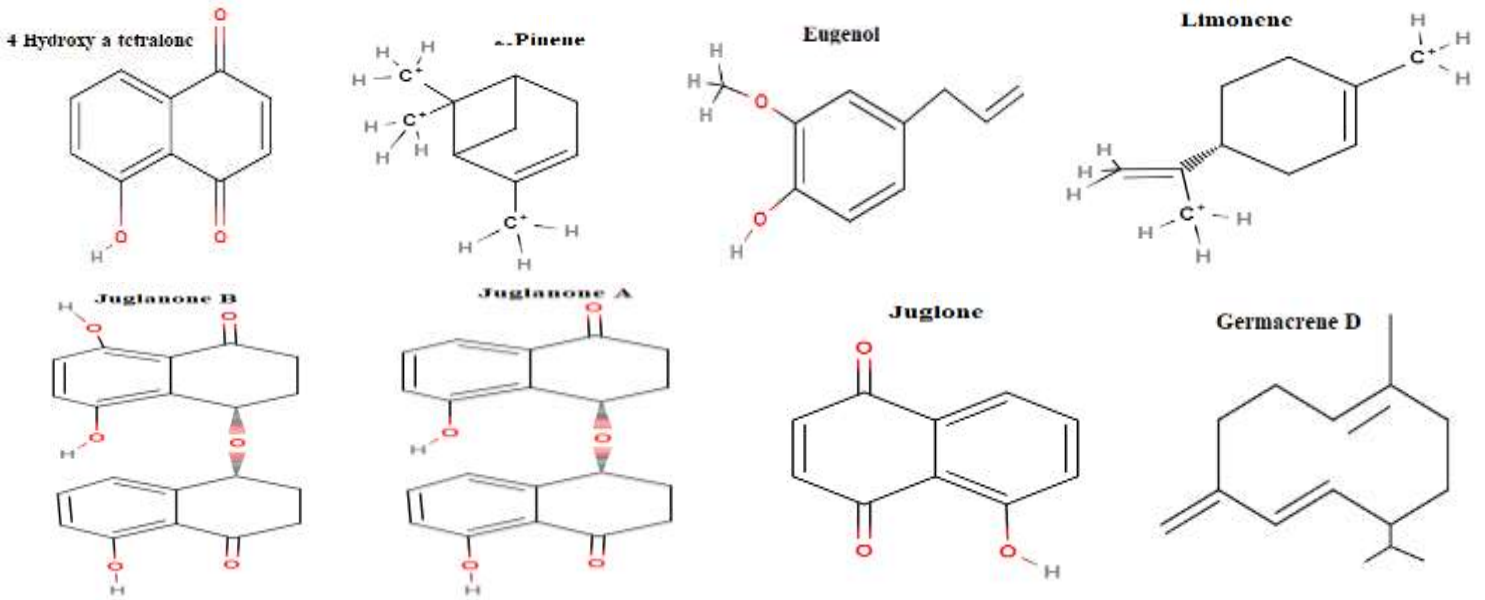
Category	Compound Name	RT*	Content	Ref
Diarylheptanoids	Juglanin A	-	0.285 ±0.001[7]	[30]
	Juglanin B	-	1.212 ±0.018[7]	[31]
	Juglanin C	-	0.139 ±0.001[7]	[31]
	Rhoiptelol	-	0.064 ±0.001[7]	[32]
	Myricananin F	-	6.8[2]	[30]
Ceramides	2-Hydroxy-tetracosanoic acid (2,3-dihydroxy-1-hydroxymethyl-heptadec-7-enyl)	-	9.3[2]	[33]
Alkanes	Octadecane	-	5.1[2]	[26]
	Docosane	7.03	0.02[8]	[26]
Steroids	β-sitosterol	-	8.5[2]	[21]
	Stigmast-5-en-3β,7α-diol	-	7.3[2]	[21]
	Stigmast-5-en-3β,7β-diol	-	7.5[2]	[30]
	Stigmasterol]	45.2 1	0.09[8]	[21]
	Daucosterol	-	5.1[b]	[26]
	Campesterol	41.0 5	0.03[h]	[33]
Triterpenoids	Oleanolic acid	-	14.4[10]	[33]
	Corosolic acid	-	8.1[2]	[34]
	Arjunolic acid	-	4.6[2]	[34]
	Ursolic acid	-	11.7[10]	[26]
	21α-Hydroxy-ursolic acid	-	0.9[10]	[34]
	2α-Hydroxyursolic acid	33	3.5[9]	[16]
	20(S)-Protopanaxadiol	-	6.4[9]	[30]
	20(S)-Protopanaxadiol-3-one	-	12.1[9]	[35]

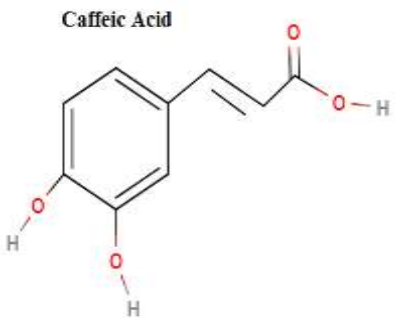
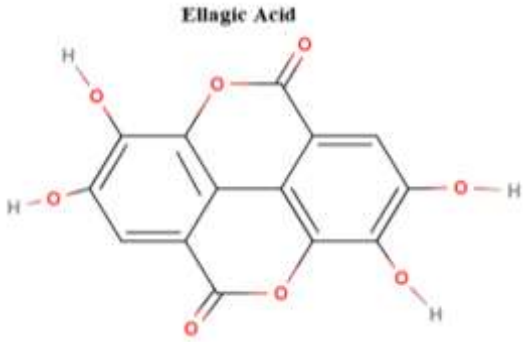
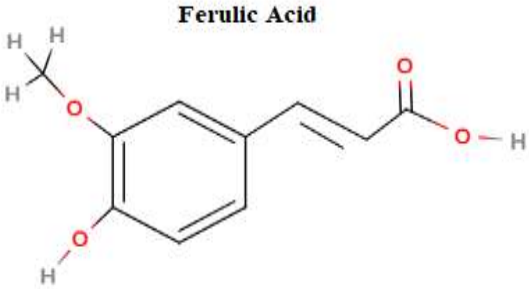
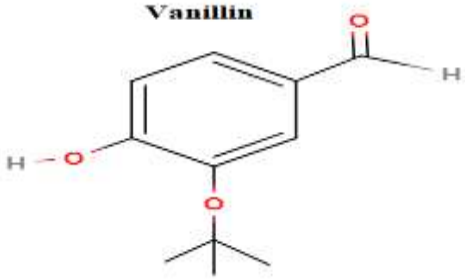
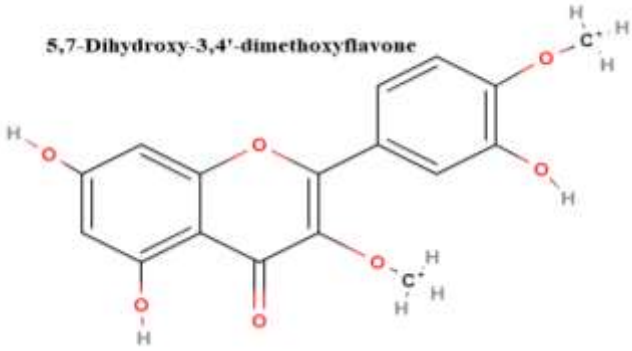
Sesquiterpenes	(+)-Dehydrovomifoliol	-	5.3[1]	[32]
	Dihydrophaseic acid	-	2.8[6]	[30]
	Blumenol A	-	1.3[5]	[36]
	Blumenol B	-	0.5[6]	[35]
Neolignans	(7S, 8R) Dihydr odehydroconife -ryl alcohol	-	2.4[6]	[35]
Vitamins	Ascorbic acid	-	5.20[11]	[36]
	α-Tocopherol	39.35	0.21[8]	[36]
Other compounds	Cyclodecasiloxane	30.5	0.19[8]	[34]
	Rhodopin	22.6	0.04[8]	[37]
	Megastigma	18.8	0.03[8]	[26]
Hydrolysable tannins	Ellagic acid	58.51	32.19±1.6[5]	[38]
	Tannic acid	-	120.4±4.19[2]	[39]
Naphthoquinones	2-Methoxy juglone	-	11.8[10]	[38]
	1-Naphthol	-	16.5±1.41[2]	[39]
	1,2-Naphatalenediol	24.84	0.011[6]	[39]
α-Tetralones	Regiolone	-	9.8[5]	[40]
	4,5-Dihydroxy-α-tetralone	-	17.2[6]	[40]
	Sclerone	-	0.8[8]	[36]
	(4S)-(+) Isosclerone	-	23.4[11]	[35]
α-Tetralone dimers	Juglanone A	-	4.9[7]	[35]
	Juglanone B	-	4.8[7]	[39]
Hydroxybenzoic acids	Benzoic acid	9.59	0.11[9]	[26]
	Gallic acid	5.25	66.72 ± 3.07[1]	[33]
	Vanillic acid	28.09	9.53 ± 0.431	[33]
	Syringol	15.38	0.11[9]	[33]
	Syringic acid	37.58	23.00 ± 1.06[1]	[41]
	Salicylic acid	52.04	186.58 ± 6.34[1]	[26]
	Protocatechuic acid	-	57.9[3]	[38]
Hydroxycinnamic acids (phenylpropanoids)	Chlorogenic acid	-	0.32 ± 0.00[3]	[26]
	Caffeic acid	30.95	2.20 ± 0.09[1]	[35]
	p-Coumaric acid	45.95	18.27 ± 0.96[1]	[26]
	Ferulic acid	49.53	24.82 ± 0.96[1]	[33]
	Trans-ferulic acid	68.63	2.74 ± 0.14[1]	[33]
	Sinapic acid	-	99.6 ± 22.3[2]	[41]
	Cilicicone b	24.3	0.2[10]	[26]
	Rosmarinic acid	-	59.5[7]	[38]
Flavonoids	(+)-Catechin	18.42	530.80 ±15.39[1]	[39]
	(−)-Epicatechin	40.39	350.33 ±11.91[1]	[26]
	Myricetin	61.56	20.76 ± 0.98	[33]
	Quercetin	70.68	8.16 ± 0.43[1]	[33]
	Sudachitin	17.7	16.7[7]	[30]
	Cirsilineol	29.1	8.2[7]	[41]

	Eriodictyol	-	3.7[4]	[26]
	Apigenin	94.2	17.5[7]	[38]
	Rutin	57.24	74.70 ± 3.43[1]	[39]

*Retention time (min), 1 mg/5.2 kg DW; 2 mg/15 kg; 3 mg, 4 mg/5.1 g; 5 mg/468.7 mg; 6 mg/321.4 mg; 7 mg/g DS; 8 peak area (%); 9 mg/10 kg; 10 mg/2.9 kg; 11 mg/100 g DW.

Table 3:- Some constituents chemical structures represented as follows

Steroidal constituents	
Essential oils	

Organic Acids	  
Phenolic Acid	 
Flavonoid	 

4. Some biological activities with previous literature outcomes are described as follows. (Figure 2)

4.1. Antioxidant and Anti-inflammatory activity

Several studies have identified the antioxidant capacity of walnut products, particularly their green fruits, and leaves to some extent bark also [11] [42]. Major cellular elements, including lipid, protein or DNA, and other biological processes altered, due to a mismatch between producing ROS and antioxidant systems, These conditions are diminished by walnut through antioxidant protection mechanism [26] [25] [43]. The highest total phenolic compound (1404 ± 23 mg Gallic acids equivalents/100 g) and antioxidant potential (191 ± 4.2 mg Trolox equivalents/g) are shown by chemical examination and identification of the bioactive compounds of peanut, nut, and pistachio varieties [4]. Recent empirical study has led to secondary metabolites in the leaves of walnut trees that produce a strong antioxidant effect [44]. Further, these reactive oxygen species initiate the various inflammatory pathways that are the roots of various mild to life threading disorders [27] [45]. Additionally dyslipidaemia [46], metabolic syndrome [47], thrombosis, type 2 diabetes [48], non-alcoholic steatohepatitis (NASH) [49], neuro-degenerative and some cardiovascular disorders [50], these are the common examples pathological body conditions. The most abundant polyphenols in walnuts are ellagitannins [51], which are hydrolyzed to release ellagic acid, which is converted by gut microflora to urolithin A and other derivatives, such as urolithins B, C, and D after consumption [52]. Ellagitannins have long been recognized for their antioxidant and anti-inflammatory properties [51] (**Figure 3**), and many studies have looked at their possible function in the prevention and development of diseases such as cancer, cardiovascular disease, and neurodegenerative disease [53]. Inflammatory cells also synthesize inflammatory mediators including arachidonic acid metabolites, cytokines, and chemokines, which attract more inflammatory cells to the site of damage and produce more reactive species [54].

- **Proposed mechanism of antioxidant and anti-inflammatory activity**

Oxidative stress is the main or key initiative for any serious pathological condition; it can further initiate the various molecular mechanism that can damage the firstly to the cells and further destroy the complete organ in a severe condition. The process of damage starts from the imbalance between the ROS and scavengers the level of oxidative stress arises; it can promote the irregular activities of the cell. Walnut has excellent potential to mask the changes, promoted by the ROS, it walnut extracts have been tested in vitro assay systems

such as the FRAP and the ORAC and shown to exhibit substantial antioxidant activity [55]. It helps to recover the antioxidant levels and potentiate the Nrf_2–EpRE pathway that further initiates the transcription factor Nrf_2, a major regulator of antioxidant and cellular protective genes, which are expressed in the cytoplasm of cells and is usually associated with Keap-1, a repressor protein. The accumulation of Nrf2 allows the binding of this protein to the antioxidant response element of genes that code antioxidant proteins. HO-1 is the inducible isoform that enzymatic degradation of pro-inflammatory free heme, as well as the production of anti-inflammatory compounds such as CO and bilirubin, plays major roles in maintaining the protective effects of HO-1, further decreases the levels of cytokines TNF-α, IL-1, IL-6, chemokines, cytokines, and adhesion molecules ICAM-1, VCAM, ELAM, moreover decreases the pro-inflammatory enzymes like COX-2, MMP-9 and iNOS factors that play a central role in inflammatory diseases of infectious or non-infectious origin.

4.2. Antidiabetic activity

Several studies have reported that certain herbal plants have beneficial efficacy in the treatment of diabetics [56]. More than 1200 medicinal plants have been shown to have a beneficial impact on lowering blood glucose levels or reducing diabetic problems [57]. Diabetes mellitus is the third leading cause of death worldwide due to its fatal complications [58]. While insulin is the most popular way to treat diabetes, dietary approaches to diabetes care are very successful in developed countries [59]. Several experiments have shown that the chemical compound juglone has anti-diabetic properties [16]. In Iranian herbal medicine, walnut leaves and fleshy green fruits are used as hypoglycaemic agents. Previous research has shown that infusing walnut and olive leaves with water lowers blood glucose levels in diabetic patients. In another study, walnut leaf infusion was shown to be beneficial in reducing blood glucose levels in diabetic patients [60]. In this group of type 2 diabetics, an ad libitum diet enriched with 56 g of walnuts a day for 8 weeks significantly increased endothelial function [61]. The administration of walnut leaf extract to diabetic rats resulted in a substantial reduction in blood glucose levels and a reduction in diabetes symptoms [62]. The administration of a hydroalcoholic extract and methanolic extract of walnut leaves and walnut barks to a STZ -induced diabetic rats caused improvements in the pancreatic functions improved insulin levels and reduce glucose levels in STZ-induced diabetic rats [63]. Moreover, Flavonoids such as quercetin improve insulin secretion, and they also prevent the aggregation of sorbitol in body tissues [64]. Flavonoids have a beneficial effect because they inhibit permeability and capillary rupture within cells; boost the immune system.

- **Proposed mechanism of Antidiabetic activity.**

It increased the phosphorylation levels of insulin receptor substrate 1 (IRS-1), phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt), AMPK, and GSK3β, and up-regulated the expression levels of GS and glucose transporter type 4 (GLUT4) [34]. These findings suggested that LPLLR exerts an anti-diabetic effect by increasing glycogen synthesis and glucose uptake, as well as decreasing gluconeogenesis. In addition, the peptide LPLLR possesses good stability under in vitro simulated gastrointestinal digestion, and the low molecular weight (610.4 Da) of LPLLRmay be beneficial for its intestinal absorption. Nevertheless, more in-depth in vivo investigation is needed to explore the stability and absorption of LPLLR. Subsequently, in high glucose-induced, IR and oxidative stress in HepG2 cells, three novel peptides, namely Leu-Val-Arg- Leu (LVRL), Leu-Arg-Tyr-Leu (LRYL), and Val-LeuLeu-Ala-Leu- Val-Leu-Leu-Arg (VLLALVLLR) from J. mandshurica at 12.5–100 μM, significantly improve glucose consumption, glucose uptake, GLUT4 translocation, and elevated the phosphorylation of IRS-1, PI3K, and Akt. The activities of GSH-Px, CAT, and SOD, the nuclear transport of Nrf2, and the protein expression of HO-1 were also increased. Furthermore, these peptides reduced high glucose-induced ROS overproduction and the phosphorylation of ERK, JNK, and p38 (Wang et al., 2020b). These results suggested that peptides from J. mandshurica could protect HepG2 cells from high glucose-induced IR and oxidative stress by activating IRS-1/PI3K/Akt and Nrf2/HO-1 signaling pathways.

4.3. Anti-hyperlipidemic Activity

Long-term use of walnuts as part of a regular diet improved plasma lipid profiles. Including walnuts in the diet at a rate of 12% of total daily energy consumption over a period of 12 months reduced average cholesterol and triglyceride levels without altering the usual diet [65]. The benefits of walnuts were more noticeable in participants with elevated overall cholesterol levels at the start of the study. In free-living persons fortified with walnuts, total cholesterol and triglyceride concentrations were significantly lower as opposed to a habitual diet, even after controlling body weight [66]. LDL-c was also decreased in a walnut-supplemented diet after balancing for body weight. In a four-week crossover trial, replacing 40% of the fat in the mediterranean diet with walnuts, almonds, or pure olive oil resulted in lower total cholesterol, medium density lipoprotein cholesterol (LDL-c), and low density lipoprotein cholesterol/high density lipoprotein cholesterol (LDL-c/HDL-c), However, no changes were observed in high density lipoprotein cholesterol concentrations [67]. These

findings are in line with previous research showing that walnut consumption increased endothelial function in hypercholesteraemic adults and reversed postprandial endothelial dysfunction caused by a high-fat diet [13]. In non-diabetic rats with elevated cholesterol, dose-dependent intake of Persian walnut oil extract lowers triglyceride, cholesterol, and low density lipoprotein cholesterol [20][53]. Moreover, it is rich in unsaturated fatty acids. It is especially rich in linoleic (57%-76%) plus linolenic acids (2%-16%) have shown that linolenic acid can perhaps reduce TG levels [68]. This influence of walnuts may be a secondary mechanism involved in preventing the development of vascular plaques. Walnut administration changed the distribution of lipids in various lipoprotein types, and walnut consumption is possibly associated with anti-atherogenic effects [31]. Low concentrations of adiponectin have been linked to obesity and visceral fat accumulation. When opposed to butter and olive oil-enriched meals, a walnut-enriched meal increased postprandial adiponectin response in healthy young adults [69]. This was followed by lower postprandial gene expression of tumor necrosis factor alpha (TNF-α) and interleukin (IL)-6 in overweight and visceral fat deposition [70].

4.4. Anticancer activity

Flavonoids are primarily found in walnut leaves. Flavonoids have antioxidant effects and are active in the modulation of immune function as well as an improvement in the body's anticancer activities [43]. Ellagitannins and their metabolites suppress cancer cell development in a variety of ways, including cell cycle arrest and apoptosis stimulation [71][72][51]. Polyphenols have anticancer properties through a variety of pathways, including the elimination of carcinogenic agents' pro-oxidative effects [73]. In vitro tumor forms, uro-A, juglone, juglanin, and walnut-extracted peptides, show unquestionable antitumor activity. Uro-A was cytotoxic on ER- the cell line (MDA-MB231) [31] [74], suggesting an estrogen-independent mode of action, promotion of apoptosis, and regulation of enzymatic activities [10] [35]. Juglone demonstrated far greater cytotoxic activity than tamoxifen, the gold standard treatment for ER breast cancer therapy, on MCF-7 cells and cell cycle progression [73][69]. Polyphenols have also been shown to function on several targets in pathways such as inflammation (INF), angiogenesis, and drug and radiation tolerance. The impact of walnut polyphenols on cancer prevention has been researched extensively [57] [75][67].

Proposed mechanism of cancer

The previous reports suggested that juglone has been inhibitory growth effects mainly blocking the S phase of the cell cycle on HCT-15 cells cultured, derived from human colon carcinoma [76]. Juglone induces apoptosis in HL-60 human leukemia cells, SGC-7901 human gastric cancer cells, and SKOV3 ovarian cancer cells through mitochondrial-dependent apoptosis pathways and the elevated ratio of Bax/Bcl-2. The anti-cancer activity on LNCaP human prostate cancer cells indicated that juglone may be a potential candidate drug for androgen-sensitive prostate cancer. The cytotoxic effect of juglone on human breast cancer cell line MCF-7 is characterized by elevated ROS levels, reduced Bcl-2 expression, increased Bax expression, decreased mitochondrial membrane potential, increased intracellular Ca^{2+} concentration, outer mitochondrial-membrane rupture, cytochrome c release, and caspase-3 activation. According to a recent study, juglone significantly inhibits the proliferation and induces the apoptosis of human bladder carcinoma cell lines (TCC-SUB and RT-4).

4.4.1. Prostate Cancer: Prostate cancer is the second most often diagnosed cancer in men and the sixth most common cause of cancer mortality. The androgen receptor, which is necessary for the production and progression of prostate carcinogenesis, is a key target in prostate cancer research. In many models, walnut extracts and ellagitannins have been linked to inhibiting prostate cancer cell proliferation and inducing apoptosis [77]. The development of prostate cancer xenografts developing in male nude mice was affected by a walnut-enriched diet. The walnut-enriched diet was observed to decrease the number of tumors and the development of LNCaP xenografts (lymph nodes carcinoma of the prostate)[78].

4.4.2. Breast Cancer: Walnut intake decreased tumor frequency, number of tumors per rodent, and tumor size substantially. The walnut diet altered the expression of various genes involved in mammary epithelial cell proliferation and differentiation, according to gene expression review [79].

4.4.3. Colon Cancer: Walnuts have also been found to slow the development of colorectal cancer by inhibiting angiogenesis [80]. Several kinds of research have shown that foods high in ellagitannins can help prevent colon cancer. Walnut leaves, green husks, and seed extracts inhibited the development of human kidney and colon cancer cells in a concentration-dependent manner [43].

4.5. Cardiovascular activity

Most nuts tend to be nutritious, but some such as walnuts can have more heart-healthy nutrients than others. Walnuts contain omega 3 fatty acids, which tend to help keep the heart healthy. The administration of walnut leaf aqueous extract was found to lower systolic, diastolic, and mean arterial pressure as compared to a test group [81]. Walnut and walnut oil intake can have a protective effect against CVD by raising HDL-C and apo A-1 levels in the blood [82]. Manipulation of the diet to reduce the risk of heart disease could be simpler, less expensive, and more desirable to those at risk, potentially delaying or reducing the need for pharmacologic interventions [83]. The effects of walnut leaf aqueous extract on rat aortic segments were investigated, and it was found that blood pressure and adrenaline-induced contraction in isolated aortas were both decreased. The relaxant effects of the extract on the muscles of arterial walls are thought to be responsible for the lower blood pressure [84]. The one study reported nuts improves endothelial markers involved in blood pressure control in hypertensive women and study conclude that nuts control or lowering BP among hypertensive women and it can be observed by modification in serum NO/ET-1 as well as ET-1 receptors expression induced by these nutritional interventions [82]. Walnut intake of about 21–91 g/day has been linked to a decrease in cardiovascular disease risk factors in both short and long-term studies. As a result, walnut intake can be linked to a lower risk of cardiovascular disease by improving lipid profile [85].

Proposed mechanism of cardiovascular activity

Injury to the myocardium initiates signaling pathways that trigger the activation of cFbs to myofibroblasts (MyoFbs). Loss of structural integrity via cardiomyocyte (CM) death also creates mechanical stress that mediates cFb to MyoFb activation. Consequences of MyoFb activation vary between repair and disease processes. There are multiple mechanisms for activation, including mechanical stimuli and paracrine factors, such as transforming growth factor- β (TGF- β) and angiotensin II (Ang II), from a variety of different sources, such as CMs and the cFbs themselves. TGF- β is an important cytokine involved in many different cellular processes, including proliferation, differentiation, and migration.[77] Its expression is altered by several stimuli, such as mechanical stretch, hormones, and cytokines. In the heart, it is the driving force for myofibroblast activation and is therefore crucial during injury and wound healing IL- 6 is a cytokine involved in processes of differentiation, growth, and survival [86].

4.6. Neurodegenerative activity:

Walnuts, which are high in omega fatty acids, have been shown in animal and human studies to enhance memory, perception, and neural effects due to oxidative stress (OS) and INF. The current research discovered that feeding 19-month-old rats a walnut diet containing 6-9 percent walnuts decreased polyubiquitinated protein aggregation and stimulated autophagy, a neuronal housekeeping feature [87], in the striatum and hippocampus. Autophagy was up-regulated in walnut-fed animals by inhibiting phosphorylation of mammalian target of rapamycin (mTOR), up-regulating gene sequences ATG7 and Beclin 1, and increasing MAP1BLC3 protein turnover [88].

Walnuts are high in antioxidants like vitamin E [89] and calcium/magnesium, which can reduce neurotoxicity caused by anticancer drugs like cisplatin without affecting their anti-tumor action. As a Monoamine oxidase inhibitor with antioxidant activity, the polyphenol-rich aqueous walnut extract (JSE) preserved dopaminergic neurons from MPP+ or MPTP-induced neurotoxicity in the current research [90]. JSE also prevented striatal dopamine and its metabolites from being depleted. Not only in the aging phase and Alzheimer's disease but also in other neurological disorders such as Parkinson's disease (PD), schizophrenia, bipolar disorder, amnesia [91], and autism, oxidative stress and inflammation are believed to play a role. Walnut extract preserved neurons, inhibited oxidative stress, and increased PD symptoms, such as muscle synchronization, postural equilibrium, and movement, in a mouse model of Parkinson's disease [92]. Walnut peptides significantly attenuated the expression of proinflammatory cytokines including IL-6, IL-1β, and TNF-α as well as the level of acetylcholinesterase (AChE) and remarkably restored the antioxidant enzyme levels [93]; in comparison with the control group, the expression of NF-κB was reduced in the hippocampus of AD mice treated with walnut peptides and it works a memory enchaining remedy for brain [94]. Walnut consumption improved memory in a scopolamine-induced amnesia model in rodents, which may be due to AChE suppression in the brain. Walnut protein hydrolysate has been shown to improve scopolamine-induced learning and memory deficits in mice by raising acetylcholine receptor numbers and up-regulating choline acetyltransferase (ChAT) mRNA expression [95]. Walnut-enriched diets were found to improve cholinergic production in the striatum of aged rats by enhancing ACh production or inhibiting AChE.Walnut protein hydrolysate has been shown to improve scopolamine-induced learning and memory deficits in mice by raising acetylcholine receptor numbers and up-regulating choline acetyltransferase (ChAT) mRNA expression. Walnut-enriched diets were found to improve cholinergic

production in the striatum of aged rats by enhancing ACh production or inhibiting AChE [96]. **Figure 4** depicts several possible neuroprotective mechanisms of action.

Proposed mechanism of Neuroprotection activity

Oxidative stress can easily lead to Aβ accumulation, which induces reactive oxygen species (ROS) generation, leading to mitochondrial morphological and functional damage, causing neurotoxicity in the brain [87]. A variety of signaling pathways regulates cell proliferation, cell growth, cell motility, and cell survival, such as AMP kinase (AMPK) and mammalian target of serine/ threonine protein kinase rapamycin (mTOR). Among them, Akt/mTOR is one of the typical autophagy regulation pathways [97]**.** Walnut decreased intracellular ROS levels, which regulated phosphorylation of ERK1/2, p38, JNK, Akt, and mTOR, resulting in the upregulation of autophagic proteins such as ATG5 and LC3-II, followed by increased autophagy formation, autophagy could restrain neurotoxicity by inhibiting ROS generation

5. CONCLUSION:

This paper brings attention to the use of walnut kernels in a variety of diseases and offers statistical support for their use. Apart from having the potential to cure various medical conditions due to the existence of active constituents such as coumarin, tannins, monoterpenes, saponins, flavonoids, alkaloids, terpenoids, and other elements. Furthermore, the plant is said to have positive findings in lowering the risk of hyperlipidemia, diabetes, asthma, cancer, neurodegenerative diseases, and cardiovascular diseases. As a result, more focus may be placed on identifying molecules, information channels, and associated genes in clinical trials.

6. CONSENT FOR THE PUBLICATION- Not applicable (No Animals/Humans were used for studies that are the basis of this research).

7. CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Abbreviations	**Full Forms**
FRAP	Ferric reducing antioxidant power
ORAC	Oxygen radical antioxidant activity
ER	Estrogen receptors
MUFA	Monounsaturated fatty acids
PUFA	Polyunsaturated fatty acids
Nrf_2	Nuclear factor erythroid 2–related factor 2
NQO-1	NADPH: quinone acceptor oxidoreductases-1

Graphical Abstract

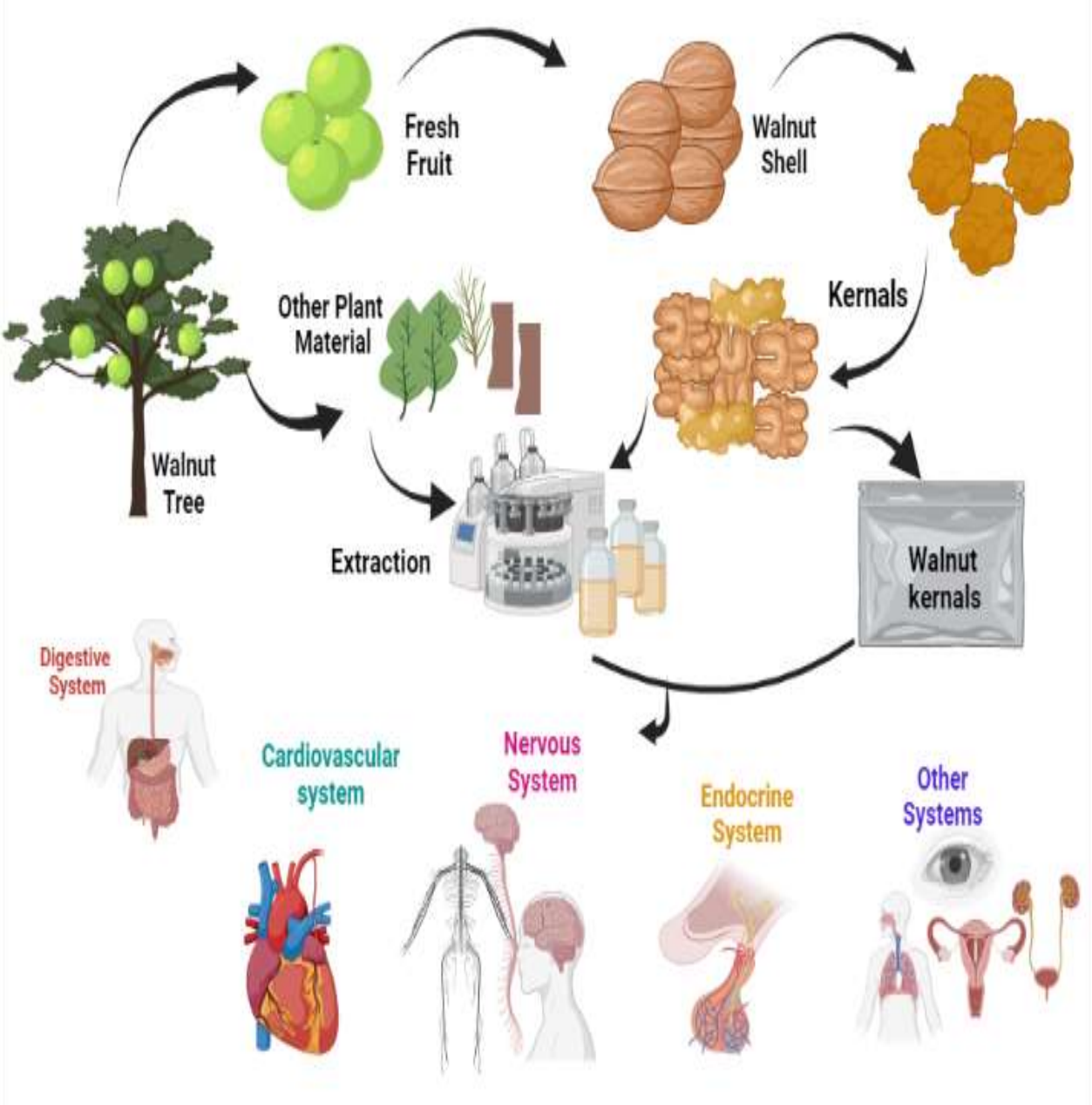
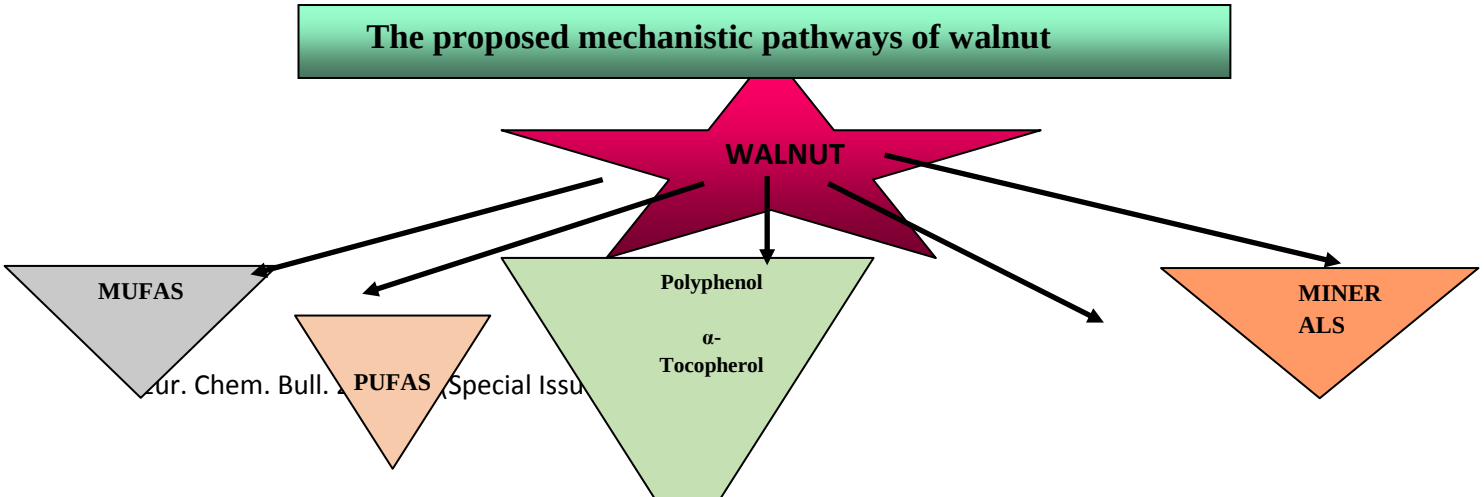

Fresh Fruit
Walnut Shell
Other Plant Material
Kernals
Walnut Tree
Extraction
Walnut kernals
Digestive System
Cardiovascular system
Nervous System
Endocrine System
Other Systems

Figure No: - 1


The proposed mechanistic pathways of walnut
WALNUT
MUFAS
PUFAS
Polyphenol
α-
Tocopherol
MINER
ALS

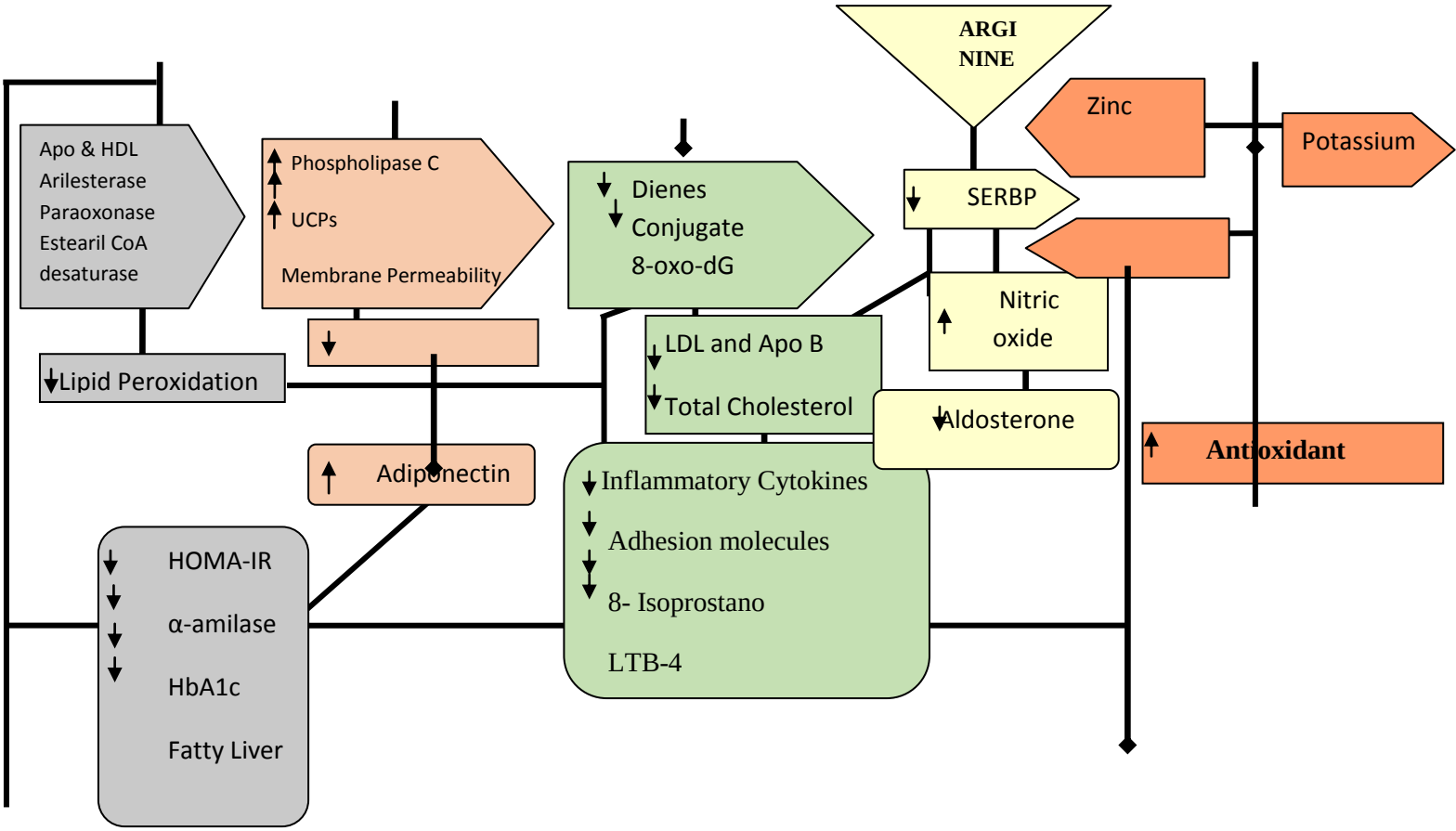

ARGI
NINE
Zinc
Potassium
Apo & HDL
Arilesterase
Paraoxonase
Estearil CoA
desaturase
Phospholipase C
UCPs
Membrane Permeability
Dienes
Conjugate
8-oxo-dG
SERBP
Nitric
oxide
Lipid Peroxidation
LDL and Apo B
Total Cholesterol
Aldosterone
Antioxidant
Adiponectin
Inflammatory Cytokines
Adhesion molecules
8- Isoprostano
LTB-4
HOMA-IR
α-amilase
HbA1c
Fatty Liver

Figure No:-2

Reported Pharmacological Activity of Walnut

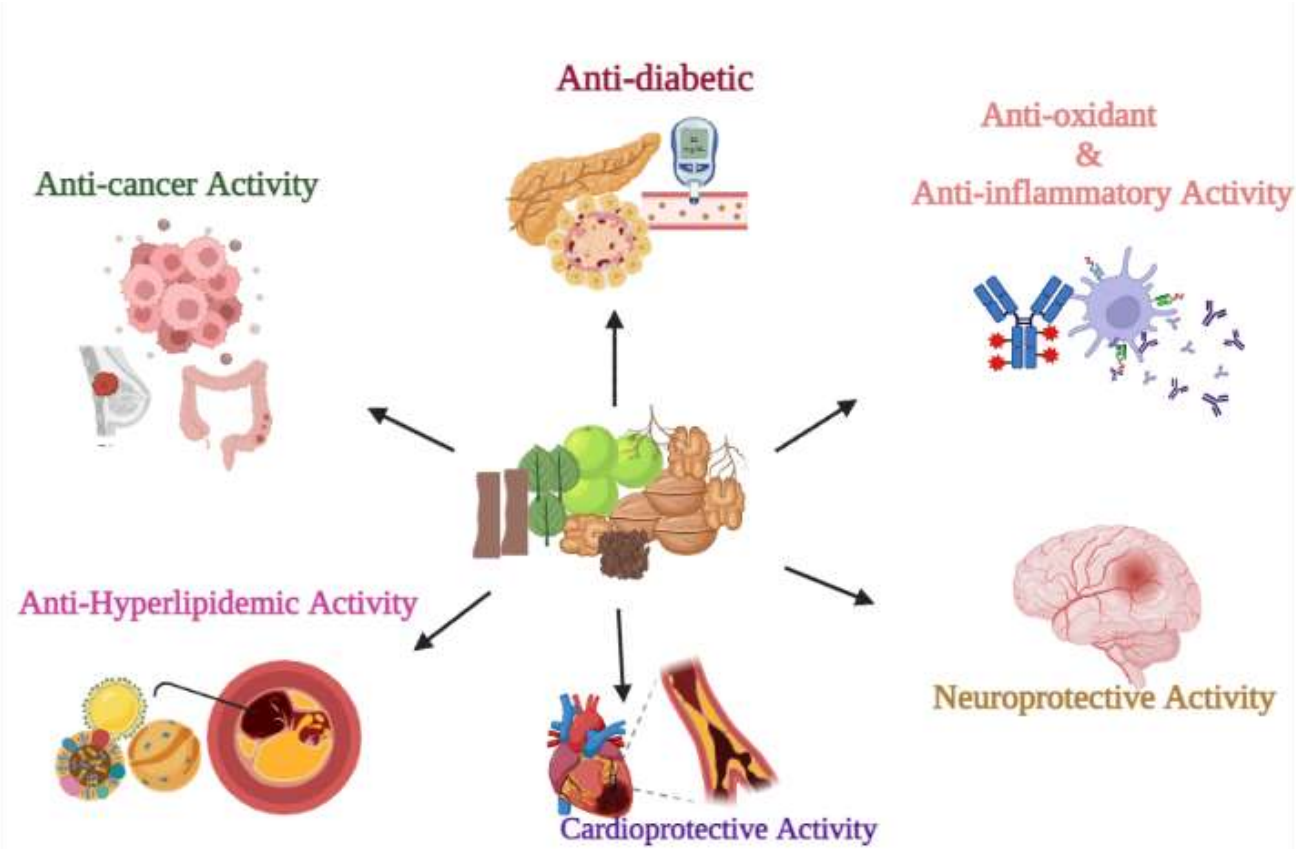


Figure No:-3

Proposed mechanistic study of walnut in inflammation and oxidative

Antioxidant effects
ROS
Free radical
Scavengers
(SOD, CAT, GPx,

Cytokines
TNF-α
IL-1
IL-6

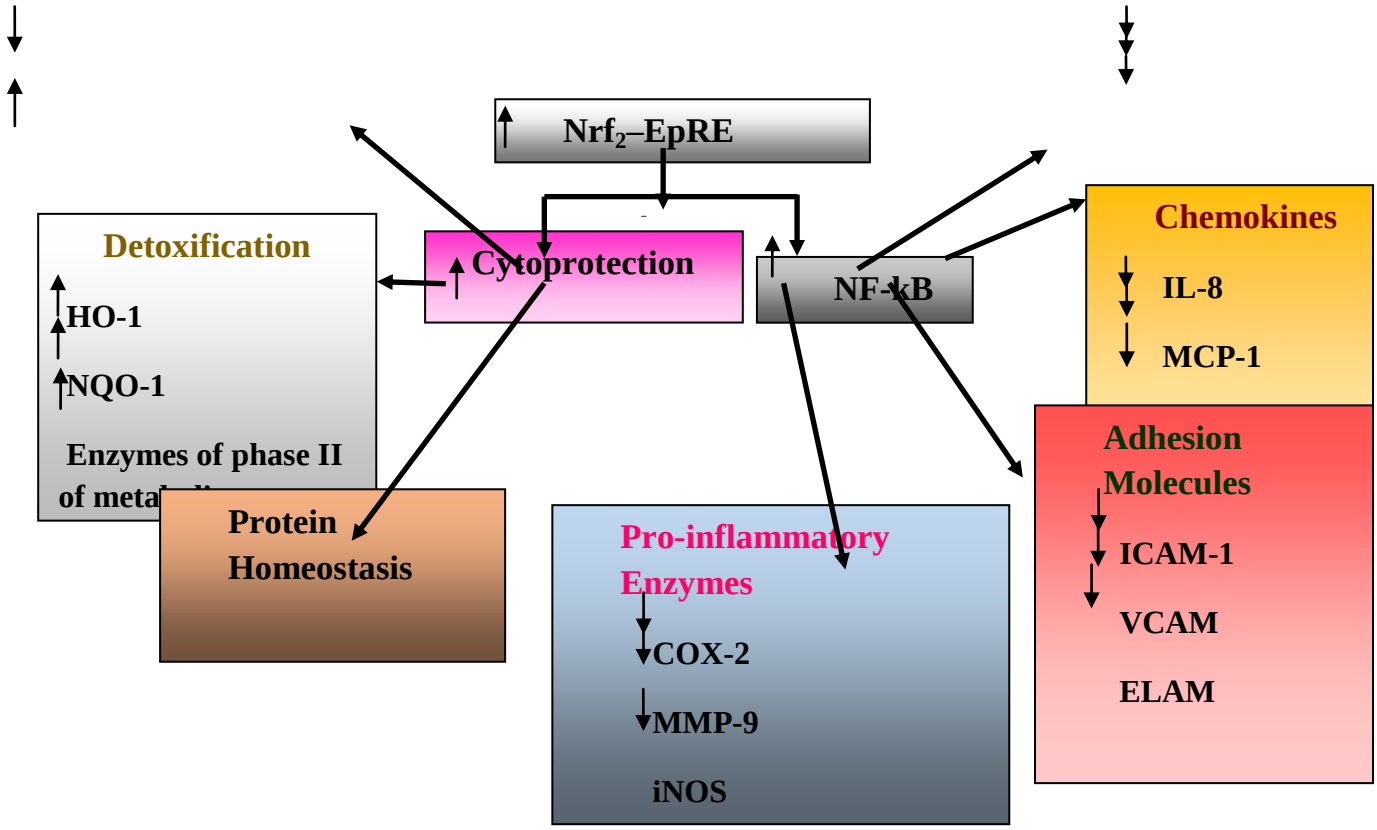
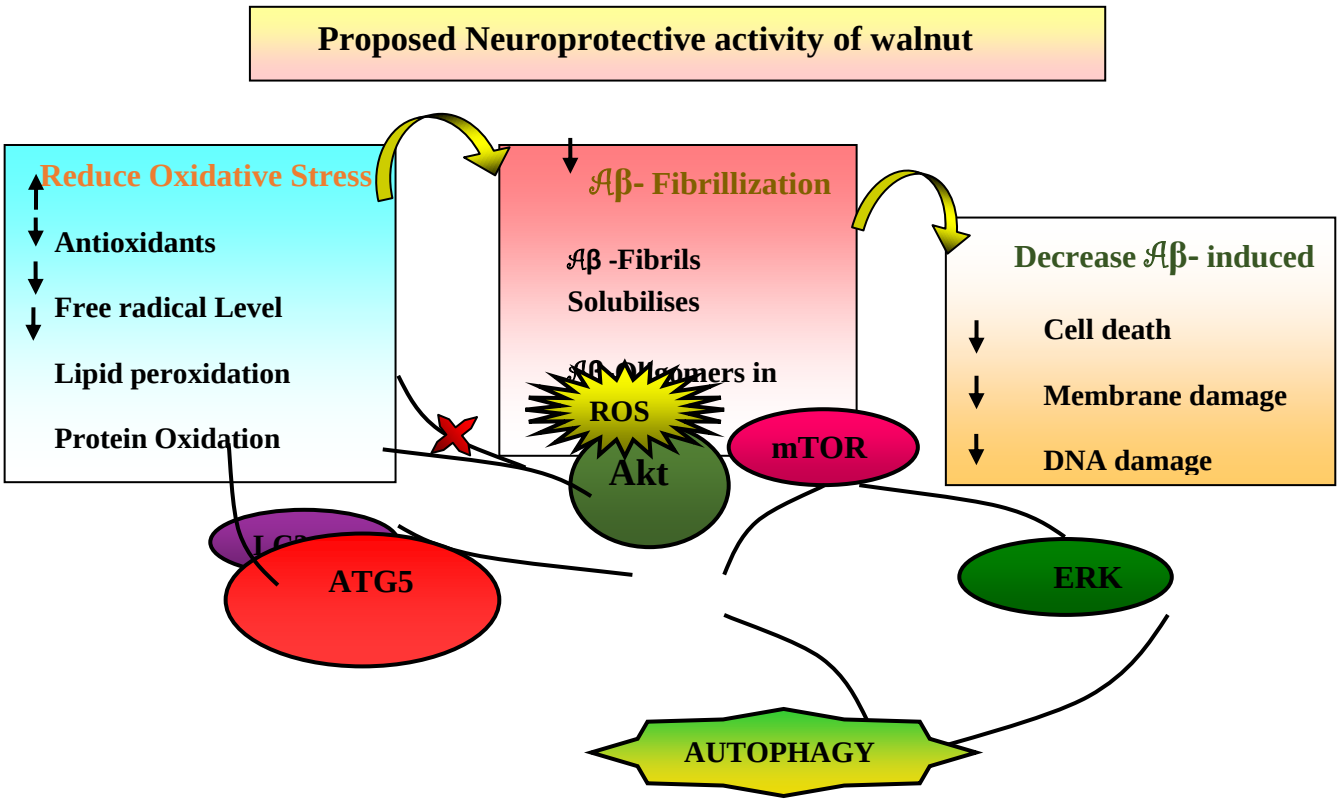

Nrf2–EpRE
Detoxification
HO-1
NQO-1
Enzymes of phase II
Cytoprotection
NF-kB
Chemokines
IL-8
MCP-1
Adhesion Molecules
ICAM-1
VCAM
ELAM
Protein Homeostasis
Pro-inflammatory Enzymes
COX-2
MMP-9
iNOS

Figure No:-4


Proposed Neuroprotective activity of walnut
Reduce Oxidative Stress
Antioxidants
Free radical Level
Lipid peroxidation
Protein Oxidation
Aβ- Fibrillization
Aβ -Fibrils
Solubilises
ROS
Akt
mTOR
ATG5
ERK
AUTOPHAGY
Decrease Aβ- induced
Cell death
Membrane damage
DNA damage