Therapeutic Effects of Walnuts (Juglans L.): Insights From Randomized Controlled Trials

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Abstract

Background: This review elucidates the multifaceted therapeutic effects of Juglans L. (J.), a medicinal plant with a rich heritage in traditional medicine and promising potential in modern healthcare.

Methods: A narrative review was conducted focusing on randomized clinical trials (RCTs) published between 2000 and 2023. A comprehensive literature search was performed in databases including PubMed, Scopus, ClinicalKey, Google Scholar, and the Persian Scientific Information Database. The keywords "Juglans" and "J." were used. Only human RCTs evaluating various parts of the plant (fruit, leaves, bark, internal septum) were included. Non-human and non-randomized studies were excluded.

Results: The findings reveal that while some trials report significant health benefits of J., others show minimal or no effects, suggesting the importance of personalized approaches in clinical application.

Conclusion: This review underscores the growing role of herbal medicine in preventive care and as a complement to standard treatments. Further studies are needed to clarify its mechanisms of action, determine optimal dosing, and evaluate long-term safety and efficacy. As global interest in natural remedies rises, J. stands out as a promising candidate in both preventive and therapeutic contexts

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Introduction

The use of medicinal plants for the treatment of diseases is a practice dating back thousands of years (1). People around the world use these plants to treat various conditions, harnessing their natural compounds for health benefits and the development of new drugs (2). Because medicinal plants are considered potential sources of new drugs with fewer side effects, numerous studies have recently been conducted on their therapeutic effects and mechanisms of action (3, 4).

One example of the traditional use of plants resulting in the production of chemical drugs is Galega officinalis L. Over the years, people discovered that using Galega reduces polyuria in diabetic patients (5). Consequently, metformin was developed from this plant (6).

One of the most well-known herbal products, due to its various therapeutic effects in traditional medicine, is the walnut plant with the scientific name Juglans L. (J.), which belongs to the Juglandaceae family (7). J. is widely distributed around the world (8). The plant contains different compounds depending on the location where it grows and the specific part of the plant used. These include phenolic acids, tannins, essential fatty acids, ascorbic acid, flavonoids, malic acid, phosphate, calcium, etc. (9, 10).

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It has been shown that these various components of J. possess multiple therapeutic properties (11). In traditional medicine, the roots of J. are used to reduce blood glucose in diabetic patients. Moreover, its leaves are also used to treat diabetes, rheumatic pain, fever, and skin diseases (12–15). Furthermore, the plant has demonstrated anti-inflammatory, antiviral, antimicrobial, and antifungal activities (14–19).

Accordingly, over the past two decades, many studies (especially animal studies) have been conducted to evaluate some of the aforementioned therapeutic effects of the leaves, fruits, internal septum, and bark of J. (20–22). Based on these animal studies, several human studies have also investigated the therapeutic effects of J. To the best of our knowledge, there is no narrative review specifically focused on randomized controlled trials evaluating the therapeutic effects of J. in humans. Therefore, the present study aims to briefly review the therapeutic effects of J. as reported in human clinical trials.

Methods

This research is a narrative review of randomized clinical trials (RCTs) conducted between 2000 and 2023, investigating the therapeutic effects of various parts of Juglans (J.). To review the relevant literature, articles were identified through searches in several databases, including ClinicalKey, Scopus, PubMed, and Google Scholar (in English), as well as Persian electronic databases such as the Scientific Information Database (SID), using the keywords Juglans and J. Relevant articles published in Persian scientific journals were also included.

Results

Anti-Diabetic Effects

Diabetes is one of the most prevalent chronic diseases, posing a significant economic burden worldwide due to its associated comorbidities. Despite the availability of a wide range of anti-diabetic agents, their effectiveness in adequately controlling diabetes and its complications remains limited. Additionally, the long-term use of these medications can lead to adverse effects. Consequently, there is a growing demand for the development of new therapeutic agents that are more effective and have fewer side effects (23).

In recent years, the use of herbal medicines for treating diabetes has increased, driven by their perceived equal or superior efficacy and lower incidence of side effects (24). The anti-diabetic properties of various parts of the J. plant (such as the whole fruit, bark, leaves, and internal septum) have been demonstrated in numerous animal studies (25–28). Different components of J. (e.g., flavonoids, alkaloids, methanolic extracts, and other phenolic compounds such as gallic acid and caffeoylquinic acid) exert anti-diabetic effects through diverse pharmacological mechanisms. For instance, quercetin, a flavonoid abundant in the leaves and internal septum of J., has been shown to stimulate insulin secretion and inhibit intracellular sorbitol accumulation. The anti-diabetic activity of flavonoids is thought to stem from their ability to reduce vascular permeability, prevent capillary rupture, and enhance the immune system. Methanolic extracts may also promote the proliferation of pancreatic β-cells, increase insulin secretion, and reduce blood glucose levels (22, 29). Moreover, it has been proposed that J. can interfere with carbohydrate absorption in the small intestine (30). Building on these findings, several human studies have been conducted to evaluate the anti-diabetic effects of J. Clinical studies conducted on the anti-diabetic and antioxidant effects of Juglans L. are summarized in Table 1.

-Leaves

In a randomized controlled trial (RCT) by Hosseini et al., a significant reduction in both hemoglobin A1c (HbA1c) and fasting blood sugar (FBS) levels was observed after two months of administering 200 mg of aqueous J. leaf extract twice daily to 58 patients aged between 40 and 65 years. A significant increase in insulin levels was also reported. In contrast, these improvements were not observed in the placebo group (7).

In another RCT by Abdoli et al., significant reductions in FBS, postprandial glucose (PPG), and HbA1c levels were noted following the administration of 250 mg of aqueous J. leaf extract three times daily for three months to 37 patients with type 2 diabetes, aged between 35 and 70 years (31).

However, not all studies have reported positive outcomes. In a double-blind, placebo-controlled clinical trial by Rabiei et al., administration of 200 mg/day of J. leaf extract for eight weeks did not result in significant changes in FBS, PPG, or HbA1c levels Interestingly, a significant improvement in PPG and HbA1c was observed in the placebo group among 39 patients with type 2 diabetes, aged between 30 and 80 years ($p = 0.030$ and $p = 0.028$, respectively) (23).

-Whole Fruit

In a randomized controlled crossover trial conducted by Ying et al., no significant changes in glycemic indices such as HbA1c, serum insulin levels, or insulin resistance were observed after administering 56 g of whole J. Regia fruit

daily for eight weeks to 24 patients with type 2 diabetes aged between 30 and 75 years (32). Similarly, in another crossover RCT by Katz et al., no significant changes were found in FBS, fasting insulin levels, or the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) after prescribing 56 g of J. fruit daily for eight weeks as part of a J. -enriched diet in 46 overweight patients aged between 30 and 75 years (33).

-Internal Septum

In a more recent study evaluating the anti-diabetic effects of J. internal septum extract, administration of 500 mg capsules three times daily did not lead to significant improvements in FBS, HbA1c, insulin levels, or HOMA-IR in 60 patients with type 2 diabetes aged between 25 and 70 years (34).

Table 1. Characteristics of the studies conducted on the anti-diabetic and antioxidant effects of Juglans L.

Authors (No.)/ Year	Part(s) used	Control group	Sample size/ Population	Dose/ Duration	Outcomes
Anti-Diabetic Effects					
Hosseini et al. (7)/ 2014	Leaves (Aqueous extract)	Placebo	58/ DM II	200 mg twice daily/ 2 months	***Mean±SD*:*** **HbA_1c:** 7.6±1.3 % after treatment *vs*. 8.5±1.% at baseline, p=0.000; **FBS:** 144±65 mg/dL after treatment *vs*. 165±54mg/dl at baseline, p=0.017; **Insulin level:** 10.4±4.7 U/L after treatment *vs*. 8.6±4.2 U/L at baseline, p= 0.007.
Abdoli et al. (31)/ 2017	Leaves (Aqueous extract)	Placebo	37/ DM II	250 mg three times daily/ 3 months	***Change from the baseline (mean±SD):*** **FPG:** 17.5±32.2 mg/dl in *J.* group *vs*. -3.9±42 mg/dl in control group, CI95%= 2 to 33.1, p=0.029; **PPG:** 48±59.7 mg/dl in *J.* group *vs*. 13.8±89.1 mg/dl in control group, CI95%= 14.9 to 81, p=0.008; **HbA_1c**: 0.9±1.2% in *J.* group *vs*. 0.3±1% in control group, CI95%= 0.3 to 1.5, p=0.003.
Rabiei et al. (23) /2018	Leaves (Hydroalcoholic extract)	Placebo	39/ DM II	200 mg daily / 8 weeks	***Mean±SD*:*** **FBS:** 179.5 ± 49.0 mg/dl after treatment *vs.* 191.7 ± 36.6 mg/dl at the baseline, p=0.309; **PPG:** 307.7 ± 99.0 mg/dl after treatment *vs.* 283.2 ± 46.8 mg/dl at the baseline, p=0.249; **HbA_1c:** 9.5 ± 1.8% after treatment *vs.* 9.6 ± 1.1% at the baseline, p=0.646; **HOMA-IR:** 2.9 ± 2.2 after treatment *vs.* 3.3 ± 2.7 at the baseline, p=0.186.
Ying et al. (32) /2010	Whole fruit	Ad Libitum Diet without *J.*	24/ DM II	56 g daily/ 8 weeks with an 8-week wash-out period.	***Change from the baseline (mean±SD):*** **FBS:** +10.0 ± 20.5 mg/dl and 2.9 ± 21.5 mg/dl in *J.* and control group, respectively, p=0.27; **HbA_1c**: -0.0±0.3% decrease compared to the baseline in both groups, p=0.85; **Insulin level:** +3.6 ± 10.4 mIU/ml and -3.4 ± 8.0 mIU/ml in *J.* and control group, respectively, p=0.02; **Insulin resistance:** +0.2 ± 0.9 and -0.2 ± 0.7 in *J.* and control group, respectively, p=0.10.
Katz et al. (33)/ 2012	Whole fruit	Ad Libitum Diet without *J.*	46/ Overweight adults	56 g daily/ 8 weeks with a 4-week washout period.	***Change from the baseline (mean±SD):*** **FBS:** -0.2±8.8 mg/dl and -1.5 ± 6.8 mg/dl in diet with *J.* and control group, respectively, p=0.457; **Insulin level:** -0.3±19.6mIU/ml and -1.7 ± 6.6 mIU/ml in diet with *J.* and control group, respectively, p=0.626; **OMA-IR:** -0.5±5.7 and -0.3 ± 1.8 in diet with *J.* and control group, respectively, p=0.81).
Afra et al. (34)/ 2023	Internal septum	Placebo	60/ DM II	1.5 g daily/ 12 weeks.	***Adjusted for baseline Pre-treatment outcome and Potential Covariates (mean±SD):*** **FBS:** 144.09 ± 4.90 mg/dl and 148.08 ± 4.99 mg/dl in *J.* and control group, respectively, p=0.58; **HbA1c:** 7.60 ± 0.15 % and 7.58 ± 0.15 % in *J.* and control group, respectively, p=0.93; **Insulin level:** 9.38 ± 0.64 mIU/ml and 8.38 ± 0.64 mIU/ml in *J.* and control group, respectively, p=0.28; **HOMA-IR**: 3.33 ± 0.28 and 3.18 ± 0.28 ml in *J.* and control group, respectively, p=0.70.
Antioxidant Effects and Endothelial Function					
McKay et al. (40)/ 2010	Whole fruit	-	21/ Healthy individuals	21 or 42 g daily/ 6 weeks with a 6-week washout period.	***Change from the baseline (mean±SD):*** **ORAC:** 2.3 ± 16.4% in 21g/d group, 5.6 ± 15.5% in 42g/d group, p=0.435; **FRAP:** -3.1 ± 10.6 % in 21g/d group, -0.8 ± 12.1 % in 42g/d group, p=0.503; **MDA:** 8.2 ± 40.6 % in 21g/d group, 2.1 ± 27.9 % in 42g/d group, p=0.522; **Total thiol:** -2.2 ± 13.2 % in 21g/d group, 1.8 ± 32.2 % in 42g/d group, p=0.680; **Total phenol:** -2.0 ± 7.0 % in 21g/d group, -2.0 ± 5.9% in 42g/d group, p=0.995; **GPX:** -1.3 ± 7.8 % in 21g/d group, -2.4 ± 7.5 % in 42g/d group, p=0.646.

Table 1. Continued

Berryman et al. (39)/ 2013	Whole fruit, skins, fat-free nutmeat, and oil[#]	-	15/ Healthy obese with mild hypercho-lesterolemia	4-week periods with at least one-week wash-out period.	***Change from the baseline (mean±SEM):*** **RHI:** -0.09 ± 0.09 in nutmeat, 0.07 ± 0.09 in oil, -0.26 6 ±.09 in skin, -0.19 ± 0.09 in whole fruit, *p*=0.01; **fRHI:** -0.02 ± 0.07 in nutmeat, 0.09 ± 0.07 in oil, -0.14 ± 0.07 in skin, -0.14 ± 0.07 in whole fruit, *p*=0.01.
Ying et al. (32)/ 2010	Whole fruit	Ad Libitum Diet without *J.*	24/ DM II	56 g daily/ 8 weeks with an 8-week wash-out period.	***Change from the baseline (mean±SD):*** **FMD:** 2.2 ±1.7% in *J.*-enriched diet, 1.2 ± 1.6 % in Ad Libitum Diet without *J.,* *p*=0.04.
Katz et al. (33)/ 2012	Whole fruit	Ad Libitum Diet without *J.*	46/ Over-weight adults	56 g daily/ 8 weeks with a 4-week wash-out period.	***Change from the baseline (mean±SD):*** **FMD:** 1.4±2.4% in *J.* enriched diet compared to 0.3±1.5%, treatment effect (95%CI) =1.1 (0.2, 2.0), *p*=0.019.
West et al. (41)/ 2010	Whole fruit	AAD	20/ Hypercho-lesterolemic patients	AAD, LA, ALA/ 6 weeks[γ]	***Mean±SD:*** **FMD (*change from baseline*):** 8.2 ± 1.0% in ALA diet *vs*. 6.1 ± 1.1% in AAD, *p*=0.02; 6.7 ± 1.05 in LA diet *vs*. 6.1 ± 1.1% in AAD, *p*=0.66; **Endothelin-1:** 1.9 ± 0.2 pg/mL in ALA diet *vs*. 2.0 ± 0.2 pg/mL in AAD, *p*=0.89; 1.7 ± 0.2 pg/mL in LA diet *vs*. 2.0 ± 0.2 pg/mL in AAD, *p*=0.38; **AVP:** 9.7 ± 0.4 pg/mL in ALA diet *vs*. 8.3 ± 0.4 pg/mL in AAD, *p*=0.04; 9.1 ± 0.4 pg/mL in LA diet *vs*. 8.3 ± 0.4 pg/mL in AAD, *p*=0.36.
Ros et al. (42)/ 2004	Whole fruit	Mediterra-nean-type diet	21/ hypercho-lesterolemic patients	*J.* consuming in diet (40-65 g)/ 4 weeks	***Mean±SD:*** **EDV:** 5.9±3.3% in *j.* diet *vs*. 3.6±3.3 in control group, *p*=0.043; **EIDV:** 12.2±4.3% in *j.* diet *vs*. 12.5±5.0 in control group, *p*>0.1; **VCAM-1:** 378±149 µmol/L in *j.* diet *vs*. 465±229 µmol/L at the baseline, *p*=0.045).

*The data of the J. group were reported in this table.

Whole fruit:85 g, skins: 5.6 g, fat-free nutmeat: 34 g, and oil: 51 g.

γ AAD: 8.7% energy of PUFA, LA: 16.4% energy of PUFA from J. and its oil, ALA: 17% energy of PUFA from J. and its oil, and flax oil for six weeks for each period.

§ Intervention group: banana bread with J. (385kcal); control group: banana bread without j. (287 kcal).

AAD: Average American Diet; ALA:Alpha-Linolenic Acid; AVP:Arginine Vasopressin; CI:Confidence Interval; EDV: Endothelium-Dependent Vasodilation; EIDV: Endothelium-Independent Vasodilation; FBS:Fasting Blood Sugar; FPG:Fasting Plasma Glucose; FRAP:Ferric Reducing Antioxidant Power; Frhi:Framingham Reactive Hyperemia Index; FMD:Flow-Mediated Dilation; GPX: Glutathione Peroxidase; Hba1c:Hemoglobin A1c; HOMA-IR:Homeostatic Model Assessment For Insulin Resistance; J.:Juglanse; LA: Linoleic Acid; MDA: Malondialdehyde; ORAC:Oxygen Radical Absorbance Capacity; PPG:Post Prandial Glucose; PUFA:Polyunsaturated Fatty Acids; RHI:Reactive Hyperemia Index; SD:Standard Deviation; VCAM-1: Vascular Cell Adhesion Molecule-1.

Overall, the available evidence suggests that certain parts and extracts of J. may improve glycemic indices in diabetic patients. However, the outcomes vary depending on the plant part used, the active compounds involved, the study design, and characteristics of the target population. This variability underscores the need for personalized approaches (e.g., individual patient factors, preferences, and broader lifestyle considerations) to dietary and therapeutic interventions. It also highlights the importance of further research to clarify these effects, understand the underlying mechanisms, and establish standardized guidelines for the use of J. in diabetes management.

Antioxidant Effects and Endothelial Function

Among all medicinal plants, J. is reported to have one of the highest antioxidant activities. Several in vitro and in vivo studies have indicated that polyphenols in J. can prevent the oxidation of plasma low-density lipoprotein (LDL) cholesterol and reduce oxidative stress (35–37).

Different parts of J., including its fruits, leaves, and whole nuts, have been shown to possess antioxidant properties. These antioxidant activities help regulate the balance between the production of reactive oxygen species (ROS) and the body's antioxidant capacity. Such properties are attributed to compounds like vitamin C, polyphenols, and others present in J. fruits and leaves, which contribute to neutralizing free radicals and protecting cell membranes (22).

Furthermore, nuts (particularly J.) are rich in alpha-linolenic acid (ALA) and linoleic acid (LA), two types of polyunsaturated fatty acids (PUFAs). Previous studies have shown that these unsaturated fatty acids can reduce the risk of cardiovascular diseases. In addition, J. is rich in phenolic antioxidants and tocopherols, which may improve endothelial function and enhance anti-atherogenic properties. While ALA and LA are highly prone to oxidation, they are naturally protected by the tocopherols and phenolic compounds present in J. (35, 38).

-Whole Fruit, Skin, Nutmeat, and Oil

Berryman et al. conducted a crossover study investigating the acute effects of J. and its components on postprandial lipemia, endothelial function, oxidative stress, and

cholesterol efflux in 15 healthy obese individuals with mild hypercholesterolemia, aged between 21 and 60 years. The study found that 240 minutes after consuming 85 g of whole fruit, 5.6 g of skin, 34 g of nutmeat, or 51 g of oil, the FRAP response varied depending on the treatment. Fat-free nutmeat consumption tended to lower the average FRAP level ($p = 0.054$), a statistically significant difference compared to the oil and skin treatments. However, no significant effects were observed on plasma total thiols or MDA levels for either treatment or treatment-time interactions. Interestingly, treatment had a significant effect on both the reactive hyperemia index (RHI) and the Framingham reactive hyperemia index (fRHI) ($p = 0.01$ for both). The skin treatment group showed a reduction in RHI from baseline ($p = 0.02$), which was significantly different from the oil group. For fRHI, although no change from baseline was observed, the oil treatment differed significantly from both the skin and whole nut treatments ($p = 0.02$ for both) (39).

-Whole Fruit

In a randomized crossover pilot study conducted by McKay et al., 21 healthy participants aged 50 years and older consumed either 21 g/day or 42 g/day of J. whole fruit over six weeks. The study found that oxygen radical absorbance capacity (ORAC), ORAC with protein precipitation by perchloric acid (ORAC-pca), and ferric reducing antioxidant power (FRAP) levels were higher in the group receiving the higher dose. Conversely, levels of malondialdehyde (MDA), a biomarker of lipid peroxidation, were lower. However, none of these changes have reached statistical significance. Additionally, total plasma thiols, total phenols, and glutathione peroxidase (GPX) levels did not significantly change over the course of the study. Interestingly, within one hour of consuming J., total plasma thiol levels increased regardless of dose, both at baseline and at the end of each intervention phase. Both doses also led to increased levels of plasma pyridoxal phosphate (PLP) after six weeks, with increases of 19.0% and 16.2% for 21 g/day and 42 g/day, respectively. However, only the higher dose showed a statistically significant improvement from baseline ($p = 0.045$). Furthermore, both doses led to an increase in red blood cell LA and ALA levels, with a significant increase in LA observed for the 42 g/day dose (40).

As mentioned earlier, the study by Ying et al. demonstrated that consumption of a J.-enriched diet improved vascular endothelial function in diabetic patients. Flow-mediated vasodilation (FMD) significantly improved when participants consumed the J. -enriched diet compared to a control diet without J. (32). Similarly, Katz et al. reported that FMD of the brachial artery significantly improved after eight weeks of consuming a J. -rich diet (mean difference between groups [95% CI]: 1.1% [0.2, 2.0]) (33).

A randomized crossover study by West et al. investigated the effects of J. - and flax oil-rich diets on hemodynamic responses to stress and vascular endothelial function in 20 hypercholesterolemic patients. The study compared three diets: a standard American diet (control), a diet rich in LA, and a diet rich in ALA. Since J. is a rich source of both ALA and LA, it was included as a representative source. The ALA-rich diet improved FMD by 34% compared to the control group ($p < 0.05$), increased arginine vasopressin by 20%, and had no significant effect on endothelin-1 levels (41).

In another randomized crossover study, Ros et al. found that consuming J. whole fruits for four weeks in 21 hypercholesterolemic patients aged between 26 and 75 years significantly increased endothelium-dependent vasodilation and decreased vascular cell adhesion molecule-1 (VCAM-1) levels (42). Details of all these studies are summarized in Table 1.

Collectively, these studies suggest that J. consumption may positively impact cardiovascular health, particularly through improvements in endothelial function. The most notable benefits appear in individuals at higher risk for cardiovascular disease (CVD). However, the magnitude and clinical significance of these effects vary. Future research should aim to clarify the long-term impacts of J., determine the most responsive populations, and establish evidence-based guidelines for its inclusion in cardioprotective diets.

Cognitive Improvement Effects

Vegetables, fruits, and essential fatty acids derived from nuts and fish have been found to possess significant neuroprotective effects (43, 44). J. is a nut rich in LA and ALA. ALA serves as a precursor to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA plays a crucial role in maintaining neuronal membrane stability, influencing gene expression, enhancing synaptic plasticity and neuroplasticity, supporting cell migration, and inducing apoptosis. It also boosts signal transduction speed, enhances neurotransmission, and increases levels of serotonin and dopamine. EPA is involved in the regulation of arachidonic acid synthesis and plays a vital role in modulating key inflammatory and immune responses (45–48).

Additionally, J. contains other neuroprotective compounds, including vitamin E, folate, melatonin, and various antioxidant polyphenols (46). These compounds have demonstrated neuroprotective effects in previous animal studies (49). Based on such findings, several human clinical trials have been conducted to explore the neuroprotective potential of J. Table 2 summarizes the

interventional clinical studies conducted on the cognitive effects and lipid-lowering effects of Juglans L.

-Whole Fruit

In a study by Pribis and colleagues investigating the effects of J. whole fruit on cognitive performance (including verbal and non-verbal reasoning, memory, and mood) in 64 college students aged between 18 and 25 years, it was found that there were no significant improvements in mood, non-verbal reasoning, or memory after eight weeks. However, inferential verbal reasoning significantly improved in the J. group (50).

In another RCT conducted by Sala-Vila et al., 636 older adults aged between 63 and 79 years consumed 30–60 g of J. whole fruit daily for two years. While no significant effects on overall cognitive function were observed in healthy elderly individuals, radiographic findings and post hoc analyses suggested that J. may help delay cognitive decline in certain high-risk subgroups (51).

Based on these studies, a J.-enriched diet appears to offer some cognitive benefits, particularly improvements in verbal reasoning among young adults and a possible protective effect against cognitive decline in specific older adult subgroups. However, the overall benefits may be limited and context-dependent. Given the current limited evidence, further research is warranted to explore these nuances and provide more targeted, evidence-based dietary recommendations.

Table 2. Characteristics of the studies conducted on the cognitive effects and lipid-lowering effects of Juglans L.

Authors (No.)/ Year	Part(s) used	Control group	Sample size/ Population	Dose/Duration	Outcomes
Cognitive Improvement Effects					
Pribis et al. (50)/ 2012	Whole fruit	Placebo	64/ College students	Intervention group:385kcal; control group:287 kcal)[§]/ 8 weeks with a 6-week wash-out period.	***Mean(95%CI):*** **Inferential verbal reasoning:** 9.9 (8·9, 10·7) in *j.* group *vs*. 8.9 (8·0, 9·8) in placebo group, p=0.009,d=0.567. **General memory** (mean(95%CI)): 62.9 (60.1, 65.6) in *j.* group *vs*. 64.2 (61.5, 67.0) in placebo group, p=0.288. **Total mood score:** 33.5 (24.7, 42.3) in *j.* group *vs*. 37.9 (29.1, 46.6) in placebo group, p=0.267.
Sala-Vila et al. (51)/ 2020	Whole fruit	*J.* abstention	636/ Geriatrics	30-60 g/day / 2years	***Mean change(95%CI):*** **Global Cognition:** −0.069 (−0.097, −0.040) in *j.* group *vs*. −0.089 (−0.118, −0.060) in control group, p=0.334 (Adjusted by ANCOVA).
Lipid-Lowering Effects					
Berryman et al. (39)/ 2013	Whole fruit, skins, fat-free nutmeat, and oil	-	15/ Healthy obese with mild hypercholesterolemia	Whole fruit, skins, fat-free nutmeat, and oil[#]/ four-period with at least one-week wash-out period.	**Change in TG:** was higher following oil (p< 0.01) and whole nut ($p \leq 0.03$) treatments *vs*. skin. At 120 minutes, TG response to oil was greater than to nutmeat (p = 0.02). Significant treatment-time point interaction led to an 89% reduction in postprandial TG AUC for the skins *vs.* oil and whole nut (p < 0.01).
Murad et al. (59)/ 2015	Whole fruit	Without *J.*	40/ hyper-lipidemic individuals	30 g daily/eight weeks	***Mean±SEM *:*** **HDL:** 38.11±1.54 mg/dl after treatment *vs*. 31.80±1.65 mg/dl at the baseline, p=<0.01.
Iwamoto et al. (60)/ 2000	Whole fruit	Average Japanese Diet	40/Japanese individuals	43 to 57g daily/ 4 weeks	***Estimated difference in diet effects (CI95%):*** **Total cholesterol:** -0.16 (-0.83–0.65) mmol/L in men *vs*. -0.21 (-1.03–0.28) mmol/L in women, p<0.05 and p<0.01, respectively. **LDL:** -0.18 (-0.88–0.41) mmol/L in men *vs*. -0.22 (-0.69–0.13) mmol/L in women, p=NS and p<0.01, respectively. **ApoB:** -51 (-240–90) mg/L in men *vs*. -78 (-190–50) mg/L in women, p<0.05 and p<0.01, respectively.
Zibaeenezhad et al. (62)/ 2003	Oil	Placebo	60/ Hyper-lipidemic individuals	3 g daily/ 45 days	**TG:** 461 and 439 mg/dl after 45 and 60 days, respectively *vs*. 527 mg/dl at the baseline, p< 0.05. **Total cholesterol:** 269 and 269 mg/dl after 45 and 60 days, respectively *vs*. 287 mg/dl at the baseline, p>0.05. **LDL:** 173 and 175 mg/dl after 45 and 60 days, respectively *vs*. 184 mg/dl at the baseline, p>0.05. **HDL:** 38 and 39 mg/dl after 45 and 60 days, respectively *vs*. 36 mg/dl at the baseline, p>0.05.

Table 2. Continued

Ros et al. (38)/ 2004	Whole fruit	Mediterranean-type Diet	21/ Hypercholesterolemic individuals	*J.* consuming in diet (40-65 g)/ 4weeks	***Mean±SD:*** **TG:** 1.43±0.77 mmol/L in *J.* group *vs*. 1.32±0.64mmol/L in control group, *p*>0.1. **Total cholesterol:** 6.43±0.69 mmol/L in *J.* group *vs*. 6.72±0.51 mmol/L in control group, *p*=0.017. **LDL:** 4.33±0.47 mmol/L in *J.* group *vs*. 4.64±0.46 mmol/L in control group, *p*=0.010. **HDL:** 1.57±0.44 mmol/L in *J.* group *vs*. 1.59±0.40 mmol/L in control group, *p*>0.1.
Ashraf et al. (61)/ 2020	Whole fruit	-	90/ hyper-lipidemic individuals	25 or 50 g daily/ 56 days	**For 25 and 50g daily, respectively (*mean±SD*): TG:** 147.3 ± 50.6 and 131.7 ± 25.5 mg/dl *vs*. 204.3 ± 40.0 mg/dl in control group, *p*<0.001. **Total cholesterol:** 159.6 ± 25.2 and 144.7 ± 15.2 mg/dl *vs*. 203.3 ± 26 mg/dl in control group, *p*=0.003. **LDL:** 129.3 ± 47.9 and 118.3 ± 13.2 mg/dl *vs*. 177.4 ± 19.8 mg/dl in control group, *p*<0.001. **HDL:** 60.9 ± 5.3 and 71.2 ± 5.1 mg/dl *vs*. 46.0 ± 8.9 mg/dl in control group, *p*=0.000.
Rabiei et al. (23)/ 2018	Leaves (Hydro-alcoholic extract)	Placebo	39/ DM II	200 mg daily / 8 weeks	***Mean±SD*:*** **TG:** 170.6 ± 81.9 mg/dl after treatment *vs*. 179.7 ± 86.1 mg/dl at the baseline, *p*=0.622. **Total cholesterol:** 169.0 ± 30.5 mg/dl after treatment *vs*. 176.5 ± 41.8 mg/dl at the baseline, *p*=0.413. **LDL:** 83.5 ± 16.0 mg/dl after treatment *vs*. 93.2 ± 31.6 mg/dl at the baseline, *p*=0.151. **HDL:** 51.1 ± 9.1 mg/dl after treatment *vs*. 49.0 ± 9.3 mg/dl at the baseline, *p*=0.337.
Katz et al. (33)/ 2012	Whole fruit	Ad Libitum Diet without *J.*	46/ Overweight adults	56 g daily/ 8 weeks with a 4-week wash-out period	***Change from the baseline (mean±SD):*** **TG:** -4.5 ± 42.0 mg/dl in *J.* diet *vs*. 4.3 ±44.9 mg/dl in control diet, *p*=0.325. **Total cholesterol:** -0.5 ±23.2 mg/dl in *J.* diet *vs*. 0.3 ±21.6 mg/dl in control diet, *p*=0.696. **LDL:** 0.4 ± 22.9 mg/dl in *J.* diet *vs*. -0.4 ±20.0 mg/dl in control diet, *p*=0.981. **HDL:** -0.1 ± 6.5 mg/dl in *J.* diet *vs*. -0.2 ±6.2 mg/dl in control diet, *p*=0.889.
Spaccarotella et al. (63)/ 2008	Whole fruit	AAD	21/ Healthy men	75 g daily/ 8 weeks with a two-week wash-out period	***Change in J. group vs. AAD, respectively (mean±SEM):*** **TG:** 1.00 ± 1.00 mmol/L *vs*. 1.00 ± 1.00 mmol/L, *p*=0.48. **Total cholesterol:** -0.18 ± 0.12 mmol/L *vs*. -0.02 ± 0.12 mmol/L, *p*=0.13. **LDL:** -0.10 ± 0.13 mmol/L *vs*. 0.03 ± 0.13 mmol/L, *p*=0.21. **HDL:** -0.05 ± 0.04 mmol/L *vs*. -0.04 ± 0.04 mmol/L, *p*=0.95.
Mirshekari et al. (64)/ 2023	Internal septum	Placebo	60/ Hypercholesterolemic patients	1.5 g daily/ 12 weeks	***Mean±SD:*** **TG:** 133 ± 63 mg/dl and 154 ± 83 mg/dl in *J.* and control group after 12 weeks, respectively, *p*=0.32. **Total cholesterol:** 131 ± 27 mg/dl and 146 ± 32 mg/dl in *J.* and control group after 12 weeks, respectively, *p*=0.42. **LDL:** 74 ± 18 mg/dl and 84 ± 25 mg/dl in *J.* and control group after 12 weeks, respectively, *p*=0.44. **HDL:** 43 ± 7 mg/dl and 44 ± 11 mg/dl in *J.* and control group after 12 weeks, respectively, *p*=0.99.

*The data of the J. group were reported in this table.

Whole fruit:85 g, skins: 5.6 g, fat-free nutmeat: 34 g, and oil: 51 g.

ɣ AAD: 8.7% energy of PUFA, LA: 16.4% energy of PUFA from J. and its oil ALA: 17% energy of PUFA from J. and its oil and flax oil for six weeks for each period.

§ Intervention group: banana bread with J. (385kcal); control group: banana bread without j. (287 kcal).

AAD: Average American Diet; ALA:Alpha-Linolenic Acid; ApoB:Apolipoprotein B; DM II:Diabetes Mellitus Type 2; HDL: High Density Lipoprotein; J.: Juglans; LA: Linoleic Acid; LDL: Low Density Lipoprotein; NS:Not Significant; PUFA:Polyunsaturated Fatty Acids; SD:Standard Deviation; TG:Triglycerides.

Lipid-Lowering Effects

The 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease (CVD) recommends a diet that emphasizes the consumption of fish, vegetables, fruits, nuts, whole grains, and legumes to help reduce risk factors associated with atherosclerotic CVD (52).

The beneficial cardiovascular effects of J. may be attributed to its compounds, such as polyphenols, gamma-tocopherol (ɣ-T), ALA, LA, and L-arginine (38, 53, 54). Most of the polyphenols found in J. (including flavonoids, phenolic acids, and tannins) are concentrated in the husk (55).

Studies have shown that both acute and chronic intake of J. at doses between 42.5 and 85 grams per day can reduce total cholesterol (TC) and LDL levels (56, 57). One study also indicated that linolenic acid in J. may decrease serum triglyceride (TG) levels (58).

-Whole Fruit, Skin, Nutmeat, and Oil

In the previously mentioned study by Berryman et al., a time-dependent effect on TG was observed. Specifically, 120- and 240-minute postprandial TG concentrations increased with the consumption of whole J. and its oil. The increase was greater following oil ($p < 0.01$) and whole nut ($p \leq 0.03$) treatments compared to skin. At 120 minutes, the TG response to J. oil was significantly higher than that of the whole fruit ($p = 0.02$). Notably, postprandial TG area under the curve (AUC) decreased by 89% with J. skin in a time-dependent manner ($p < 0.01$). No significant effects were observed on TC, LDL, or high-density lipoprotein (HDL) cholesterol levels, but whole J. did increase cholesterol efflux (Table 2) (39).

-Whole Fruit

A crossover study by Murad et al. reported an increase in HDL levels after eight weeks of consuming 30 g/day of whole J. fruit, compared to baseline, in 40 hyperlipidemic patients aged between 20 and 65 years (59).

In a controlled single-blind crossover study by Iwamoto et al., 40 participants who consumed 43–57 g/day of J. whole fruit experienced a reduction in serum total cholesterol (TC) compared to the reference diet. The mean difference in TC between groups (95% CI) was –0.16 mmol/L (–0.83 to 0.65; $p < 0.05$) in men and –0.21 mmol/L (–1.03 to –0.28; $p < 0.01$) in women. LDL cholesterol levels also decreased during the J. diet period, although the change was not statistically significant in men (mean difference: –0.18 mmol/L [–0.80 to 0.41]) but was significant in women (–0.22 mmol/L [–0.69 to –0.13]; $p < 0.01$). The LDL/HDL ratio also declined (mean difference: –0.16 [–0.67 to –0.28]; $p < 0.05$ in men, and –0.11 [–0.41 to –0.21]; $p < 0.05$ in women), as did apolipoprotein B (ApoB) levels (–51 mg/L [–240 to –90]; $p < 0.05$ in men, and –78 mg/L [–190 to –50]; $p < 0.01$ in women). No significant changes were observed in TG or apolipoprotein A1 (ApoA1) levels (60).

Ros et al., in a previously mentioned study, reported that consuming J. as part of the diet significantly reduced TC and LDL levels after four weeks (42). A recent study by Ashraf et al. showed that consuming 25 g or 50 g of J. kernel daily significantly improved the lipid profile of 90 hypercholesterolemic patients over 56 days. Higher doses and longer durations led to more significant reductions in TG and LDL levels, as well as a notable increase in HDL (61).

-Oil

In a randomized, double-blind case-control study, Zibaeenezhad et al. demonstrated that daily use of 500 mg of J. oil significantly reduced triglyceride (TG) levels after 45 days in 60 hyperlipidemic patients aged between 28 and 65 years (62).

Spaccarotella et al. also found no significant effects on serum levels of triglycerides (TG), total cholesterol (TC), HDL, or LDL after administering 75 g/day of whole J. fruit for eight weeks in 21 healthy men aged 45 to 75 years (63).

-Leaves

In contrast to the aforementioned studies, Rabiei et al. (as previously mentioned) found that administering 200 mg/day of J. leaf extract for eight weeks had no significant effects on the lipid profile (23). Similarly, Katz et al. reported no significant changes in lipid parameters (33).

-Internal Septum

Additionally, Mirshekari et al. reported no significant effects on the lipid profile after administering 1,500 mg/day of capsules containing lyophilized J. internal septum extract to 60 hyperlipidemic patients aged 25 to 70 years (64). All relevant data are summarized in Table 2.

Overall, based on the available studies, J. and its components generally have a favorable effect on the lipid profile, particularly in reducing TG and, in some cases, improving TC and HDL levels. However, the magnitude and consistency of these effects vary depending on individual characteristics and study design. These findings support the potential role of J. in promoting cardiovascular health but also underscore the importance of personalized dietary recommendations tailored to individual health needs.

Anti-Hypertensive Activity

Based on previous studies, the inclusion of J. in the diet may reduce the prevalence of cardiovascular diseases, potentially due to its high content of PUFAs, ALA, and LA (65–67). In some epidemiological studies, a high intake of ALA has been associated with lower diastolic blood pressure (DBP) and a reduced risk of coronary heart disease (41, 68).

Moreover, several pharmacological studies have explored the mechanisms by which J. may contribute to blood pressure reduction. These studies suggest that flavonoids, quercetin, and phenolic acids are responsible for the antihypertensive properties of the plant through various mechanisms. For example, quercetin is believed to modulate the adrenergic system by reducing norepinephrine-induced vasoconstriction, while flavonoids may influence both

the adrenergic system and inhibit angiotensin-converting enzyme (ACE) activity (22).

-Leaves

In the aforementioned study by Rabiei et al., it was found that consumption of hydroalcoholic leaf extract of J. led to a significant reduction in systolic blood pressure (SBP) (23).

-Whole Fruit

Like the leaves, in a study by West et al. (previously mentioned), the ALA and LA content in J. contributed to a PUFA-rich diet that significantly reduced DBP and total peripheral resistance by 4% under both resting and stress conditions during an 18-week trial (41).

In contrast, the study by Katz et al. (as mentioned earlier) showed a non-significant decrease in both SBP and DBP over eight weeks (33).

In the study by Ying et al., no significant changes in blood pressure were observed after the consumption of J. – enriched diets. Interestingly, significant changes in SBP and DBP were noted in the ad libitum control diet without J. (32).

Likewise, Spaccarotella et al. reported no significant changes in SBP or DBP following the administration of 75 g of J. whole fruits daily for eight weeks (63). Details of these studies are summarized in Table 3.

In conclusion, although J. is generally considered beneficial for cardiovascular health, current findings suggest that its effects on blood pressure can vary depending on factors such as individual health status, administered dose, the specific component of J. used, and other contextual variables. These observations underscore the need for further research to clarify the underlying mechanisms and determine which populations may benefit most from J. consumption.

Table 3. Characteristics of the studies conducted on the anti-hypertensive, anti-tumoral, and weight-lowering effects of J.

Authors (No.)/ Year	Part(s) used	Control group	Sample size/ Population	Dose/Duration	Outcomes
Anti-Hypertensive Activity					
Rabiei et al. (23)/2018	Leaves (Hydro-alcoholic extract)	Placebo	39/ DM II	200 mg daily / 8 weeks	***Mean±SD*:*** **SBP:** 121.1 ± 8.8 mmHg after treatment *vs*. 126.1 ± 9.5 mmHg at the baseline, p=0.005. **DBP:** 77.4 ± 4.8 mmHg after treatment *vs*. 79.2 ± 6.7 mmHg at the baseline, p=0.185.
West et al. (41)/2010	Whole fruit	AAD	20/ Hypercholesterolemic patients	AAD, LA, ALA/ 6 weeks[ɣ]	***Mean±SD:*** **SBP (Average):** 129.2 ± 3.3 mmHg in LA diet *vs*. 128.7 ± 3.3 mmHg in AAD diet, p=0.92; 126.± 6 3.3 mmHg in LA diet *vs*. 128.7 ± 3.3 mmHg in AAD diet, p=0.92. **DBP (change from the baseline):** -2 to -3 mmHg, $p \leq 0.001$.
Katz et al. (33)/2012	Whole fruit	Ad Libitum Diet without *J.*	46/Overweight adults	56 g daily/ 8 weeks with a 4-week wash-out period.	***Change from the baseline (mean±SD):*** **SBP:** -2.6±11.0 mmHg in *J.* group *vs*. 1.2±10.7 mmHg in control group, p=0.070. **DBP:** -3.6 ±18.8 mmHg in *J.* group *vs*. -0.6 ±7.7 mmHg in control group, p=0.352.
Ying et al. (32)/2010	Whole fruit	Ad Libitum Diet without *J.*	24/ DM II	56 g daily/ 8 weeks with an 8-week wash-out period.	***Change from the baseline (mean±SD):*** **SBP:** 4.0 ± 9.2 mmHg in *J.* group *vs*. -4.9 ± 11.7 mmHg in control group, p=0.01. **DBP:** 1.6 ± 4.6 mmHg in *J.* group *vs*. -2.5 ± 6.4 mmHg in control group, p=0.02.
Spaccarotella et al. (63)/2008	Whole fruit	AAD	21/ Healthy men	75 g daily/ 8 weeks with a two-week wash-out period.	***Change in J. group vs. AAD, respectively (mean±SEM):*** **SBP:** -3.05 ± 2.78 mmHg *vs*. -1.65 ± 2.78 mmHg, p=0.61. **DBP:** -3.45 ± 1.52 mmHg *vs*. -2.50 ± 1.52 mmHg, p=0.54.
Anti-Tumor Activity					
Spaccarotella et al. (63)/2008	Whole fruit	AAD	21/ Healthy men	75 g daily/ 8 weeks with a two-week wash-out period.	***Change in J. group vs. AAD, respectively (mean±SEM):*** **Total PSA:** 0.05 ± 0.36 µg/L *vs*. -0.07 ± 0.35 µg/L, p=0.75. **Free PSA:** 0.13 ± 0.10 µg/L *vs*. 0.05 ± 0.10 µg/L, p=0.56. **α-T/γ-T ratio:** -3.49 ± 1.99 *vs*. -0.51 ± 1.99, p=0.01.

Table 3. Continued

Weight-Lowering Effects					
Rabiei et al. (23)/2018	Leaves (Hydro-alcoholic extract)	Placebo	39/ DM II	200 mg daily / 8 weeks	***Mean±SD*:*** **Weight:** 71.7±13.8 kg after intervention *vs*. 73.0±15.1 kg at the baseline, *p*=0.028. **BMI:** 28.7±5.3 kg/m^2 after intervention *vs*. 29.2±6.0 kg/m^2 at the baseline, *p*=0.030.
Farr et al. (81)/2018	Whole fruit	Placebo	10/ Obese patients	48g daily/5 days with a one-month wash-out period.	***Mean±SD:*** **Appetite (VAS):** 6.12±1.16 in *J.* group compared to 7.65±.099 in control group, *p*<0.05. **Amount of eating (VAS):** 6.44±1.01 in *J.* group compared to 7.55±0.99 in control group, *p*<0.04.
Katz et al. (33)/2012	Whole fruit	Ad Libitum Diet without *J.*	46/ Overweight adults	56 g daily/ 8 weeks with a four-week wash-out period.	***Change from the baseline (mean±SD):*** **Weight:** 0.4 ± 3.7 Ib in *J.* group *vs*. -2.0 ± 5.4 Ib in control group, *p*=0.439 and *p*=0.019, respectively. **BMI:** 0.1 ± 0.6 kg/m^2 in *J.* group *vs*. -0.3 ± 0.8 kg/m^2 in control group, *p*=0.481 and *p*=0.016, respectively. **Waist circumference:** -0.7 ± 3.7 cm in *J.* group *vs*. -0.3 ± 2.4 cm in control group, *p*=0.344 in *J.* group.
Bitok et al. (82)/2018	Whole fruit	Normal habitual diet	306/ Geriatrics	28, 42, or 56 g daily / 2 years	***Mean(95%CI):*** **Weight:** 76.7 kg (74.1, 79.2) in *J.* group *vs*. 75.0 kg (72.4, 77.6) in control group, *p*=0.671. **Body fat:** 26.4 kg (25.3, 27.4) in *J.* group *vs*. 26.0 kg (24.8, 27.1) in control group, *p*=0.528.

*The data of the J. group were reported in this table.

Whole fruit:85 g, skins: 5.6 g, fat-free nutmeat: 34 g, and oil: 51 g.

ɣ AAD: 8.7% energy of PUFA, LA: 16.4% energy of PUFA from J. and its oil ALA: 17% energy of PUFA from J. and its oil and flax oil for six weeks for each period.

§ Intervention group: banana bread with J. (385kcal); control group: banana bread without j. (287 kcal).

AAD: Average American Diet; ALA:Alpha-Linolenic Acid; BMI:Body Mass Index; DBP:Diastolic Blood Pressure; DM II:Diabetes Militias Type 2; J.: Juglans; LA: Linoleic Acid; PSA:Prostate-Specific Antigen; PUFA:Polyunsaturated Fatty Acids; SD:Standard Deviation; SBP:Systolic Blood Pressure; VAS: Visual Analog Scale; A-T: Alpha Tocopherol; Γ-T:Gamma Tocopherol.

Anti-Tumor Activity

In some previous in-vitro studies, the anti-apoptotic and anti-tumor effects of the hexane leaf extract of J. have been proven (69, 70). Moreover, other studies have indicated that flavonoids and juglone contribute to the anti-tumoral effects of J. due to their antioxidant capacity and their ability to boost the immune system (22). In addition to these in-vitro and in-vivo studies, several human studies have also been conducted on the anti-cancer effects of J.

J. is a rich source of polyphenols, omega-3 fatty acids, and other phytochemicals, which have been shown to induce apoptosis in tumor cells and inhibit their growth. The anti-apoptotic effects are believed to result from the modulation of various cellular signaling pathways involved in cell survival and death. In contrast, the antitumor properties might be linked to the ability of these compounds to reduce inflammation, oxidative stress, and enhance immune surveillance. Although the exact mechanisms are still under investigation, the consumption of J. has been associated with a reduced risk of certain types of cancer, suggesting that it may play a beneficial role in a cancer-preventive diet (71-73).

-Whole Fruit

In a study by Spaccarotella et al., which was mentioned in previous sections, it was demonstrated that J. can improve some prostate cancer biomarkers, such as the alpha-tocopherol (α-T)/ γ-T ratio, which is important in prostate cells. The results of this study indicated that although there was no significant effect on testosterone levels, the α-T/γ-T ratio decreased significantly. Furthermore, a linear mixed model revealed that while the PSA levels remained unchanged, there was an increase in the ratio of free PSA to total PSA, which neared statistical significance (63).

Totally the effect sizes for aforementioned study are relatively small and not statistically significant, except for the α-T/γ-T ratio. However, the trends in percent free PSA (0.99 ± 1.03 % and 1.03 ± 1.03 % in J. containing diet and average American diet, respectively vs. 38.8 ± 1.04 % at the baseline, p = 0.07), α-T (-2.65 ± 1.30 µmol/L and -0.71 ± 1.30 µmol/L in J. containing diet and average American diet, respectively vs. 29.3 ± 2.19 µmol/L at the baseline, p = 0.13), and γ-T (0.83 ± 0.52 µmol/L and 0.26 ± 0.52 µmol/L in J. containing diet and average American diet, respectively vs. 4.14 ± 0.43 µmol/L at the baseline,

p = 0.08) might warrant further investigation with larger sample sizes or longer duration to determine if these effects are genuinely beneficial or clinically relevant.

Effects on Weight Reduction

Numerous epidemiological studies have shown that nut consumption can reduce oxidative stress and inflammation, improve lipid profiles, and enhance glucose metabolism (74–77).

Despite its high caloric and fat content, the consumption of J. has increasingly been associated with weight management and reduction. J. is rich in unsaturated fatty acids, protein, and fiber, all of which contribute to increased satiety and a feeling of fullness, potentially reducing overall caloric intake. Studies suggest that incorporating J. into the diet does not lead to weight gain and may support weight loss by promoting healthier metabolism and enhanced fat oxidation. Furthermore, the omega-3 fatty acids in J. are believed to play a key role in regulating metabolism and appetite. Regular consumption of J., when included as part of a balanced diet, has been linked to improved weight control and a reduced risk of obesity-related diseases. However, the exact effects and underlying mechanisms remain under investigation (78–80).

-Leaves

In a study by Rabiei et al., it was shown that administering 200 mg/day of J. leaf extract for eight weeks significantly affected patients' body weight and body mass index (BMI) (23).

-Whole Fruit

Farr et al., in a double-blind, randomized crossover study, demonstrated that consuming 48 g/day of J. whole fruits for five days reduced appetite and food intake in 10 obese patients, consequently contributing to weight loss (81).

In the previously mentioned study by Katz et al., the consumption of J. did not significantly alter anthropometric values compared to baseline. Interestingly, body weight and BMI significantly decreased in the control group (p = 0.019 and p = 0.016, respectively) (33).

In an RCT by Bitok et al., which examined the long-term effects of J. supplementation on body weight in 306 older adults over 60 years of age, it was found that after two years, body weight significantly decreased while body fat increased compared to baseline (p = 0.031 and p = 0.0001, respectively). However, no significant difference was observed between the J. and control groups in terms of weight loss (82). These findings are summarized in Table 3.

Overall, based on these studies, while there are promising indications of the health benefits of J., particularly in appetite regulation, its effects on weight and body composition appear to be modest under the studied conditions. Further research is needed to clarify these effects and determine their clinical significance.

Discussion

According to our research, various in vitro and in vivo studies have been conducted on the effects of J. These studies demonstrate that components of J. possess numerous therapeutic properties, including anti-diabetic, antioxidant, antihypertensive, antimicrobial, and antifungal activities. Additionally, J. has been shown to improve endothelial function and inferential verbal reasoning, as well as to exhibit lipid-lowering, anti-tumor, and weight-reducing effects. Owing to these positive and significant findings, several human clinical trials have been undertaken.

Most of these clinical trials have focused on the properties of the whole fruit and leaves of J. Notably, the most frequently evaluated therapeutic effects were its anti-diabetic and lipid-lowering properties.

Various dosage forms derived from J. components have been developed (including capsules, tablets, total extracts, and powders) using different extraction methods such as hydroalcoholic, aqueous, and hexane-based processes. The dosage ranges have varied considerably, largely due to the diversity of the products used. This variability also explains why a specific effective dose has not been established.

Previous studies have identified a variety of bioactive compounds in J. Phenolic acids and flavonoids are predominant in the leaves. The bark contains active ingredients such as emulsion, glucose, and organic acids, while the fruit is rich in fatty acids, tocopherols, phytosterols, tannins, and antioxidants. Another study reported that the internal septum of J. contains bioactive compounds such as gallic acid, phthalic acid, and catechin (10, 83).

The therapeutic effects of J. are mediated through multiple interconnected mechanisms. These include antioxidant activity via free radical scavenging by phenolic compounds, enhancement of insulin secretion by flavonoids such as quercetin, alkaloids, and methanolic extracts, and inhibition of sorbitol accumulation in tissues—mechanisms that contribute to its antidiabetic, antioxidant, and lipid-lowering properties. Additionally, the modulation of lipid metabolism through PUFAs and tocopherol content, along with antihypertensive effects through ACE inhibition and reduction of norepinephrine-induced vasoconstriction, further demonstrates the pharmacological potential of the plant. J. also exhibits anti-inflammatory, antitumor, and antimicrobial activities, largely attributed to its rich composition of polyphenols, phenolic acids, flavonoids, and juglone (10, 22, 29, 35–37, 45–48, 68).

As mentioned earlier, most studies to date have focused on the whole fruit and leaves of J. Consequently, a wide range of effects (such as anti-diabetic, antioxidant, lipid-lowering, antihypertensive, cognitive enhancement, and weight reduction) have been reported in human clinical trials evaluating these plant components. Although no human studies have evaluated the toxicity of J. components, several animal and analytical studies have confirmed that J. and its constituents do not exhibit toxic effects (10, 84). Finally, to introduce J. as an approved therapeutic product for managing these conditions, further studies with larger sample sizes are required due to existing inconsistencies in the current findings. Additionally, pharmacokinetic studies are essential to better understand its absorption, distribution, metabolism, and excretion. Moreover, future clinical trials should adopt standardized protocols regarding dosage forms, extraction methods, and treatment durations to enhance comparability across studies. Comparative evaluations of different plant parts (such as leaves, fruit, and internal septum) are also needed to clarify their respective therapeutic contributions. Finally, detailed mechanistic investigations at the molecular level are warranted to explain how specific bioactive compounds exert their effects, ultimately guiding evidence-based integration of J. into clinical practice.

Conclusion

This narrative review highlights the therapeutic potential of J., particularly its antidiabetic, antioxidant, lipid-lowering, antihypertensive, and weight-reducing effects as demonstrated in recent RCTs. However, findings across studies remain inconsistent, suggesting that its efficacy may vary based on dosage, part of use, patient characteristics, and study design. To clarify these effects and ensure safe clinical use, further research is warranted. In this regard, well-designed human trials are needed to determine optimal dosing and long-term safety.

Conflict of Interests

The author(s) declared no potential conflicts of interest.

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