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Review

A review of phytochemistry and pharmacology profile of *Juglans regia*

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ABSTRACT

Walnuts are among the most widely spread and commercially grown tree nuts in the world. It is known for its wide array of benefits which includes its use in cardiovascular disease, type II diabetes mellitus, anti-infectives, anti-microbial, anti-fungal, anti-hypertensives, hepato-protective and lipid lowering agents. It has also shown its pharmacological properties in the treatment of diarrhea, sinusitis, anorexia, thyroid disorders, skin disorders which includes eczema. The present review article will provide the insights of the available literature on its ethnobotanical use, phytoconstituents, traditional uses, pharmacological activities performed in-vivo, in-vitro and clinical trials and current research prospects of the *Juglans regia* L. Due to the increased inclination towards naturopathy and ayurveda, several investigations are being aimed at scientific validation, isolation and identification of active constituents of crude extracts from various natural sources.

1. Introduction

Walnut (*Juglans regia* L.) also commonly known as Persian walnut, Circassian walnut and English walnut, belongs to Juglandaceae family. It is most commonly found in Southeast Europe and extends up to the Himalayas and Southwest China. This plant is native to Kyrgyzstan, where walnut tree grows up to 1,000–2,000 m (3000–7000 ft) altitude. The walnut tree is used since ages to treat various ailments. The vast range of its medicinal properties is primarily due to presence of phytochemical constituents such as flavonoids, alkaloids, carotenoids, nitrogen-containing compounds along with other polyphenolic components (Girzu et al., 1998). Nearly all the parts of this plant like bark, kernel, flowers, leaves, green husk, septum, oil etc. has their own medicinal properties. In-depth research has proven that *Juglans regia* exhibits anti-oxidant, anti-histaminic, bronchodilator, anti-fertility, analgesic, immunomodulatory, anti-ulcer, anti-diabetic, hepatoprotective, anti-microbial, anti-inflammatory, lipolytic anti-hypertensive, neuroprotective, insecticidal, anticancer, wound healing and several other therapeutic properties (Girzu et al., 1998). The present review article will provide the insights of the available literature on its phytoconstituents, traditional uses with various pharmacological activities performed *in-vivo*, *in-vitro* and clinical trials.

2. Habitat and Ecology

Juglans regia is native to the Kazakhstan, Uzbekistan and southern Kirghizia and mountains ranges of Nepal, Tibet, Bhutan, northern India, Sri Lanka and Afghanistan (Loacker et al., 2007). The common walnut is a commercial species and requires special climatic conditions for its growth. It is usually grown in as individual trees, rather than within mixed woodland. The presence of warm and sheltered site is of utmost importance for its growth. It grows in deep and rich soils, having pH values between 6 and 7.5 (neutral pH). It requires a good amount of sun-light and is highly susceptible to weed and sensitive to winters and late spring frosts. It is preferred to be germinated in mild winters, which is said to be a changing climate with warmer winters that prove to be beneficial for its optimum growth and maturation (GruenwaldBrendler and Jaenjke, 2002).

3. Taxonomical classification

The taxonomical classification of *Juglans regia* is described below in Fig. 1.

4. Phytoconstituents and its activity

The chemical composition of phytoconstituents varies and that depends upon the geographical location, climatic conditions and nature of soil. Research performed across the globe evaluated that the leaves, bark and fruits of *Juglans regia* exhibit therapeutic activity. The details of compounds of *Juglans regia* along with its activities is described in Table 1. Also, pictorial representation of walnut fruit is shown in Fig. 2.

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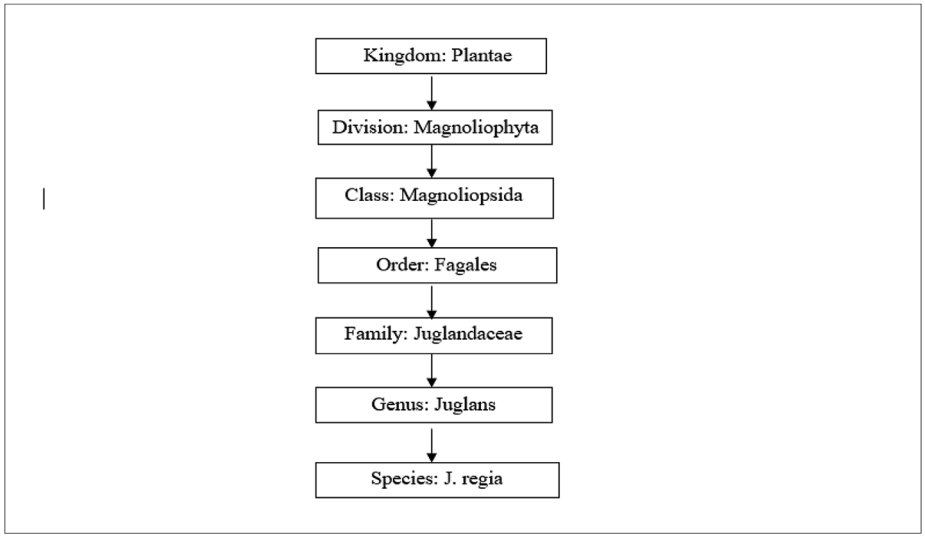

Fig. 1. Taxonomical hierarchy of *Juglans regia* plant.

Table 1
Different part of *Juglans regia* containing phytoconstituents with its pharmacological activity.

Part	Compounds	Pharmacological activity
Leaf	Phenolic acids, tannins, essential fatty acids, ascorbic acid, flavonoids, caffeic acid, paracomaric acid, juglone [**4–6**]	Anti-oxidant activity, Lipid-lowering effect, anti-hypertensive effect, anti-microbial effects
	Flavoniods: Quercetin galactoside, quercetin pantocid derivatives, quercetin arabinoside, quercetin xyloside and quercetin rhamnoside. [**4–6**]	Anti-diabetic effect, anti-cancer effect
Green husk of fruit	Emulsion, glucose, organic materials such as citric acid, malic acid, phosphate and calcium oxalate [**7–8**]	Liver and kidney protective
Fruit	Fatty acids, tocopherols, phytosterols, total phenolic (tannins), anti-oxidant activity [**9–10**]	Anti-microbial effects
Seeds	Glutelins, globulins, albumin and prolamins [**10,11**]	Wound healing

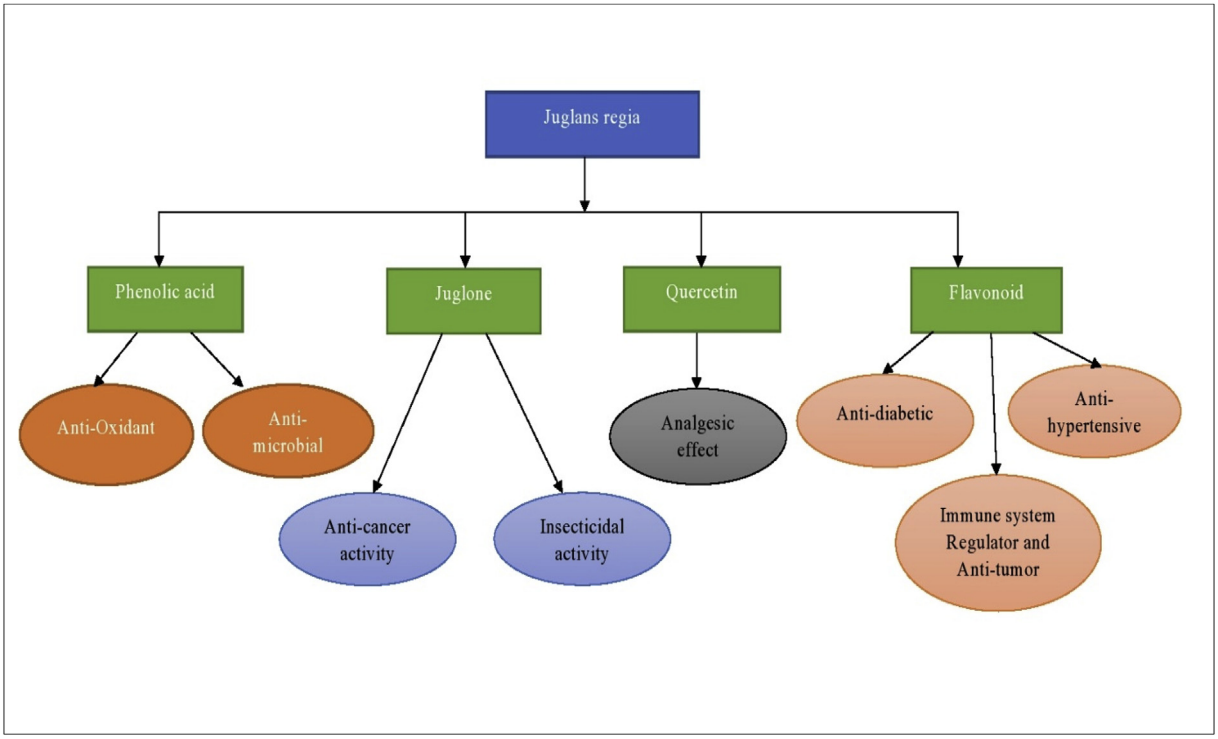

Fig. 2. Pharmacological activity of main phytoconstituents of *Juglans regia*.

Fig. 2 Unripe fruit of Juglans regia (Indian Walnut).

Juglans regia is a good source of essential fatty acids and tocopherols and is found to contain several potential neuroprotective compounds such as gamma tocopherol (vitamin E), long-chain omega-3 fatty acids docosa hexaenoic acid, docosa pentaenoic acid and ecosa pentanoic acid. Also, research carried out had revealed its role on treatment of dementia and Alzheimer's disease (Subhan and Bagchi, 2017; Muthaiyah et al., 2014).

Juglans regia seeds commonly contain the phenolic compounds such as phenolic acids, namely gallic, ellagic, syringic, caffeic, p-coumaric, ferulic and sinapic acids and tannins, such as glansrins A, B and C, casuarinin, stenophyllarin, between others. In relation to walnut leaves, its phenolic composition has already been studied by some researchers and its pharmacological effect has already been elucidated (Martínez et al., 2010). The detailed summary of the active constituents of *Juglans regia* is depicted in Fig. 2.

5. History

Walnut is one of the medicinal plants which, like most herbal medicines of traditional medicine, is not commercially used despite having great therapeutic potential. In traditional medicine, walnut roots were used to treat diabetes, its leaves were used to treat rheumatic pains, fever, diabetes, skin diseases; and its flowers were used to treat malaria and rheumatic pain. In Iranian traditional medicine, this plant is widely used in treatment of different disease and also used in Persian cuisine as well. Walnut leaves are used in traditional medicine to reduce blood glucose and improve diabetes. Based on studies conducted, walnut leaves contain compounds effective on health; and they are widely used in traditional medicine for the treatment of venous insufficiency and haemorrhoids symptoms. In some report's walnut has been reported to be used as anti-diarrhoeal, anti-parasitic, as well as a blood purifier. The available data suggest that extensive research in the past two decades has been conducted on the pharmacological effects of walnut. Also, it has been found that attenuation of the lipid level had been reported with the administration of walnut leaves in streptozotocin-induced diabetic rats (Delaviz et al., 2017a).

In addition, recent studies have shown that this plant is associated with analgesic and anti-microbial effects. Studies have shown that the walnut extract is rich in total phenolic components which has anticancer and anti-inflammatory properties.

6. Pharmacological activites

The details of the pharmacological activities shown by Juglans regia is depicted in **Fig. 4.**

6.1. Anti-oxidant activity

Various research has been carried out to explore the anti-oxidant effect of *Juglans regia*. It has been reported that phenolic compounds from walnut have promising results on improving conditions of coronary heart disease, anti-inflammatory action, anti-mutagenic properties and may prevent or stop the progress of various oxidative stress-related diseases (Subhan and Bagchi, 2017; Muthaiyah et al., 2014; Martínez et al., 2010; Stampar et al., 2006; Valko et al., 2007; Basri et al., 2017; Bratkov et al., 2016). Gallic acid, salicylic acid, ellagic acid, epicatechin, caffeic acid, chlorogenic acid, synapic acid, vanillic acid, ferulic acid, genistein, protocatechic acid, catechin, and juglone are phenolic components obtained from walnut plant (Delaviz et al., 2017a). Several studies have been carried out to explain the activity of phenolic compounds. These Phenolic compounds are a group of secondary metabolites which are found in significant amount in nature and has been seen to exhibit several therapeutic properties. One of the potential benefit of these phenolic compounds is their anti-oxidant potential which is mainly due to their redox properties, which allow them to act as reducing agents, metal chelators, free radicals scavengers, singlet oxygen quenchers and hydrogen donors (Raja et al., 2012; Shah et al., 2015; Almeida et al., 2008). A study carried out by G. Raja showed that *Juglans regia* L can reduce oxidative deoxyribose damage in dose dependent manner (Raja et al., 2012).

6.2. Antimicrobial and antifungal activity

Due to the increasing use of chemical preservatives, development of antibiotic resistance and side effects of standard microbicidal therapy, the inclination towards the use of natural products has tremendously increased. This has led to increase in utilization and subsequent researches to explore new and potential candidates that exhibits microbicidal activities without having above mentioned side effects. One of the activities shown by *Juglans regia* includes microbicidal activity as well. Several researches have been carried out which demonstrates that components of walnut products which includes barks, husks, fruits has shown to exhibit antimicrobial activities (Delaviz et al., 2017b). It has been reported that *Juglans regia* was shown to be effective against acne lesions through its anti-microbial, anti-inflammatory and anti-oxidant activities (Qa'dan et al., 2005).

Along with the anti-microbial activity, *Juglans regia* has been shown to exhibit anti-fungal activity as well. In a research by *Pereira JA.* et al. showed that methanolic extracts of *Juglans regia* was active against all candida strains which can be helpful in the treatment of oral candidiasis (Noumi et al., 2010; Pereira et al., 2007).

6.3. Antidiabetic activity

With the increasing number of population getting affected by diabetes, it is become a matter of great concern to explore novel ways to prevent/treat this disorder and at the same time reducing the side-effects due to current medication used in the treatment of diabetes. Although conventional therapy is effective and satisfactory, but there is an urgent need to develop new drugs derived from natural sources to prevent the side effects of synthetic medication. Increasing number of side-effects associated with the current therapies had shifted the focus of researchers on exploring various plants having antidiabetic properties. Various studies have been conducted which confirmed the therapeutic potential of medicinal plants in the treatment of diabetics and its associated complications (Suksomboon et al., 2011; Mohammadi and Naik, 2008a, 2012; Ebrahimi et al., 2019). Results of research from Ayurveda has shown that more than 1200 medicinal plants has promising results in diabetes and related complications (Ziyyat et al., 1997; Zargari, 1990). It was initially reported that walnut leaves had some chemical substance which disposes of parasites and therefore may be beneficial in the treatment of tuberculosis and diabetes (Zargari, 1990). During early evolution of Iranian traditional medicine, fleshy green fruits and leaves of walnut trees were used as hypo-glycaemic agents (Ahmad and KhanAbdul Wahid, 2012). Several other studies have concluded that infusion of walnut with olive leaves and infusion of walnut leaves alone has blood glucose lowering effects in the patients suffering from diabetes (Zargari, 1990; Silva and Fernandes Júnior, 2010; Rutledge et al., 1999). It is also reported that hydro-alcoholic extract of *Juglans regia* has dose dependent effect in decreasing the blood glucose level in rats which is comparable to one of the most promising and commonly used drug, metformin (Fathiazad et al., 2006). Some researchers have reported in the past that the administration of leaf extract of *Juglans regia* significantly decreased blood glucose levels in diabetic rats which ultimately led to improvement of diabetes (Divband et al., 2010; Almario et al., 2001; Jelodar and Nazifi, 1999; Noureddini and Rezaee-Joshogani, 2013). In another study, the effect of ether, ethanol, and the cyclohexane extract of walnut leaves on blood biochemical parameters in diabetic rats was examined and the results showed a drop-in glucose, cholesterol, triglyceride, and blood urea nitrogen (Noureddini and Rezaee-Joshogani, 2013).

Study conducted by Mohammadi et al. has reported that administration of hydro-alcoholic extract of walnut leaves bring about some changes in the pancreas tissue in streptozotocin (STZ)-induced diabetic rat as evidenced by improvement in islets of Langerhans and by restoration of β-cell function (Mohammadi et al., 2011, 2012a). Also, study carried out has been reported the hydro-alcoholic extract of walnut leaves on administration to the nicotinamide-induced type-2 diabetic rats also led to restoring β-cells of pancreas by improvement of islet of Langerhans function. This results ultimately leads to increase in level if insulin and which further brings about decrease in the levels of triglycerides, glycosylated haemoglobin, low-density lipoprotein cholesterol and total cholesterol (Jelodar and Nazifi, 1999; Noureddini and Rezaee-Joshogani, 2013; Mohammadi et al., 2011, 2012a, 2012b).

The mechanism behind the reduction in glucose level by the administration of walnut extract may be due to increased release of insulin from the remaining β-cells of pancreas, increasing insulin sensitivity, emulate β-cells, by interfering with the absorption of carbohydrates obtained from diet specially in the small intestine and thereby increasing the uptake of glucose via. peripheral-mediated or insulin-dependent-glucose transporter (Jelodar and Nazifi, 1999; Noureddini and Rezaee-Joshogani, 2013; Majidi et al., 2015; Asgary et al., 2008; Fabricant and Farnsworth, 2001).

6.4. Anti-hypertensive effect

Study carried out in young people prone to cardiovascular disease, by consuming walnut has brought significant change in the lipid profile (Mohammadi and Naik, 2008b; Jouad et al., 2001; Javidanpour et al., 2012; Craig, 1999; Reza et al., 2006; Feldman, 2002; Anderson et al., 2001). Also, another study, carried out between two arms taking walnut and control group has depicted that by consuming walnut helps in reducing the diastolic, systolic and mean arterial pressure as compared to the control arm (Anderson et al., 2001).

In a pre-clinical study carried out by Perusquia et al. on rats showed the effect of walnut leaf extract on aortic segments has helped in reduction of blood pressure and noradrenaline-induced contraction in isolated aorta. This effect was attributed to the muscle relaxant effect of aq. walnut leaves extract on arterial walls (Kushwaha et al., 2016). Also, in a recent study, it has shown the preventive effects of walnut extract on dexamethasone-induced hypertension along with improvement in nitrous oxide production resulting ion prevention of antioxidant system. These results were comparable to captopril; an angiotensin-converting enzyme inhibitor used for the treatment of hypertension and some types of congestive heart failure (Perusquía et al., 1995).

Another research by Meng Liu et al., it has been reported that a novel ACE-inhibitory peptide named P-2a2 purified from walnut protein had shown promising results against angiotensin converting enzyme inhibition which indicated that it has anti-hypertensive properties (Joukar et al., 2017; Liu et al., 2013).

In addition to the above mentioned pre-clinical study, it has also been elucidated that co-administration of walnut leaf aqueous extract and acetylcholine (neurotransmitter used at the neuromuscular junction) has bene found to significantly reduce the diastolic, systolic and mean arterial pressure in comparison with the control group. Also, preventive treatment with walnut leaf aqueous extract has been found to reduce blood pressure caused by the adrenaline (increases blood pressure) (Ziai et al., 2006).

It has been already reported that flavonoids cause relaxation of contracted muscle (e.g. aortic smooth muscle) which is triggered by non-adrenaline activity along with potassium chloride (Ebrahimiyan et al., 2016). Another group of researchers reported in animal model that quercetin, one of the flavonoids present in walnut leaves extract, helps in reduction of non-adrenaline induced vasocontraction mediated through L-type calcium channel (Duarte et al., 1993). Therefore, as mentioned above, most of these studies in *in-vivo* and *in-vitro* models has proved that walnut leaf extracts had hypotensive effect and thus can be beneficial in conditions related to hypertension and its resulting complications. Most of its hypotensive effect is due to the presence of flavonoids and phenolic compounds. Mainly flavonoids like quercetin pantocid, quercetin arabinoside, quercetin rhamnoside and quercetin galactoside (Roghani et al., 2010).

All these researches/studies have helped us in concluding the effect of walnut leaf extract in hypertension associated complications.

6.5. Hepatoprotective and renal protective property

Various studies have been carried out to explore the hepato-protective and renal protective properties. In these studies, it was concluded that, walnut leaf extract can significantly lower the hepatic enzymes level which includes serum alanine aminotransferase, aspartate aminotransferase, total protein, plasma albumin and alkaline phosphatase levels. Also, no significant changes in the levels of BUN, bilirubin, alkaline phosphatase enzyme activity and creatinine was noted at the same time (Chaleshtori et al., 2011; Akram et al., 2011).

Apart from hepato-protective properties, it was also reported that walnut extract has renal protective properties. In a study carried out by Ahn CB et al., it was reported that walnut extract had a significant impact over acute renal failure condition which might be due to nephron cell regeneration both *in vivo* or *in vitro* models (Mohammadi et al., 2014).

6.6. Antinociceptive and anti-inflammatory activity

Several studies have been carried out to explore the antinociceptive and anti-inflammatory properties of *Juglans regia*. It had been reported that aqueous and ethanolic extracts of *Juglans regia* has central and peripheral antinociceptive effects. This effect is mediated through non-opioid receptors or inhibition of cyclo-oxygenase enzyme. Also, these extracts had shown to be effective against acute and especially chronic inflammatory condition (Ahn et al., 2002). Various flavonoids such as quercetin, hesperidin and luteolin has produced significant effect as antinociceptive and/or anti-inflammatory activities (Hosseinzadeh et al., 2011; Mada et al., 2009; Ghogare et al., 2009; Erdemoglu et al., 2008; Saeed et al., 2010; Carballo et al., 2010). Therefore, it can be concluded that the aqueous and ethanolic extracts of *Juglans regia* active constituent isolation can prove to be a promising compound for anti-inflammatory and analgesic activity and may be used for the treatment of rheumatoid arthritis, allergy, asthma, coeliac disease, glomerulonephritis, hepatitis and inflammatory bowel diseases.

6.7. Lipid lowering and cardiovascular activity

It has been known since long that walnuts are a rich source of ω-3 and ω −6 PUFA. Some of the studies suggests that ω −6 PUFAs might be one of the factors associated with increased.

proinflammatory vascular response. Also, it has been well established that ω-3 and ω-6 PUFAs acts a prophylactic treatment of cardiovascular complications (Güvenç et al., 2010). It has been postulated by Davis et al. that walnut consumption is inversely proportional to the Endothelin-1 level i.e. on increasing the level of walnut, the ET-1 receptor level decreases, thereby has positive effect of cardiovascular system mediated via endothelin receptors (Manuelli et al., 2017).

In a study carried out by Almario et al., it has been reported that there is a direct effect of walnut extract on the level of cholesterol, triglyceride and LDL-C cholesterol in animal model of hyperlipidaemic rats (Almario et al., 2001). Also, many other researches have been carried out to confirm the results reported by Almario et al., which has proved that walnut leaves extract has the potential to decrease the levels of triglycerides, serum cholesterol but increasing the level of HDL (good cholesterol) (Savage, 2001; Mohammadi et al., 2012a). These effects can bring about promising results with anti-atherogenic effect

which might also acts as a preventive alternate for plaque formation (Jouad et al., 2001). In a research carried out in hydro-alcoholic extract of walnut leaves is was postulated that walnut helps in lowering blood glucose level mainly due to juglone. Juglone acts as precursor in effectively reducing the increased blood glucose level by stimulating the insulin production or by increasing the sensitivity of receptors in cells towards insulin (Zhang et al., 2015).

Also, in an *in vitro* study it was revealed that walnut green hull extract is found to have inhibitory action against thrombin-induced platelet aggregation and protein secretion by 50%, without any cytotoxic effects on platelets. The mechanism behind this was due to suppression of reactive oxygen species generation and in caspase pathway activation in thrombin stimulated platelets. It was presumed that the antiplatelet activity of this extract is due to its polyphenolic compounds and their antioxidant properties. Therefore, it can be considered as a candidate for thrombotic disorders and may be beneficial in ischemic cardiovascular conditions (Qing et al., 2015).

6.8. Anti-cancer effect

Low therapeutic index and development of resistance towards current chemotherapy and radiotherapy which are major limits of anticancer treatments. Therefore, inclination towards the use of natural products having lesser side-effects are becoming promising therapy and the isolation of bioactive molecules has gained importance. Many active constituents have been isolated from various plants which have anticancer properties. Of these plants, *Juglans regia* is one of the most commonly found plant is northern India. Most of the studies carried out had elucidated that walnut have pharmacological activities in various severe chronic conditions. These conditions include cancer as well which is mainly due to the active components in plant which are present as polyphenols, quinones, proteins, and essential fatty acids. It has been found out that *Juglans regia* extract contains ellagitannins which has anti-cancer along with anti-inflammatory properties (Meshkini and Tahmasbi, 2017; Mozafarian, 2012; Kaur et al., 2003; Amaral et al., 2004a,b).The most active component of walnut is juglone (5-hydroxy-1, 4- naphthoquinone). This compound is only found in fresh leaves not in dried leaves of walnut. Other several phenolic compounds with antioxidant properties have been identified in *Juglans regia* leaves. *Juglans regia* leaf extract induces potent growth inhibitory effects against human prostate cancer cells (PC3) by inducing apoptosis and by altering the cell cycle phase distribution in these cells (Amaral et al., 2004a,b).

7. Outcomes from clinical trails

From the above-mentioned pharmacological benefits of walnut, it can be concluded that walnut has shown promising results in the attenuation of complications associated various disorders. So, there is need of an hour to focus for conducting clinical trials for the use of walnuts in the treatment of diseases. Some of the studies mentioned have provided significant results in reducing the burden associated with cardiovascular disorders. In these studies, it was postulated that, consuming nuts is associated with the reduction on the rates of cardiovascular disorders mainly coronary heart disease, cancer along with in cardiovascular and mortality due to cancer (Mayhew et al., 2016; Aune et al., 2016). Also, it has been postulated that there is a dose associated effect between the consumption of nut and reduced cardiometabolic risk. In another largest prospective study relating exposure to nuts in the diet to cardiovascular outcomes, it confirmed a consistent cholesterol-lowering effect of nuts, however no effect in the blood pressure of the subject was seen (Del Gobbo et al., 2015). In another randomized controlled trial carried out by Nutrition Program, University of New Mexico, USA, it was concluded that walnuts are the main source of Phytomelatonin (plant melatonin) with an average content of approximately 350 mg/100g. It has been found that in combination with alpha-linolenic acid (ALA) and anti-oxidants it has shown beneficial effect on the mood observed in a small 6-week trial of walnut supplementation in healthy young men (Pribis, 2016). Also, various meta-analysis has been carried out which confirms.

Thus, extension of these studies can be carried out to further explore the therapeutic benefits associated with walnuts.

8. Discussion and conclusion

The present review article provides brief information regarding the research done on walnut and its active constituents and their pharmacological properties published in last few years. The studies conducted in the past reported that walnuts are a rich source of important nutrients that can be beneficial to human health in providing nutrients as well. This paper provides highlights regarding the traditional use of this plant in the wide array of diseases and provide scientific validation of the claimed pharmacological activity *in vivo* as well as *in vitro* experimental models. These studies have proved that this plant contain flavonoids, alkaloids and terpenoids. Due to the presence of other active constituents which includes coumarin, tannins, monoterpenes, saponins, flavonoids, alkaloids, and other components, it has the potential to be used in various medical conditions. Further the use if this plant is suggested to bring promising results in reducing the risk of hypolipidemic, diabetes mellitus, hypertension, cancer, and microbial activity. Therefore, is can be suggested that more emphasis should be laid in clinical trials to be conducted to identify molecules, information pathways, and related genes.

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