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REVIEW ARTICLE

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Therapeutic Potential of the Juglandaceae Family: Role of Bioactive Components and Secondary Metabolites from Ancient to Modern Medicine

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ABSTRACT

Indian traditional medicine has been using parts of plants to extract and formulate herbal formulations in order to treat a number of long as well as short term diseases. There has been tremendous progress in the development and advances in herbal medicines extracted from edible as well as non-edible parts of several plants. A detailed research conducted in various studies on the leaves, husk, kernel and shell of walnut has indicated several biological importance of the plant and a way in which it can prove to be beneficial in the production of herbal medicines as an alternative to synthetic ones. Juglone found in walnut tree parts has a variety of potential uses in medicine, agriculture as a biocide for organic farming and pest control. Secondary metabolites (SM) are important natural products produced by plants for several mechanisms; such as communication of plants with other organisms, defence against stress caused to the plant, etc. Most of the secondary metabolites possess biological activities that exert medicinal properties. Due to some adverse side effects exerted by synthetic drugs, it is essential to produce such products using natural resources without chemical modification. This review article provides an overview of the brief research conducted on the biologically active components of Juglans species and the secondary metabolite juglone.

Keywords: Juglone, Walnut, Secondary metabolite, *Ayurveda*, Anticancer, Neuroprotective, Antimicrobial and Phytochemicals.

INTRODUCTION

According to '*Ayurveda*' – ancient Indian science, nuts of all kinds in moderation, nut milks, nut butters and nut seeds are excellent for pacifying *Vata*. *Vata* contains the properties of the elements ether and air and is responsible for energy, movement and nerve impulses of a human body. Breath, speech, blood circulation, and digestion are all the manifestations of *Vata*.

Nuts have been a food staple for thousands of years in different parts of the world. Walnuts are astringent, and eating in moderation is good for people trying to balance *Kapha*. *Kapha* is a *dosha* in *Ayurveda* that governs all structure in the mind and body. It controls weight, growth, lubrication for the joints and lungs, and formation of all the seven tissues — nutritive fluids, blood, fat, muscles, bones, marrow and reproductive tissues. One walnut a day is good for children, as it is considered to have *medhya* qualities — nourishing for the brain. Walnuts are considered natural "stress-busters." Several treatments have been a part of Ayurvedic medicine including *Pathya vyavastha* treatment. This treatment mainly emphasizes on diet, activity, habits, and emotional status of the mind and body. *Pathya vyavastha* mainly gives knowledge about foods in different diseases. It is done with the view of enhancing the therapeutic effects of diet, thereby stimulating the digestion power, and assimilation of food. Mental health is essential for a healthy person and stimulation of patient's mind by nuts helps in relaxation through reduction in stress and indirectly improves other bodily activities (<https://www.mapi.com/ayurvedic-knowledge/ayurvedic-diet/nuts-are-good-for-you.html>; *Maharishi Ayurvedic Products International, Inc. (MAPI)*). As per *Ayurveda*, proper food selection and dietary schedule helps to control the mind and consequently maintain health. Edible as well as non-edible parts of plants have been used in the history of mankind in the form of *Ayurvedic* formulations. Several natural products have been extracted and isolated from various parts of plants for development of new drugs. There are numerous biological components extracted in their natural forms from medicinal plants, their vegetables and fruits, which possess biological activities. Leaves of many plants have been used for medicinal purposes till date. For instance, the studies conducted on the antimicrobial action of 70% methanol extracts from the leaves of *Mikania glomerata* (guaco), *P. guajava* (guava), *Baccharis trimera* (carqueja), *Mentha piperita* (peppermint) and *Cymbopogon citratus* (lemongrass), and *A. sativum* (garlic), *Syzygium aromaticum* (clove) and *Zingiber officinale* (ginger) plants in nature were performed all showed some activity against *S. aureus*, and the most effective extracts were those from clove at the concentration of 0.36 mg/ mL and guava at 0.56 mg/mL (Betoni *et al.*, 2006). *Aloe vera* too, is one of the medicinal plants found throughout India. There are over 100 active constituent are found in *Aloe vera* plant which possesses astringent, haemostatic, antidiabetic, antiulcer, antiseptic, antibacterial, anti-inflammatory, antioxidant, anticancer, anti-diarrhoeal, and wound healing properties (Chatterjee *et al.*, 2013). The mucilage content present in leaves of this plant that is also called as aloe gel is used for various cosmetics and medical applications (Hashemi *et al.*, 2015). *Aloe vera* leaves pulp was found to have better and faster wound healing effect than standard drug Povidone Iodine ointment (5 % w/w) on excision wound model (Purohit *et al.*, 2012). Apart from the uses of leaves of plants, the roots, bark, kernel, shells of dry fruits too have been found to possess biologically active components. According to research conducted on leaves, bark and kernel of *Juglans regia*, several biologically active components are reported till date. Several natural products, which possess biological activities, have been extracted and isolated from various parts of plants for the development of new drugs (Cragg *et al.*, 2013).

THE SECONDARY METABOLITE 'JUGLONE'— ITS POSITIVES AND NEGATIVES

Secondary metabolites (SM) are important natural products produced by plants for several mechanisms; such as communication of plants with other organisms, defence against stress caused to the plant, etc.

Most of the secondary metabolites possess biological activities that exert medicinal properties. Because usage of synthetic drugs leads to different adverse side effects, it is essential to produce such products using natural resources without chemical modification. Juglone [(C₁₀H₆O₃) :1, 4 – naphtha quinone, 5 hydroxy – 8Cl] is an aromatic compound reported to be found in *Juglans regia*, *J. nigra*, *Juglans cineraria* and in other species of the family Juglandaceae such as *Cary*, *Olivivae formis*, *Pterocarya caucarica* and *P. stemoptera* (Thomson, 1957). The hulls of the walnut tree have been used for treatment against parasites, ringworm, itchy and restless feet, to heal ulcers and other fungal infections or skin eruptions and cracks in palm (Morton *et al.*, 1974); Kirtikar *et al.* 1975). In the Indian, Greek, and Arab cultures, the walnut tree has been extensively used as a treatment for common illnesses and even certain type of cancers (Sharma *et al.* 009). In the early 1900s, American doctors prescribed juglone for the treatment of various skin diseases (Soderquist, *et al.*, 1973). Edible and non-edible parts of the walnut tree are not only used as herbal medicine, but also for developing other commonly used products such as toothbrush, hair dye and lip dye. (Alkhawajah *et al.*, 1997). A considerable volume of research has been conducted on various utilities of walnut tree. Tinctures from parts of the walnut tree were reported to be astringent and keratolytic (Bézanger-Beauquesne *et al.* 1990), antifungal (Nahrstedt *et al.* 1981), antimicrobial (Clark *et al.* 1990; Sharma *et al.* 2009), antidiarrheal, anthelmintic, depurative and tonic (Wichtl 1994), antihemorrhagic (Dorland 1981), anti-scrofulous (Fournier 1948), hypoglycemic (Neef *et al.* 1995), diuretic, laxative, blood purifying, and detoxifying (Haque *et al.* 2003; Bhatia *et al.* 2006; Stampar *et al.* 2006). Antiviral activity of the tree against Vesicularis Stomatitis Virus (Husson *et al.* 1986), the vascular protective properties (Perusquia *et al.* 1995), inhibition of tumours (Bhargava 1968 & Westfall 1968) has also been reported. It has also been used as a sedative for animals (Westfall *et al.* 1961 [26]; Auyong *et al.* 1963; Girzu *et al.* 1998). Despite great biological significance of the parts of walnut, the effects that juglone exerts on neighbouring plant life is considered as a setback for advances in herbal medicine preparation from walnut tree (Von Kiparski *et al.* 2007). Stunting of growth via partial or total wilting to death of the affected plant is one of the most commonly reported symptoms of walnut toxicity (Leuty 2010). Juglone is a toxic secondary metabolite that is stored in a non-toxic form in the walnut tree. In 1943, juglone was shown not to be present in the innerroot bark and husks, but rather in the a-hydrojuglone form that is non-toxic and upon exposure to air becomes oxidized to juglone (Gries *et al.*, 1943). Less than a decade later, another research discovered that juglone is stored in the walnut tree as the 5-glucoside of 1,4,5-tri-hydroxynaphthalene (Daglish *et al.*, 1950). The glucoside was demonstrated to be extremely labile and easily hydrolyzed to glucose and a-hydrojuglone. Other than the use of walnut tree parts in production of herbal medicine, parts of the walnut tree can be used in development of herbal pesticides. The toxicity of juglone can be used to inhibit or control the growth of certain problem-causing species of plants, fungus, insects, etc. Juglone can travel to the target organism through several routes: evaporation or rain-wash from leaf surfaces, secretion from roots, and decaying tree material being few of them (Soderquist, 1973). The root theory was first proposed in the beginning of the 20th century, and it shows that juglone is released via plant roots (Cook 1921; Massey 1925). In 1958, a research conducted on this theory suggested a different route called leaf theory. This theory indicates that the secondary metabolite juglone is released via the leaves. (Bode 1958).

However, since juglone is produced in several parts of the walnut tree (roots, hulls, fresh leaves, husks, and inner root bark), it seems that the most likely pathway encompasses a combination of both these theories. Besides, juglone toxicity depends on its accumulation and concentration in the soil where it comes in contact with the roots of the target or adjacent plant (Von Kiparski *et al.* 2007).

BIOLOGICALLY ACTIVE COMPOUNDS IN WALNUT

In a recent research conducted on the shells of walnut species (*Juglans regia*), 12 bioactive components were identified (Jadhav *et al.*, 2019) from methanolic extracts of the shells of *Juglans regia* using Gas chromatography mass spectrometry. The compounds identified were Tridecanoic acid, Acetoxyacetic acid nonyl ester, 2-hexenal 2-ethyl, Eicosanoic acid phenylmethyl ester, Undecane, Benzeneacetic acid decyl ester, (1-pentyl-allyloxymethoxymethyl)-benzene), 9,12-octadecadienoic acid(Z,Z) phenylmethyl ester, Benzyl oxytridecanoic acid, 6,9,12- octadecatrienoic acidphenylmethyl ester (Z,Z), 9- octadecanoic acid (Z) phenylmethyl ester, 9,12,15- octadecatrienoic acid, Z [(trimethyl (sil)oxy, 1 – trimethyl (sily)oxy] ethyl ester (Z,Z,Z). According to several previous studies, these compounds have been shown to exert various biological activities. For example, Tridecanoic acid has been identified in the plant *Mollugo cerviana*, which is reported to have antimicrobial properties (Padmapriya *et al.*, 2016). The presence of Acetoxyacetic acid, nonyl ester in the shells of walnut has also been studied in *Prunus domestica*, a medicinal plant used for therapeutic purposes (Beltagi *et al.*; 2019). Another compound, Eicosanoic acid phenyl methyl ester was extracted from plants *Cleome gynandra* as well as *Cassia fistula* and was found to have anti-inflammatory activity(Ahmad John *et al.*, 2016), (Mohanad Jawad Kadhim *et al.*, 2016). The antifungal and antitumor activity of *Scapania verrucosa* Heeg. is due to the presence of several biologically active components including Benzeneacetic acid decyl ester (Z,Z) (Lei Guo *et al.*, 2008). Phytochemicals identified in leaves of *Jatropha gossypifolia* were 9-Octadecenoic acid (Z)-, phenylmethyl ester with anti-inflammatory, cancer preventive properties; 6,9,12-Octadecatrienoic acid, phenylmethyl ester, (Z,Z,Z) and 9,12,15-Octadecatrienoic acid, 2-(acetyloxy)-1[(acetyloxy)methyl]ethyl ester, (Z,Z,Z) with anti-inflammatory, cancer preventive and hepatoprotective activities (Bharathy *et al.*, 2012). Moreover, 9,12- Octadecadienoic acid (Z,Z) present in *Vitis Vinifera* seed exhibits antioxidant effect because of the presence of polyphenols and natural phenols and is present in plants that are used in cosmetic industries (Suma *et al.*, 2018).

ANTICANCER PROPERTIES OF WALNUT

Cytotoxic, anti-proliferative and antiinvasive effects of Black walnut species were studied on C6 rat glioma cells in vitro (Meskelevicius *et al.*, 2017). This study found that juglone at the highest non-cytotoxic concentration of 4 μ M, suppressed C6 cell proliferation and invasiveness (Meskelevicius *et al.*, 2017). Anti-tumour properties of juglone have been reported till date (Bhargava & Westfall 1968; O'Brien 1991; Paulsen & Ljungman 2005; Xu *et al.* 2010). Mice with spontaneous tumour were treated with juglone (synthetic) extracts, which showed that juglone decreased significantly the gain in tumour size and growth in weight over the period of 9 days of injections (Bhargava and Westfall *et al.*, 2017). Another study suggests that juglone could be used as a promising chemo-preventive agent for treatment of human intestinal neoplasia (Sugie *et al.* 1998).

Walnut leaves are considered as effective as the seeds and have been widely used in Ayurveda and several traditional medicine-based treatments of skin inflammations, ulcers and as antidiarrheic, anti-helminthic, antiseptic and astringent (Lee *et al.*, 1969, Bruneton *et al.*, 1999). In some European and Asian countries, the leaves are also used to prepare infusions (Pereira *et al.*, 2007). Anti-radicalar and antibacterial activities have also been recently described for different *J. regia* varieties (Pereira *et al.*, 2007). The by-product of the walnut production – the green husk of walnut is formed in large amounts. A recent study on the aqueous extract of green husk that possesses antimicrobial activities was suggested to be used as a low-cost natural source of phenolic compounds (Oliveira *et al.*, 2008). Although studies have shown juglone to be cytotoxic in nature, juglone has shown effective results against both human leukaemia (HL-60) cells and doxorubicin-resistant human leukaemia (HL-60R) cells (Segura-Aguilar *et al.*, 1992). A research reported that juglone prevented cancer-affected cells from entering the stage of mitosis (Okada *et al.*, 1967. In a study by Edenharder and Tang (1997), on juglone-treated tumors, chromosomes in the prophase stage of cell division appeared diffused and sticky, and the accumulation of abnormal metaphase figures was observed. Sugie *et al.* (1998) reported that male rats on a juglone-rich diet had a lower incidence and multiplicity of tumors in the small intestine after administration of azoxymethane (a carcinogen particularly effective in inducing colon carcinomas or malignant tumor). Their studies suggested that juglone could be a promising chemo-preventive agent for human intestinal neoplasia. Juglone is reported to be a strong inhibitor of the peptidylprolyl isomerase Pin1 (Chao *et al.*, 2001). The depletion of Pin1 in various human cancer cell lines resulted in mitotic arrest in cancer cells and apoptosis (Zhang *et al.*, 2008). Pin1 is a potential therapeutic target for anticancer research, and juglone being its inhibitor may be used as a potential anticancer drug. In the treatment of tamoxifen-resistant breast cancer, role of Pin1 was studied as it is an important determinant of resistance to tamoxifen (a drug to treat breast cancer). The results showed that Pin1 increases E2F-4- and Egr-1-driven expression of LC-3; an autophago some marker that is highly expressed in the cytoplasm of cancerous cells but not in noncancerous cells Juglone, a potent Pin1 inhibitor, significantly suppressed the TPA (Tumour promoter)-induced expression of E2F-4 as well as Egr-1 transcription factors, which control LC-3 gene expression (Namgoong *et al.*, 2010). The results of a study on antioxidant and antiproliferative activity of *J. regia* leaves on human cancer cell lines represent the first evidence that walnut seed, green husk and leaf methanolic extracts possess effective antihemolytic and antiproliferative activities (studied conducted in human renal cancer cell). These properties seem more likely related to its phenolic constituents. It is therefore suggested that *J. regia* may be used as an inexpensive and easily accessible source of effective natural antioxidants and chemopreventive agents, and future clinical investigations on this medicinal plant should be encouraged (Carvalho *et al.*, 2009). The toxicity effect of juglone is considered to be imparted either by oxidative stress or by electrophilicity (Gant *et al.*, 1986; Öllinger and Brunmark, 1991; Varga *et al.*, 1996. In general, juglone was found to be more cytotoxic than the parent molecule 1, 4-naphthoquinone (Doherty *et al.*, 1987; Babich and Stern, 1993).

NEUROPROTECTIVE PROPERTIES OF WALNUT

In *Ayurveda*, several herbal studies in ancient history in Indian traditional medicine represent herbal therapeutics that not only boost memory (Shinomol *et al.*, 2011), but also restore cognitive deficits and improves mental function.

Components and application of the traditional herb “*Brahmi*” that corresponds to two plants, *Bacopa monnieri* and *Centella asiatica* were studied, which indicates that both plants possess neuroprotective properties and have nootropic activity, with therapeutic implications for patients with memory loss (Shinomol *et al.*, 2011). Among dry fruits and berries, study conducted on Goji berries fed to rats decreased anxiety and depression-like behaviours and spatial memory. These properties of goji berries have been attributed to the presence of polysaccharides (Karakas *et al.*, 2016). In a recent study, the shells of walnut – *Juglans regia* is reported to possess antipsychotic activity. In vivo studies conducted on *Caenorhabditis elegans* showed that the biologically active compounds present in the walnut shells have a great potential to regulate the serotonin from the NSM neurons, thus exerting an antipsychotic effect. This study suggests that the walnut shells being a natural source, can be used as an alternative to the synthetic antipsychotic drugs having side effects. (Jadhav. R, *et al.*, 2019).

ANTIMICROBIAL PROPERTIES OF WALNUT

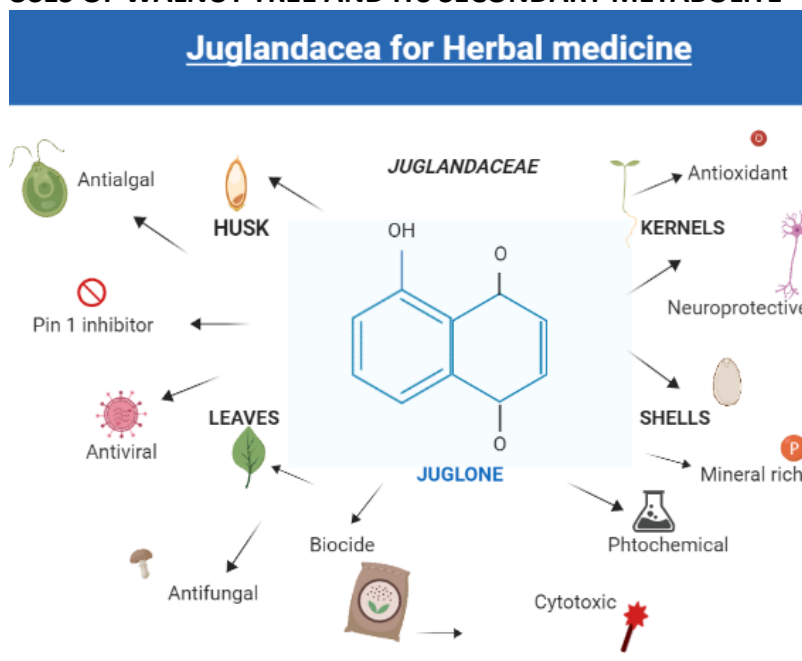
Antifungal activity of juglone has been compared to other known antifungal agents, such as griseofulvin, clotrimazole, tolnaftate, triacetin, zinc undecylenate, selenium sulfide, liriodenine, and liriodenine methiodenine (Clark *et al.* 1990). This study determined that juglone exhibited moderate antifungal activity similar to zinc undecylenate and selenium sulfide, which are commercially available antifungal agents. Juglone’s antimicrobial activity was established to be low-to-moderate, with moderate activity against Gram-positive and acid-fast bacteria and no-to-low activity against Gram-negative bacteria. Another study showed that juglone can inhibit three key enzymes from *Helicobacter pylori*, a microorganism that can cause stomach related illness such as gastritis, peptic ulceration, and gastric cancer in humans. *Helicobacter pylori* affect approximately 50% of the world’s population and its antibiotic resistance is a rising problem. In this case, Juglone could become a new antibacterial agent to treat infections from this bacterium (Kong *et al.* 2008). Growth of algal blooms that produce neurotoxins, which are harmful to local wildlife, as well as farm animals and pets can be inhibited by Juglone. *Anabaena variabilis* and *Anabaena flos-aquae* (significantly inhibited), *Nostoc commune* (moderately inhibited), and *Scenedesmus acuminatus* (slight inhibition) (Krajci & Lynch, 1978; Randall & Bragg 1986) are few of the algae species’ growth that can be inhibited by juglone via allelopathic mechanism.

WALNUT TREE AND ITS USES IN DIET

The most followed healthy diet known is the Mediterranean diet. This diet has an immense impact on promoting positive health and longevity because of its plant-based food and monounsaturated fat-rich food source. It consists of nutrition-rich nuts that are filled with fibre, antioxidants, vitamins, protein, unsaturated fat and omega-3 fatty acids. As a part of this diet, nuts are consumed on regular basis as a snack instead of processed heavy meals. There is ample of evidence that suggests that nuts in the context of the Mediterranean Diet may prevent peripheral artery disease (PAD). The most commonly consumed nuts in the Mediterranean diet are walnuts. Walnuts are not only consumed as a snack, but also as an addition to maximum of the recipes in this diet. Research conducted on leaves, bark, shells of *J. regia* revealed presence of antioxidants, phytosterols, antiproliferative compounds, and several other biologically active compounds.

Among them, phytosterols and antioxidants have attracted considerable attention for their health-promoting activities, which are reported to prevent diseases related to life style; diseases such as obesity, diabetes mellitus, hyperlipidemia, hypertension, etc. A study conducted on six black walnut varieties and English walnut variety indicated that the concentrations of 13 phytosterols present in them varied significantly. β -sitosterol was found to be the most abundant sterol in all the investigated nuts. Several minor sterols, including Δ -5,23-stigmastadienol, cycloeucalenol and 28-methylobtusifoliol, were identified and quantified in black walnut kernels for the first time. However, total phytosterol concentrations of all the black walnuts were not significantly different from that of the English walnut used in this study (Danhet *et al.*, 2018). Due to the cholesterol-lowering effects of walnut, they are considered as one of the best natural sources as an alternative to synthetic sources or medicines. Epidemiological studies have consistently shown a significant positive relationship between regular consumption of walnuts and reduced risks of cardiac diseases (Blomhoff *et al.*, 2006) and some types of cancers (Chang, *et al* 2016). These properties have been attributed to high content of antioxidants, polyphenols and other phenolic compounds present in the walnut kernels. Walnuts are good sources of essential fatty acids (linoleic acid is its major fatty acid), tocopherols and tocotrienols, proteins, fibers, melatonin, sterols, folate, tannins and other polyphenols (Pereira *et al.*, 2008). Among several nut types, walnuts consist highest content of antioxidants. However, the reason attributed to this antioxidant activity is not yet clear.

OVERVIEW OF USES OF WALNUT TREE AND ITS SECONDARY METABOLITE



CONCLUSION

Majority of the studies conducted on the medicinal plants available in nature have reported the great potential of those plants. One of such plants is walnut whose stem, roots, green husk, shells, kernel, which has been extensively used in *Ayurveda* and are known to possess various biologically active compounds. Moreover, being natural extracts, these parts of the plant can be used in different applications.

Juglone the secondary metabolite present in walnut tree. It is known to be toxic and can be used in the production of biocides, herbal pesticides, etc. The biologically active components Tridecanoic acid, Acetoxyacetic acidnonyl ester, 2-hexenal 2-ethyl, Eicosanoic acid phenylmethyl ester, Undecane, Benzeneacetic acid decyl ester, (1-pentyl-allyloxymethoxymethyl)-benzene), 9,12octadecadienoic acid(Z,Z) phenylmethyl ester, Benzyl oxytridecanoic acid, 6,9,12- octadecatrienoic acid, phenylmethyl ester (Z,Z), 9- octadecanoic acid (Z)phenylmethyl ester, 9,12,15- octadecatrienoic acid Z [(trimethyl (sil)oxy, 1 – trimethyl (sily)oxy] ethyl ester (Z,Z,Z) present in the methanolic extract of the shells of *Juglans regia* were shown to possess several bioactive properties, which suggest that the shells of walnut can be used in production of herbal medicine. The walnut shells extract exerted an antipsychotic effect on *C. elegans*, suggesting that the phytochemical constituents have great potential for regulating serotonin release from the NSM neurons. Besides the shells' use in production of neuroprotective drugs, the leaves, bark and kernel too, can potentially be used as source of herbal medicine thereby replacing synthetic drugs in pharmaceutical industries. However, there are lacunae persists in study of walnut bioactivity, and more focus should be on exploring the biosynthetic pathways and the mechanisms of action of the secondary metabolites. Detailed research on its mode of action would help to potentially increase the application of the bioactive compounds in the plant and broaden the spectrum of juglone application. Such studies can further allow scientists to understand its versatile pathways, which could result in cross-application of the plant in other industries as well.

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