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Resource efficiency and environmental impact of juglone in *Pericarpium Juglandis*: A review

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Black walnut (*Juglans nigra*) is considered one of the most valuable plants, with a global production of 3.5 million tons of dried fruit yearly. Throughout the past two millennia, its allelopathic effects have been widely recognized. Black walnuts produce a natural naphthoquinone called juglone, which occurs naturally in all parts of the tree, particularly the green husk, and contributes significantly to the allelopathic effects of black walnut. Except for the fruit's edible nature, the walnut green husk (*Pericarpium Juglandis*) has been used for centuries to make wine, natural dyes, and traditional medicines to cure certain diseases. Within the extracts of walnut green husk, 1,4-naphthoquinones, gallic acid, caffeic acid, and quercitrin were separated and characterized. Among these compounds, the major active ingredient with a good application prospect is juglone, which has proven to be a natural chemical compound with anticancer, antitumor, antibacterial, and antiviral activities, especially the strong anticancer activity. Juglone is also an environmentally friendly biological pesticide and herbicide. Certainly, the environmental impact of juglone also needs to be considered. Significant quantities of walnut green husk are currently produced as a byproduct of walnut production; however, its value has not been fully utilized and explored, which raises environmental concerns. This review attempts to: 1) summarize the origin and historical use of walnut and walnut green husk; 2) introduce the structure, biosynthesis pathway, extraction method, biological activity, and potential applications of juglone, as well as its environmental impact assessment.

KEYWORDS
Juglone, walnut green husk, anticancer, environmental impact assessment, natural product (NP)

1 Introduction

Walnut is one of the most important dried fruits in the world, and it is from the Juglandaceae family, which is considered one of the oldest cultivated nut species worldwide in human history. The Juglandaceae family consists of two major clades, two tribes, two sub-tribes, seven genera, and about 60 deciduous and monoecious species

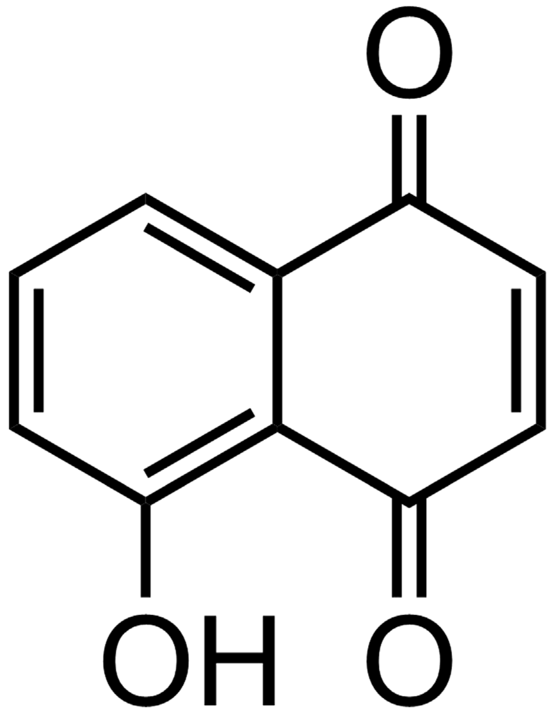


FIGURE 1
The chemical structure of juglone.

(Thakur 2011). Due to its high commercial values, the Juglandaceae family has been artificially cultivated in most temperate regions of the northern hemisphere, including central Asia, the Balkan regions of Europe, the Indian sub-continent, and those on the periphery (Polunin 1977; Manning 1978; Manos and Stone 2001).

Walnut has high nutritional value and health care functions, and the walnut tree has been widely cultivated in more than 50 countries and regions all over the world. In recent years, with the improvement of living standards and enhancement of health awareness, the demand for walnut products is rapidly increasing. According to the data from United Nations Food and Agriculture Organization (FAO), the trading amount of walnuts has increased year by year, and China is one of the most important suppliers of walnuts all over the world. As a matter of fact, China's walnut industry chain has been fully improved from the planting, picking, primary processing and deep processing to a wide variety of walnut and walnut-related products. All of these observations indicate that walnuts manufacturing industry has become the pillar industry in specific regions of China (Liu et al., 2021).

Apart from being used as economic plants, the species in the Juglandaceae family have also been recognized as medicinal plants necessary to cure certain diseases and produce bioactive natural products. In traditional medicine, different parts of walnut trees almost had essential uses. For example, ethanol extracts of green husks (*Pericarpium Juglandis*) had an antihypertensive activity and could inhibit the effects of angiotensin-converting enzyme (ACE) by 40% (Ziai et al., 2006). Moreover, walnut roots were generally used to treat diabetes, its leaves have been used to treat rheumatic pains, fever, diabetes, and skin diseases, and its flowers to treat malaria and rheumatic pain (Mohammadi et al., 2011; Shah et al., 2013; Delaviz et al., 2017).

Juglone (Figure 1), derived from the word "Juglans" as a part of the scientific name for walnut trees, is a substantial natural product existing in *Juglans regia*, *Juglans nigra*, *Juglans cineraria,* and other species belonging to the family Juglandaceae, for example, *Carya olivivaeformis*, *Pterocarya caucarica,* and *Pterocarya stemoptera* (Thomson 1971).

Sina et al. established an RP-HPLC method to determine the juglone content in different species of *Juglans regia* and in different parts of the plant. According to the findings, juglone was found primarily in the green husk (average value of cultivars is about 31.308 mg/100 g, ranging from 20.56 to 42.78 mg/100 g) and leaves (average value of cultivars is about 12.289 mg/100 g, ranging from 5.42 to 22.82 mg/100 g), implying that walnut green husk and leaves are the most important sources of juglone and related walnut phenolics. In addition, the juglone content in green husks is significantly higher than that in the leaves of all cultivars (Cosmulescu et al., 2011).

Furthermore, the allelopathic effects of several species in the Juglandaceae family have been recorded for at least 2000 years. The allelopathic properties, also called "walnut blight," were known to kill or destroy nearby plants (Willis 1985; Jose 2002). However, the cause of walnut blight was almost unknown for centuries until the isolation of walnut lignin from walnut trees for the first time in the 1850's (Vogel and Reinschauer 1856). In 1881, the first scientific paper explaining walnut allelopathy was published (Stickney and Hoy 1881), and in 1887, this "walnut lignin," also called juglone, was first synthesized and characterized (Bernthsen and Semper 1887; Maryon; Strugstad and Despotovski, 2012). Since juglone and related naphthoquinones were rich in walnut green husks, which had allelopathic effects and medical properties, this review first provides a brief overview of the historical uses of walnut green husk and its environmental impact, and then concentrates on the biosynthesis, extraction, properties, and potential uses of juglone as the most important phenolic lignin in the green husk.

1.1 Historical uses of walnut green husk

Wine-making is one of the most prestigiously historical uses of walnut green husk; other applications include dyeing and traditional medical use. The Italian nocino (Culpeper 1826) and traditional walnut liqueur (Stampar et al., 2006) were made of black walnut husks. Nocino, a dark-brown liqueur, was made from unripe green walnuts. According to a sixteenth-century publication by Conrad Gessner, nocino was used to relieve pain from wounds and deadly anthrax. Drinking nocino could also make people immune to pestilence and certain diseases (Culpeper 1826). Also, walnut liqueur, rich in phenolic compounds and vitamins, is a truly popular wine in Slovenia. It is reported that the young green walnuts are much appreciated in traditional folk medicine for making an alcoholic wholesome drink–walnut liqueur. This liqueur takes the walnut green husk just before the hardening of the endocarp (Stampar et al., 2006).

Textile and clothing serving as an essential part of human beings' everyday life is one of the most important global industries in the world, which created a value of 3 trillion USD each year, contributes 2% of the entire global gross domestic product (GDP) and employs over 300 million people worldwide (Desore and Narula 2018; Gbolarumi et al., 2021). Natural dyes were used for coloration of various textile industry, as well as cosmetic industry, pharmaceutical industry, food industry, etc. (Yusuf et al., 2017). The green husk, containing valuable phenolics (natural colorants) and quinonoids which are widely dis-tributed and occurs in large numbers in nature ranging from yellow to red, was used as a natural source of dye of long standing (Beiki et al., 2018). Further, several studies indicated that all parts of walnuts could also be used as a dye. For instance, the Romans used the walnut tree for dyeing black fabric. Evidence of dyeing with the walnut tree was also found at Pompeii. Walnut shells from the *Juglans regia* species were found in Viking settlements (Hedeby) and on burial sites (Oseberg), and Vikings used the walnut tree as a dyeing source. In the Middle Ages, the guilds in European countries structured the different steps in the dyeing process and even had a group dedicated to black dye in Germany. With research and studies, books about dyeing were already published in the mid-sixteenth century. Moreover, in India, it can be traced back to the Bhotiya community in Kumaon, where walnut trees were grown extensively throughout Himalayan Uttarakhand. Native Americans also used the Juglans nigra species, the black walnut, which led to the Meskwaki tribe of the Great Lakes being known for producing black dye from the bark (Bose and Nag 2012). This natural dyes are currently classifyied as disperse dyes that are water insoluble dyes and dye polyester and acetate fibres and possess remarkable antimicrobial activity. Sadeghi-Kiakhani et al. (2019) used two natural dyes extracted from Pomegranate peels and Walnut Green husks to dye for wool fibers and achieved antimicrobial finishing of wool fibers. Moreover, it can be used for antimoth finishing and show an quite effective activity in protecting wool fabric against black carpet beetles (Park et al., 2005).

Walnut green husk is a great source of traditional Chinese medicine, with high medicinal value and broad developmental prospects. For over a thousand years, the green husk and its stem bark have been used as a clinical application in traditional Chinese medicine. The medical use of green husk was originally published in *Kaibao Bencao* (the Song Dynasty), which described its effects in tonifying and repairing the essence of the kidney, astringing the lung and reducing the effects of asthma, inhibiting bacteria, suppressing cough, and acting against cancer. These effects have also been documented in *Chinese Materia Medica*. In addition, medicinal applications of husk include fever relief, liver function improvement, and the treatment of eye infections (Li et al., 2022).

Furthermore, allelopathy is an important mechanism for mediating plant interference by introducing secondary products produced by plants into the soil rhizosphere (Weston and Duke 2003). Allelochemicals can be found in all types of plants and tissues and are released into the soil rhizosphere to make sense. Juglone is the most common plant-produced secondary product and allelochemical in walnut. With the exception of juglone, many substances exist in the inner and outer husk, buds, and bark of walnut, including quinones and their derivatives, flavonoids, tannins, diarylheptanoids, triterpenoids, coumarins, phenylpropanoids, and volatile oils. Previous studies identified a total of 83 compounds in the cultivar Persian walnut (Medic et al., 2021a). It was also noted that juglone was not the only allelochemical representation in the extraction from Juglans regia (Medic et al., 2021b). Cui et al. (2012) have investigated the mechanism, and with different polarity solvents, the extraction from the rhizosphere soil, the rhizosphere, and adjacent soil beneath walnut trees, inhibited seed germination and the length of cabbage seedlings than control, indicating the presence of compounds in the rhizosphere soil of walnut trees with allelopathic effects on cabbage. The extractions from different parts of walnut trees have been reported to inhibit rooting of Tomato (Bamel and Gupta 2022) and exhibited strong inhibition against the seed germination and seedling growth of plants, including Wheat, Cabbage, Mung bean (Yan et al., 2012), Ryegrass, Cole, Radish, Shamrock, Cucumber (Zhao et al., 2005), Ballonflower (Xiaobang et al., 2011a), Salvia miltiorrhiza Bunge (Xiaobang 2011) and Scutellaria (Xiaobang et al., 2011b). Sun et al. researched the interaction between juglone and soil microorganisms and proved that juglone inhibited the growth of soil microorganisms, including Gram-positive bacteria, Gram-negative bacteria, fungi, and actinomycetes. Meanwhile, soil microorganisms could promote the decomposition of juglone (Sun et al., 2013).

In addition to allelopathy, which has been observed for at least two millennia, because of its antibacterial (Fernández-Agulló et al., 2013; Han et al., 2021a), antiprotozoal activities have been reported (Jha et al., 2015; Jahanban-Esfahlan et al., 2019) as well as the toxicity and cytotoxicity of quinones (Arasoglu et al., 2017). More and more studies are focusing on using walnut green husk as a natural pesticide, such as bioherbicidal (Soto-Maldonado et al., 2022) and nematicides (Maleita et al., 2022). Moreover, as the dyed hair exhibited appropriate color strength and had excellent morphology, walnut green husk could be used in practice as a natural hair dyeing agent that demonstrated maximum antimicrobial activity compared with semi-synthetic and commercial hair dyes (Beiki et al., 2018). It has also been reported that it is used as a natural dye, and researchers always extract the juglone from walnut green husk using ultrasonic radiation (Han et al., 2018). Thus, this eco-friendly and green tool possesses not only good dyeing properties but also strong antifungal and solar ultraviolet ray protection properties (Ebrahimi and Gashti 2015).

Furthermore, the extraction of the green husk has a long history of use in traditional medicine and has been widely reported to have antitumor properties. As a result, juglone and its derivatives are used to prepare chemotherapeutic agents against malignant brain tumors (Hua and Mao, 2021). It also has anticancer properties, showing proliferation inhibition and apoptosis induction of colon cancer cell lines cultured *in vitro* and the inhibition of gastric cancer cells that grow both *in vivo* and *in vitro* (Bayram et al., 2019; Zhang et al., 2022). In addition, recent studies indicate that juglone has inhibitory efficacy against the main protease of SARS-CoV-2, which has significantly impacted world politics, the economy, human life, and health since 2020 (Cui and Jia 2021).

1.2 The environmental impact of walnut

As the most common dried fruit in the world, more than 3.5 million tons of walnuts are produced and commercialized annually. China, the United States, and Chile are the world's largest exporters of walnuts. There are a number of planting areas for walnut in the world, and the global walnut resources are vibrant (Yanyshyn et al., 2020). In the process of walnut production for edible products, there are usually three categories of waste: green husks, walnut shells, and walnut cleaning industrial wastewater. Among the three kinds of waste, green husk and walnut shells, as agricultural solid waste, are the most difficult to treat (Huang et al., 2021; Liu et al., 2021). For the treatment of solid wastes, incineration and landfill are usually adopted. However, they may result in hazards such as fire and explosions, vegetation destruction, unpleasant smell, landfill settlement, groundwater pollution, etc. (ElFadel et al., 1997). Due to their adaptation to the Italian climate and soil, walnut trees are reported to cover more than 6,500 ha in Italy alone. They are used mainly for furniture production, generating a large amount of walnut waste (Cambria and Pierangeli 2012; Doty et al., 2016). In addition, industrial wastewater from walnut husk washing was implied to have damage and inhibition on lettuce (cv) and spinach (radicle) (Ciniglia et al., 2012). Consequently, the peel derelict of hazardous substances from walnut fruit picking and processing has given rise to concerns worldwide (Yang et al., 2014). Currently, there are fewer methods for treating walnut waste, mainly through recycling. Due to the physical characteristics of walnut shell (density, compressive strength, inelasticity, etc.), it is ground and broken to make building materials by filling and mixing, as well as filler to produce modified composite materials (Salasinska et al., 2018; Jannat et al., 2021). Additionally, due to the porosity of walnut shell, it is used as a biological adsorption material and its properties were tested, demonstrating that industrial wastewater can be treated, recycled, and utilized through water treatment methods (Kerrou et al., 2021). However, recycling green husk has become a significant challenge in waste disposal. Since 2010, China has successively issued official documents including "Technical Guidelines for Agricultural Solid Waste Pollution Control," "Guiding Opinions on Accelerating the Development of Agricultural Productive Service Industry," and "Opinions on Comprehensively Strengthening Ecological Environmental Protection and Resolutely, Fighting the Tough Battle of Pollution Prevention and Control." In these issued documents, financial funds were authorized to support the resource utilization of agricultural waste, to carry out green planting and breeding circular agriculture, and to increase forest and grassland ecological protection subsidies, etc. Chinese government has also strived to realize the recycling, reduction and harmlessness of agricultural solid waste. As mentioned earlier, the walnut green husk contains juglone (average value of cultivars is about 31.308 mg/100 g) and other phenolic or quinonoid compounds, which have positive utilization prospects and deserve to be utilized effectively. According to government information, a project in Baoji, Shaanxi Province (located in the southwest of the province), is planned to produce 5 tons of walnut green husk extraction (juglone) per year. The annual revenue of this project is expected to reach 86 million yuan and an annual profit of 13.5 million yuan. Such projects can solve not only solid waste pollution but also generate thriving economic benefits. Thus, it is believed that it will be promoted and applied on a larger scale in the future.

2 Biosynthesis, extraction, properties, and potential uses of juglone

2.1 The structure and chemical of juglone

Juglone ($C_{10}H_6O_3$) has a scientific name, 5-hydroxy-1,4 naphthoquinone. It is also called regianin as a synonym and a trade name. As shown in Figure 1, the structure of juglone has a bicyclic skeleton with a naphthoquinone functional group. It is made of yellow needles from benzene plus petroleum ether and gives a purplish-red solution in aqueous solutions of alkalis. It has a melting point of 155°C and a solubility that is slightly soluble in hot water, as well as soluble in alcohol, acetone, chloroform, benzene, and acetic acid. As a natural naphthoquinone pigment, juglone exists in the green husks, roots, leaves, bark, and wood of walnuts. Many plants,

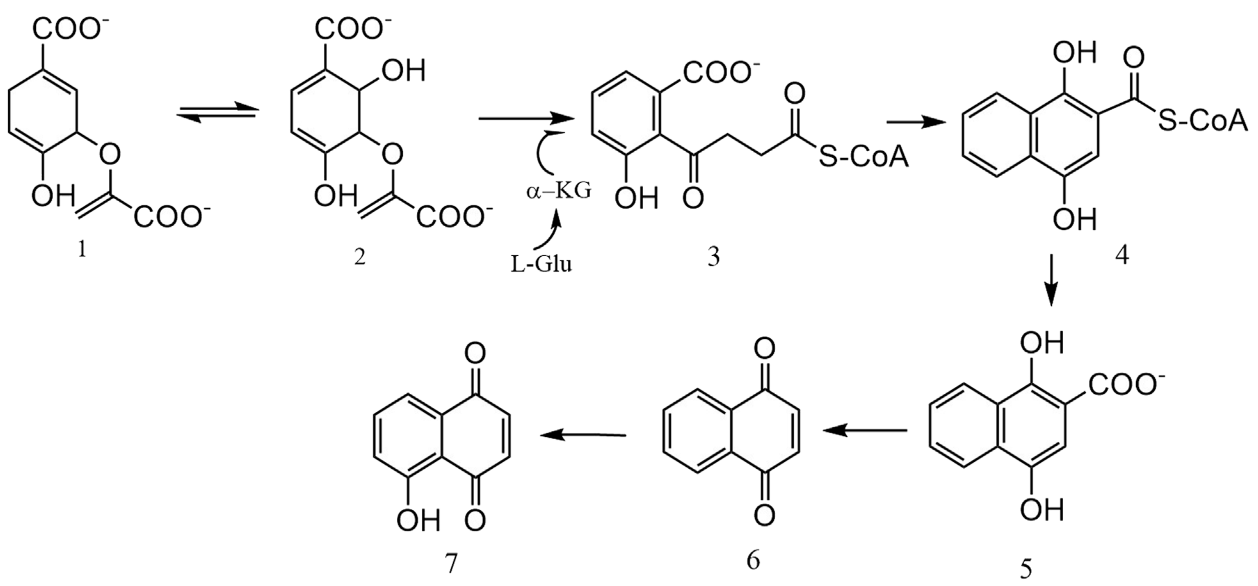


FIGURE 2
Biosynthetic pathway of juglone in walnut (McCoy et al., 2018).

including tomatoes, potatoes, cucumbers, etc., may be damaged or killed when placed within the root zone of juglone-releasing trees due to their chemical properties with allelopathy (Program U. S., 1999).

2.2 Biosynthesis of juglone in walnut

The biosynthetic pathway of juglone is shown in Figure 2. All plants synthesize phylloquinone (Vitamin K1), which is required for blood coagulation and bone and vascular metabolism in humans and other vertebrates. In addition, phylloquinone from green leafy vegetables and vegetable oil represents the primary dietary source of vitamin K for humans (Basset et al., 2017). The classical labeling experiments using English walnut leaves for radiotracer studies revealed that the benzene ring of juglone derives from shikimate (Leistner and Zenk 1968). Later labeling experiments revealed that o-succinylbenzoic acid (OSB) and 1,4-dihydroxynaphthoic acid (DHNA) could be incorporated into juglone, which suggests that juglone's quinone ring originates from L-glutamate via α-ketoglutarate pathway (Müller and Leistner 1976). McCoy et al. hypothesized that biosynthesis of juglone's naphthalenoid moiety is shared with biochemical steps of the phylloquinone pathway. They began by using targeted metabolic profiling and comparative RNA sequencing (RNA-seq) to inspect the co-occurrence between 1,4-naphthoquinones (1,4-NQs) natural product pools and the expression of phylloquinone pathway genes in organs of black walnut, the species with the highest content of juglone. Second, they investigated whether stable isotopically labeled glutamate fed to axenic black walnut root cultures is incorporated into juglone with the same mass shift as expected. If so, juglone is derived from an intermediate of the phylloquinone pathway. However, the results fit the previous hypothesis. Using comparative transcriptomics and metabolic profiling, it was observed that phylloquinone pathway genes encoding enzymes involved in DHNA formation are expressed in black walnut roots to support the production of a metabolite other than phylloquinone, demonstrating that labeling DHNA fed to English walnut leaves could be incorporated into juglone. Feeding stable isotopically labeled glutamate to axenic black walnut root cultures revealed that labeling glutamate incorporates juglone with the same mass shift as that expected for phylloquinone, which can reveal that juglone is *de novo* synthesized in black walnut roots from the DHNA derived via the phylloquinone pathway (McCoy et al., 2018).

2.3 The extraction and purification of juglone from nature origin.

Due to the limited concentration of juglone in walnut green husks (Han et al., 2018), which essentially affects its biological activity and use, it must be extracted and purified using specific methods. Common methods include vacuum distillation (Molong et al., 2007), supercritical carbon dioxide extraction (Ramezani et al., 2020; Romano et al., 2021), high-pressure solvent extraction (Seabra et al., 2019), microwave-assisted efficient extraction (Sharma et al., 2009; Xu et al., 2016), a combination of ultrasonic and microwave methods (Xu et al.,

TABLE 1 The conditions and effects of different extraction methods.

Extraction methods	Conditions	Times	Extractive	Yield of juglone	Reference
Vacuum distillation	Ultrasonic power 300–500 W, temperature 30–50°C	Extraction time 10–30 min	1,4-naphthaoquinone/ 5-hydroxy-1,4-naphthaoquinone/ 5-hydroxy-1,4-naphthaoquinone	0.09%	Molong et al. (2007)
Supercritical carbon dioxide extraction	p = 300 bar, T = 50°C, flow = 10 ml min^{-1}	Extraction time 195 min	Juglone, Ferulic acid, Syringic acid, Hydroxybenzoic acid	1192.04 ± 17.26 mg/100 g	Romano et al. (2021)
High-pressure solvent extraction	45°C and 30 MPa (maximum juglone yield)	1st step (8.7–17.6 min) 2nd step (21.5–126.6 min)	Juglone, 1,4-naphthoquinone, isosclerone, neophytadiene, etc.	0.39–2.34 mg/g	Seabra et al. (2019)
Microwave-assisted efficient extraction	150 W microwave power and 50°C temperature	Extraction time 20 min	Juglone, Gallic acid, Caffeic acid, Quercitrin, Myricetin, Quercetin	0.0147% (ethyl acetate solvent)/ 0.0029% (methanol solvent)	Sharma et al. (2009)
Combination of ultrasonic and microwave methods	solvent to sample ratio 300:1 and ultrasonic power 600 W	Ultrasonic time 25 min, microwave time 90 s	Juglone	624.2–840.9 μg/g	Xu et al. (2016b)
Using macroporous resin	Static adsorption (Sealed on a 175 r/min shaker at 25°C)	Adsorption for 12 h, desorption for 12 h	Juglone with high purity after separation by D101 macroporous resin	Maximum adsorption rate 81.85%, desorption rate 76.5%	Ma et al. (2016)
	Dynamic adsorption (different flow rate)	The flow rate was 1.0 ml/min; the elution rate was 0.33 ml/min			

2016), and even using resin (macroporous resin) (Ma et al., 2016). The extraction effects of the above six methods are shown in Table 1. It can be observed that the different extraction methods and solvents have significant effects on phenolic components and the antioxidant capacity of walnut extract (Trandafir et al., 2017).

2.4 The biological activity and potential use of juglone.

As a natural product, juglone exhibited striking anticancer, antibacterial, and antiviral activities. In recent years, pesticides and herbicides containing juglone as the main ingredient have also been developed. Due to its antiplatelet aggregation properties, it has long been used for dyeing and as an effective medicine for treating high blood pressure.

2.4.1 Anticancer

Nowadays, a number of studies have been conducted to evaluate the anticancer activity of juglone. In addition, juglone derivatives were also designed, synthesized, and tested for anticancer activities. The anti-cancer mechanisms of juglone can be classified as inhibition of tumor cell proliferation, induction of autophagy, antiangiogenesis via inhibiting vascular endothelial growth, inhibition of tumor cell migration and invasion, and others including antiplatelet and inhibition of cellular transformation through PI3K (Phosphati-dylinositide 3-kinases) signaling, inhibition of protein SUMO1-sumoylation (Small ubiquitin-related modifier 1- sumoylation), promotion of DNA damage, inhibition of the growth of cancer stem cells (CSCs) and enhancement of immune function (Tang et al., 2022). For instance, juglone exhibited potent anticancer activity against human cervix cancer (Zhang et al., 2012), breast cancer (Ji et al., 2016), prostate cancer (Mahdavi et al., 2019), colon cancer (Seetha et al., 2020), gastric cancer (Zhang et al., 2022), pancreatic cancer (Narayanan et al., 2022), ovarian cancer (Fang et al., 2015), and several kinds of glioblastomas (like malignant gliomas). So far, twenty-seven naphthoquinones and derivatives have been extracted and identified from walnut green husks. The results from biological evaluation indicated that a few derivatives inhibited the growth of HepG-2 human cancer cells bearing a juglone skeleton (Figure 3), with the IC_{50} values below 22.38 μM (Table 2). Other structurally different naphthoquinones possessed lower cytotoxic activities, with the IC_{50} values far beyond 56.87 μM or without any cytotoxic activity (Zhou et al., 2015). Shi et al. investigated the anticancer activity of juglone against OVCAR-3 ovarian cancer cells, and the results demonstrated that juglone significantly inhibited the growth of OVCAR-3 with an IC_{50} of 30 μM. Juglone displayed an IC_{50} value of 100 μM against human normal SV40 ovarian cells. The results indicated that juglone was a somewhat selective anti-ovarian cancer drug candidate. In addition, the mechanistic investigations implied that juglone caused nuclear fragmentation of the OVCAR-3 cells, leading to the apoptosis of cancer cells. At 60 μM, the percentage of the apoptotic OVCAR-3 cells increased from 2.15% in control to 45.24%. Moreover, upon incubation, juglone caused an upsurge in the Reactive Oxygen Species (ROS) levels in OVCAR-3 cells. It suppressed the migration and invasion of the OVCAR-3 cell, demonstrating the benefit of juglone in ovarian cancer treatment (Shi et al., 2020). Bayram et al. investigated the antiproliferative

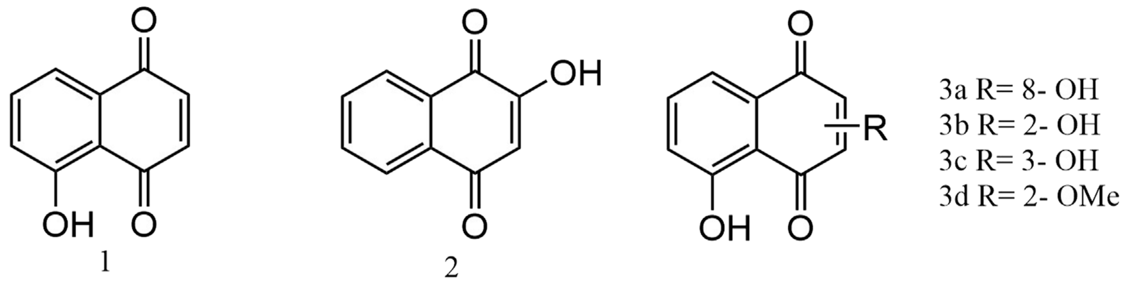


FIGURE 3
Chemical structures of anticancer compounds with juglone skeleton.

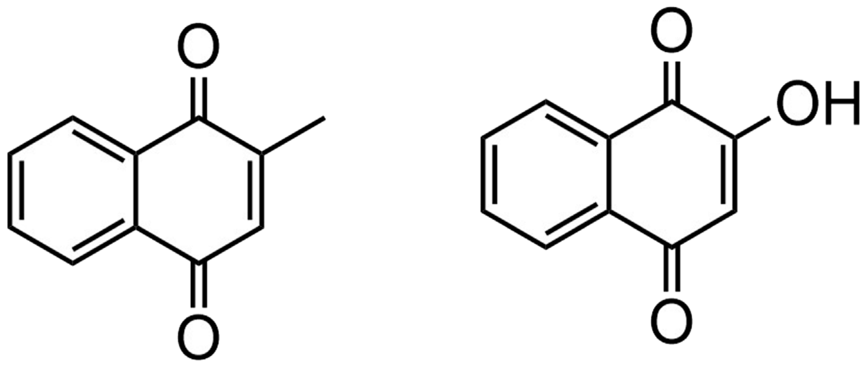
TABLE 2 The IC_{50} value of the compounds bearing juglone skeleton.

Compound	IC_{50} for HepG-2 (μM)	Standard deviation	Reference
1	8.14	1.95	Zhou et al. (2015)
2	18.83	2.98	
3a	15.37	1.63	
3b	7.33	0.52	
3c	22.38	0.66	
3d	56.87	4.27	

activity of juglone against CCL-228-SW-480 colon carcinoma cells and found that the growth inhibition rate was higher in the CCL-228-SW-480 cells treated with juglone compared to control cells. The natural naphthoquinone significantly inhibited cellular proliferation and induced the apoptosis of CCL-228-SW-480 cells *in vitro* (Bayram et al., 2019). Furthermore, based on the chemical structure of juglone, several novel hybrids were synthesized by Mallavadhani et al. and were evaluated for their anticancer activities against seven human cancer cell lines, including the cervix (ME-180 and HeLa), breast (MCF-7, MDA-MB-453, and MDA-MB-231), prostate (PC-3), and colon (HT-29) cells *in vitro*. The results showed that most of the synthesized compounds exhibited strong anticancer activities. Two compounds, in particular, demonstrated more potent antiproliferative activities against prostate and breast cancer cells than etoposide as the positive control (Mallavadhani et al., 2014). In addition, juglone could potentiate the anticancer activity of certain compounds against the proliferation of cancer cells. Arikoglu et al. evaluated the synergistic effects of Juglone-Selenium combination on invasion and metastasis in PANC-1 and BxPC-3 pancreatic cancer cell lines and suggest that the combination has a cytotoxic and dose-dependent suppressive effect on invasion and metastasis of these two pancreatic cancer cells (Arikoglu et al., 2022). Nowadays, with the development of nanomaterials and nanoscience, juglone nanoparticles have been prepared to increase the anticancer activity of juglone. Zhao et al. created juglone-loaded metal-organic frameworks, JMIL101NPs, by encapsulating juglone into porous Fe-based MOFs and then coating them with a cell membrane for homologous tumor-targeting capability. The mechanism of this drug is that the pH-responsive NPs will degrade to selectively release anticancer juglone once they reach the intracellular environment. On the one hand, the released juglone can inhibit Pin1 activity, causing apoptosis. On the other hand, intracellular H_2O_2 levels will be elevated based on the juglone-mediated electron reduction cascade reaction spontaneously. The results showed that, both *in vitro* and *in vivo*, the usage of this nanoparticle with metal-organic frameworks could activate the cascade to provide sufficient H_2O_2 with outstanding antitumor efficacy (Zhao et al., 2022).

2.4.2 Antibacterial

Juglone demonstrated excellent antibacterial activities by inhibiting the formation of bacterial or fungal biofilms or by inducing abnormal oxidative stress and DNA insertion (Gumus et al., 2020). The function object includes *Escherichia col*i (Wang et al., 2016a), *Staphylococcus aureus* (Wang et al., 2016a), Oral Pathogens (Jeon et al., 2009) (including *Porphyromonas asaccharolytica*, *Porphyromonas gingivalis*, *Streptococcus mutans*, *Streptococcus sobrinus*, *Actinomyces viscosus*, *Streptococcus salivarius*, *Lactobacillus rhamnosus*) etc. And the



1 2

FIGURE 4
Menadione (1) and 2-Hydroxy-1,4-naphthoquinone (2).

TABLE 3 The antibacterial activities of juglone.

Bacterial species	Gram-negative/Gram-positive bacterium	Bacterial distribution	Activity of juglone	Reference
Escherichia coli	Gram-negative	Commonly found in the gut of warm-blooded organisms	MIC = 75 μg/ml	(Yuan 2009; Wang et al., 2016b)
Staphylococcus aureus	Gram-positive	Parasitic on human and animal skin, nasal cavity, throat, stomach, etc	MIC = 37.5 μg/ml	Yuan (2009)
Porphyromonas asaccharolytica	Gram-negative		MIC = 0.25 mg/disc	
Porphyromonas gingivalis	Gram-negative		MIC = 0.25 mg/disc	
Streptococcus mutans	Gram-positive		MIC = 0.25 mg/disc	
Streptococcus sobrinus		Human or animals oral Pathogens	MIC = 0.10 mg/disc	Jeon et al. (2009)
Actinomyces viscosus			MIC = 0.10 mg/disc	
Streptococcus salivarius			MIC = 0.10 mg/disc	
Lactobacillus rhamnosus			MIC = 0.5 mg/disc	

activities are shown in table 3. In addition, Han et al. examined the inhibitory effects of juglone against *Pseudomonas syringaepv Actinidiae* (*P. syringae*) and found that juglone, at a concentration of 20 μg/ml, exhibited significant inhibition against *P. syringae* (107 CFU/ml). It was also found that upon the application of juglone, the permeability and integrity of the cell membrane of *P. syringae* were damaged. In addition, juglone not only caused abnormal intracellular oxidative stress but also became embedded in genomic DNA and affected the normal function of DNA in *P. syringae*. Moreover, the environmental scanning electron microscopy results indicated that juglone efficiently restricted extracellular production and prevented cell membrane formation (Han et al., 2021a). The authors also evaluated the activity of juglone against the drug-resistant *Pseudomonas aeruginosa* (*P. aeruginosa*). It was found that juglone destroyed the permeability and integrity, induced the abnormal accumulation of ROS in cells, and affected the formation of cell membranes. The RT-qPCR study showed that five virulence genes and two genes that participated in the production of extracellular polymers were blocked by juglone to decrease the toxicity and infection of *P. aeruginosa* and prevent the extracellular polymers. Additionally, the juglone nanoparticles have been used for antibacterial assays (Han et al., 2021b). Several experiments have demonstrated that the antibacterial activity of nanoparticles is superior to that of free juglone (Arasoglu et al., 2017). For example, Gumus et al. (2020) prepared juglone nanoparticles using a single emulsion solvent evaporation method and studied their effects against *Candida albicans* and biofilms, which were compared with free juglone and fluconazole. The result showed that the less active juglone nanoparticles could achieve a similar inhibition due to controlled release. For pre-established biofilms, juglone nanoparticles were shown to strongly inhibit it, which demonstrated that juglone encapsulated nanoparticles were much more effective.

2.4.3 Antiviral

Compared to anticancer and antibacterial activities, there are relatively fewer assays on the antiviral activity of juglone. Acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV) is the most difficult to treat. During the life cycle of HIV, the reverse transcriptase (RT) enzyme is the most significant factor in viral replication. The enzyme mainly has the following activities: RNA-dependent DNA polymerase (RDDP) activities, DNA-dependent DNA polymerase (DDDP) activities, and ribonuclease H (RNase H) activity, respectively. Min et al. discovered a series of natural products capable of selectively inhibiting RNase H activities. These naturally occurring compounds include benzoquinones, naphthoquinones, anthraquinones, and diterpenoid quinones. In addition, the naphthoquinone juglone demonstrated potent inhibitory activity against RDDP. It also exhibited an IC_{50} value of 5 μM against DDDP. The results indicated that juglone is a bi-target inhibitor against the replication of HIV. Conversely, its single hydroxylated derivative demonstrated much lower inhibitory potency against RNase H activities with an IC_{50} value of only 95 μM (Min et al., 2002). Relevant studies have also been conducted employing computational molecular simulations to explore the antiviral activity of juglone (Vardhini 2014), and the molecular docking studies between juglone and surface glycoproteins of *Influenza viruses* were also investigated (Yang et al., 2013). Recent studies indicate that juglone has inhibitory activity against the main protease (M^{pro}) of SARS-CoV-2, contributing to the replication and transcription of SARS-CoV-2 in host cells. This study synthesized a series of 1,4-naphthoquinones with a juglone skeleton and evaluated their inhibitory efficacy against SARS-CoV-2 M^{pro}. The results showed that more than half of the tested naphthoquinones exhibited potent inhibition against the target enzyme, with an inhibition rate of more than 90% at a concentration of 10 μM. The results from *in vitro* antiviral activity evaluations showed that the most potent M^{pro} inhibitor could significantly restrict the replication of SARS-CoV-2 in Vero E6 cells with an EC_{50} value of about 4.55 μM; however, without any toxicity towards the host Vero E6 cells under tested concentrations (Cui and Jia 2021). The research results provided the rational basis for further research and development of new drug candidates for the SARS-CoV-2 epidemic.

2.4.4 Juglone as a natural pesticide

Researchers have been widely concerned about walnut blight (Meyer et al., 2021; Motmainna et al., 2021). However, with the extraction and isolation of different walnut parts, the allelopathic effects of juglone have been widely reported and gradually developed into green pesticides (Soderquist 1973; Rietveld 1983; Rietveld et al., 1983). It was reported that at high concentrations, juglone could be toxic to associated plants, which Macias thought was a natural alternative for weed control and was developed as a natural pesticide (Macias et al., 2007). Some naturally occurring and semi-synthetic naphthoquinones with naphthoquinone backbones were proposed for barnyard grass and perennial ryegrass allelopathy. And some of them showed strong inhibitory effects on root length, indicating their potential as models in the development of natural herbicides (Duran et al., 2019). In addition, the insecticidal effect of juglone, its disturbance in the metabolic profiles of *Aphis gossypii* (Lv et al., 2018), and the acaricidal and enzyme inhibitory activities of naphthoquinones and their analogs against *Psoroptes cuniculi* (Shang et al., 2018) have been reported, indicating that juglone can be used as a potential alternative bio-acaricide in agriculture.

2.4.5 Miscellaneous

In addition to the above-mentioned biological activities, many studies have reported its application in dyeing. Juglone is an environmentally friendly natural dye that imparts a natural red-brown color (Waseem ul et al., 2021) and has better dyeing performance with sodium sulfate as a mordant (Han et al., 2018). It exhibited antibacterial activity and also reduced UV absorption to achieve a protection effect (Ebrahimi and Gashti 2015). Based on the dyeing activity, juglone demonstrated the potential to be a natural colorant for biodegradable polymers (polylactide and polyhydroxybutyrate), with no change in the properties of the polymers, including mechanical properties and thermal stability (Latos et al., 2019). Moreover, it can be used as an antihypertensive agent that exerts its antihypertensive effect through vasorelaxation, which is mediated by nitric oxide, inhibition of intracellular calcium release, and opening of K^+-channels (Ahmad et al., 2020). Similarly, it can be used to design and develop collagen with juglone functionalized silver nanoparticles as a novel wound dressing material with the potential to be used in rapid wound closure (Natarajan and Kiran 2019). Trypanosomiasis (including American trypanosomiasis and African trypanosomiasis caused by *Trypanosoma cruzi* and *Trypanosoma brucei*) is a serious illness that is eventually fatal if not treated and has variable surface antigens which makes it non-availability of vaccines against trypanosomes. Rani et al. have researched the juglone and their derivatives as potential drug molecules against trypanosome parasites and enumerated the antitrypanosomal properties of more than 30 compounds which all showed excellent activities (Rani et al., 2022). Furthermore, more advanced research also involves electrochemistry, renewable-juglone-based high-performance sodium-ion batteries developed by a renewable-biomolecule-based electrode. Also, the hybridized electrodes can be fabricated with arbitrary size and shape and exhibit superior capacity and cycle performance, which is expected to find application in future energy-storage devices (Wang et al., 2015).

3 Environmental impact of juglone

Naphthoquinones, a group of highly reactive organic chemical species, are found in the environment as byproducts of fuel combustion, tobacco smoke, and plants. Juglone is the primary derivative of 1,4-naphthoquinones and 1,2- and 1,4-naphthoquinones, which are toxic metabolites of naphthalene, the major polynuclear aromatic hydrocarbon present in ambient air. When exposed to the environment, they interact with biological systems and induce toxicity (Kumagai et al., 2012). For example, relevant particles less than 2.5 μM in diameter activate the epidermal growth factor receptor (EGFR) system (Blanchet et al., 2004), causing structural damage to the bronchial epithelium and triggering asthma (Davies et al., 2003).

3.1 Effects of juglone on marine organisms

Juglone (5-hydroxy 1,4-naphthoquinone) and also its derivative plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) were reported to have the most significant toxicity against most aquatic organisms (Wright et al., 2007a). Juglone was reported to be an apparent fish toxicant (Marking 1970), which demonstrated that at concentrations ranging from 27 to 88 ppb within a 96-h treatment period, juglone was highly toxic to nine species of fish, including rainbow trout (*Salmo gairdneri*), northern pike (*Esox lucius*), goldfish (*Carassius auratus*), carp (*Cyprinus carpio*), whitesucker (*Catostomus commersoni*), black bullhead (*Ictalurus melas*), channel catfish (*Ic-talurus punctatus*), green sunfish (*Lepomis cyanellus*), and bluegill (*Lepomismacrochirus*). Juglone has been shown to be toxic to *Tetrahymena pyriformis (T. pyriformis),* and it has almost the highest toxicity of the eight naphthoquinones. It was also concluded that the quinone toxicity was not related to hydrophobicity or the oxidative stress mechanism, with the initiation of cell damage rooted in the ability of the quinone to form free-radical metabolites such as semiquinones (Schultz and Bearden 1998). Juglone also exhibited toxicity toward other marine organisms such as *Glenodinium* (the chloroplast deterioration was apparent after 7 days of exposure), *phytoplankton* (juglone concentrations as low as 0.1 mg/L inhibited phytoplankton growth), and *Vibrio fischeri* (the toxicity could reach as low as 0.005 mg/L) (Wright et al., 2007b). In addition, the possible toxicity of *Daphnia magna (D. magna)*, a *planktonic crustacean*, plays a vital role in aquatic food webs. Though there is no direct experimental evidence, the derivative and isomeride of juglone, menadione, and 2-hydroxy-1,4-naphthoquinone (Figure 4) have been reported to be toxic to *D. magna*, with the 48 h EC_{50} of 0.531 mg/L (very toxic) and 20.297 mg/L (harmful), respectively (Song et al., 2011). Moreover, these two compounds have also been reported to be toxic to zebrafish (*Danio rerio*), with a 96 h LC_{50} of 0.178 mg/L (very toxic) and 25.752 mg/L (harmful), respectively (Song et al., 2010). Another study found that both compounds are toxic to *Chlorella pyrenoidosa,* with a 72 h EC_{50} of 5.367 mg/L (toxic) and 18.485 mg/L (harmful) (Guo et al., 2010). The toxicity of chemicals for the above three assays was classified into three classes according to the guidelines of the European Chemicals Bureau (European, Commission and Fang 1996) and the Organization for Economic Co-operation and Development (OECD 2002). However, a study indicated that 1,4-Naphthoquinone derivatives showed no toxicity toward zebrafish embryos, indicating the need for further research (Janeczko et al., 2018).

3.2 Effects on animals

Researchers have suggested that juglone could completely inhibit the formation of rat aortic new vessels, reduce the number of endothelial cells, stimulate the existing blood vessels in the chorioallantoic membrane of chick chorioallantoic, and have vascular stimulation, hemolyzation, and agglutination in a dose-dependent manner, with the inhibition of angiogenesis at a concentration of 12.5 mumol/L, indicating that juglone can inhibit the formation of new vessels (Chen et al., 2010). According to previous studies, juglone can inhibit the development of bovine oocytes by directly inducing ROS accumulation, apoptosis, and mitochondrial dysfunction (Mesalam et al., 2021). The toxicity of juglone to isolated rat hepatocytes has been evaluated previously. Both 5-OH (5-OH-1,4-NQ the juglone) and 2-OH (2-OH-1,4-NQ the lawsone) -1,4-naphthoquinone induced concentration-dependent cytotoxicity to isolated rat hepatocytes accompanied by intracellular glutathione depletion. Furthermore, the mechanism of juglone toxicity involves the formation of its corresponding naphtho semiquinone, active oxygen species, and redox cycling, as it stimulates a disproportionate increase in both microsomal NADPH oxidation and oxygen consumption (d'Arcy Doherty et al., 1987). Another study also investigated the effect of hydroxy substitution on 1,4-naphthoquinone toxicity in cultured rat hepatocytes. The findings revealed that the toxicity of the quinones decreased from 5,8-dihydroxy-1,4-naphthoquinone > 5-hydroxy-1,4-naphthoquinone > 1,4-naphthoquinone > 2-hydroxy-1,4-naphthoquinone. Further tests showed that the toxicity of 1,4-naphthoquinone and 5-hydroxy-1,4-naphthoquinone has an electrophilic addition component, whereas the toxicity of 5,8-dihydroxy-1,4-naphthoquinone is due to free radical formation (Ollinger and Brunmark 1991). Furthermore, the complexes based on the juglone ($Fe_{(III)}$ and $Fe_{(II)}$) were toxic to isolated rat hepatocytes within the naphthoquinone series, with the order of toxicity being $Fe_{(II)}$ > parent naphthoquinone > $Fe_{(III)}$. The juglone complex had higher toxicity than the lawsone complex, and the juglone complex facilitates the formation of stable semiquinone species (Kumbhar et al., 1996). Additionally, it has been concluded that the isomeride 2-hydroxy-1,4-naphthoquinone has hemolytic activity and nephrotoxicity in rats (Munday et al., 1991). Beyond these, the derivatives of juglone, 2-hydroxy-3-alkyl-1,4-naphthoquinones (Munday et al., 1995a), 2,3-dialkyl-1,4-naphthoquinones (Munday et al., 1995b), etc., have also been reported to be toxic to animals, indicating that the biotoxicity of juglone and its derivatives should be given significant consideration.

4 Discussion

According to previous studies, more than 3.5 million tons of walnuts are produced worldwide annually. Consequently, walnut green husks, an abundant byproduct of dry fruit production, have not been fully explored and utilized, and their value has also not been fully recognized and developed.

This review describes in depth the historical application and environmental impact of walnuts (Juglans regia) and walnut green husks. The natural naphthoquinone juglone, produced in walnut green husks, contributed to the biological activity of the husk. Its structure, biosynthesis pathway, extraction method, biological activity, and potential application were also discussed, as well as its environmental impact assessment.

Juglone is natural product, which was isolated from the husks, leaves, roots of walnut trees and efficient synthetic methods of the natural naphthoquinone have also been developed in recent years (Shvydkiv et al., 2012; Pasha et al., 2022). Juglone exhibited potent anticancer, antibacterial, and antiviral activities as a natural naphthoquinone. With the development of nanotechnology that described above (Arasoglu et al., 2017; Natarajan and Kiran 2019; Sadeghi-Kiakhani et al., 2019; Gumus et al., 2020) and the gradual discovery of synergistic effects ((Arikoglu et al., 2022)), the biological activities of juglone have been greatly improved. However, due to the lack of clinical applications, clinical studies of juglone should be further explored (Tang et al., 2022). It is also an environmentally friendly biological pesticide and herbicide, which offers a new option for developing novel natural product-based effective pesticides and agrochemicals. This chemical is a major component of the yellow-orange pigment for dyeing. All of these properties suggest an excellent application prospect for this natural naphthoquinone. However, its impact on environmental ecosystems should be further investigated, especially for marines and animals, and the mechanisms therein should also be explored significantly.

Juglone occurs naturally in all parts of walnut trees, especially in the green husk, and the dry fruit industry generates vast quantities of green husks as a byproduct. Therefore, its potential use should be developed to avoid producing solid waste as well as reduce wastewater production. As an allelochemical product, juglone produced by walnut trees should also be investigated for its applications across various agricultural applications, as conventional synthetic pesticides and agrochemicals pose severe environmental threats to contemporary agriculture. Establishing an efficient extraction method for juglone from green husks and using this allelochemical as a green pesticide to meet consumer needs for greener and more sustainable agricultural solutions should be one of the resolutions to reduce the environmental impact of a huge amount of green husks. The most significant aspect is that this natural active ingredient can be used in many fields to maximize the use of natural resources and improve the efficiency and quality of resource utilization. Unquestionably, it is crucial that we pay more attention to this deep-seated utilization of natural resources.

Author contributions

The conception and design of this review was primarily done by the first author and supervised by the two corresponding authors. The first and second authors collected literature and data together. The paper writing and the drawing of the pictures used in the paper are done by the first author and the second author. Corresponding author Pro. JC guided the two authors to complete the revision and improvement of the paper.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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