Agricultural Uses of Juglone: Opportunities and Challenges

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Abstract: Application of conventional synthetic pesticides and agrochemicals has boosted the yield and productivity of crops by reducing pest infestation and promoting crop growth yet increasing reliance on many of these products poses serious environmental threats. This has led to growing interest in obtaining more environmentally friendly alternatives to conventional pesticides and agrochemicals. Allelochemicals produced by plants, fungi, and microbes offer options for developing novel natural product-based pesticides and agrochemicals that are effective but with lower environmental half-lives. Here, we review the current state of knowledge about the potential use of juglone (5-hydroxy-1,4-naphthoquinone), the allelochemical produced by black walnut trees (Juglans nigra), which has been investigated for applications across a range of different agricultural purposes. We then offer our perspective on what opportunities and challenges exist for harnessing juglone as a component of sustainable agriculture.

Keywords: allelochemical; agrochemical; biostimulant; Juglans; juglone; natural product; pesticide; sustainable agriculture; urease inhibitor

1. Introduction

Juglone, 5-hydroxy-1,4-naphthoquinone (Figure 1), is a quinoid compound that functions as an allelochemical when released from trees in the walnut family (Juglandaceae) into the rhizosphere. Juglone has been isolated from several Juglandaceae members, including Juglans nigra L. (black walnut), J. regia L. (English walnut), J. ailantifolia Carr., J. mandshurica Maxim., Carya tomentosa Nutt., C. ovata (Mill.) K. Koch, C. illinoensis (Wangenh.) K. Koch (pecan), Pterocarya fraxinifolia (Lam.) Spach, and Platycarya strobilacea Siebold & Zucc. [1,2]. Juglone is excreted from roots and exuded from litterfall in its reduced form, hydrojuglone [3–6]. Hydrojuglone is colorless, nontoxic, and is abundant in leaves, roots, husks, and bark [7]. Upon release, hydrojuglone is oxidized in air to its toxic form, juglone [8–10]. Juglone taken up by sensitive plants has general inhibitory effects on growth and development [4]. Moreover, juglone is the bioactive compound in certain plant parts used in traditional medicines for treating ailments including allergies, gastrointestinal abnormalities, cancer, and different fungal, bacterial, and viral infections [9]. Due to its general toxicity, juglone itself is unlikely to ever become a clinically significant drug. However, efforts are ongoing to synthesize juglone analogs with enhanced bioavailability, lower toxicity, and improved selectivity [11].
The allelopathic effects of black walnut on neighboring plants have been reported for centuries and remain a concern for home gardeners today [8,12–14]. Plinius Secundus (Pliny the Elder) is credited with being the first to report the phytotoxic effects of black walnut. It was not until the 1850s, however, that juglone, previously known as nucin, was first isolated [15]. By 1887, juglone could be synthesized [16], and in 1881 the first scientific article related to its allelopathy was published [17]. In 1928, juglone was determined to be the compound responsible for the phytotoxicity of walnut trees [18]. Today, natural products like juglone are touted as promising alternatives to synthetic agrochemicals due to their reported pesticidal properties and other biochemical activities of agricultural interest. Perhaps most notably, juglone exhibits inhibitory effects on several weed species [19], as characterized by effects like leaf wilting and yellowing or damaging the roots through induction of reactive oxygen species (ROS) together with calcium accumulation resulting to death [20,21]. Juglone is also reported as being lethal to larval development and insect flight muscle mitochondria, to have sedative effects on fish and other animals, to have mutagenic, carcinogenic, and lethal effects on animal cells, and to have repellent, antifeedant, antimicrobial, antifungal, and antiparasitic properties [19,22–26]. However, toxicity of juglone varies depending on several factors, such as the donor plant species, quantity released and amount accumulated, soil pH, texture, and organic matter content [27,28]. Therefore, it is worth investigating the use of juglone in agricultural applications and to study the factors precluding it from being implemented as a chemical tool. In this review, we provide an overview of the current state of knowledge on juglone, which encompasses nearly 100 years of research and observations. We also address the challenges and prospects to harnessing it as a natural product-based pesticide and/or agrochemical. Finally, we identify areas where further research is needed to implement juglone across areas of sustainable agriculture.

2. Prospects of Juglone as a Natural Product-Based Pesticide

Since the dawn of agriculture, pests have posed threats to crops, fish, livestock, and non-target insects. When it comes to food crops, for example, it is estimated that over 140,000 species of insects, weeds, nematodes, and microorganisms, including pathogenic fungi, viruses, and bacteria contribute to agricultural losses [29]. On average, 26–50% of crop losses have been reported in rice, potato, coffee, maize, cotton, wheat, soybean, barley, and sugar beet [30]. In total, around one-third of the total production of major crops is damaged due to pests worldwide [31]. More recently, the Food and Agriculture Organization (FAO) of the United Nations estimated that 19–30% of cereals, 33–60% of roots and tubers, and 37–55% of fruits and vegetables are damaged globally by crop pests [32].

To meet the demand for the agricultural output needed to sustain an increasing global population, 3.5 billion kg of active ingredient is used in the form of synthetic pesticides each year by farmers [33]. While pesticides are regulated in certain countries, farmers and their environments in developing countries are often exposed to toxic chemicals that are banned or restricted in other countries. This exposure is further exacerbated when inappropriate dosages, application techniques, equipment, and/or storage practices are employed [34]. Continued use of the same pesticides has also increased the rate at which pests develop resistances to available chemical active ingredients. Moving forward, developing new pest control products will be constrained by stringent environmental, toxicological, and regulatory requirements [35]. This opens the door for producing natural product-based pesticides. Natural products are compounds biosynthesized by living organisms and which have biological activities resulting from Darwinian selection. Thus, they offer a diverse source of new chemical
structures and modes of action. They are also likely to be met with more public and regulatory acceptance than synthetic chemicals, especially considering that they generally have lower environmental half-lives [36]. Juglone has emerged as a strong candidate for developing natural product-based alternatives to currently used pesticides for controlling insect pests, microorganisms, nuisance algae, and weeds. In the sections that follow, we highlight literature reporting on the effectiveness of juglone in controlling these pests.

2.1. Insecticidal Properties

Toxic effects, such as weight reduction, antifeedant activity, deterioration of morphology and sexual development, and reduction in egg hatching, of juglone and other naphthoquinones on certain phytophagous insects have been widely reported [25,37–40]. The melon or cotton aphid (*Aphis gossypii* Glover) is a major insect pest of cotton, melon, pumpkin, pepper, and tomato worldwide [41], causing damage to crops through direct feeding, photosynthesis inhibition, and acting as a viral vector [42,43]. As a result, plants become stunted and senesce [44]. To control the pest, large amounts of chemical insecticides are applied every year, which has led to broad-spectrum resistance to organophosphate, carbamate, and pyrethroid insecticides [45]. Using NMR-based “metabonomics,” a subset of metabolomics in which metabolomes are measured and mathematically modelled, Lv et al. [25], found that juglone causes physiological disturbances in *A. gossypii* hemolymph that may underly its insecticidal properties.

*Galleria mellonella*, or the greater wax moth, is a grave threat to apiculture as its larvae feed on honeycombs, pollen, honey, and beeswax in hives [46], causing significant losses [47,48]. In Turkey, some beekeepers use *J. regia* leaves and/or walnut husks to control *G. mellonella* infestation in beehives. To identify the role of juglone in this control mechanism, Altuntaș et al. [26], and Erbaş and Altuntaş [48] incorporated the compound into the *G. mellonella* first-instar larvae diet and found that juglone prolonged larval developmental time, decreased pupal and adult weights, and lowered total egg numbers and egg hatchability. These findings are supported by similar results from other studies in which juglone was incorporated into insect diets [26,37,40,49,50]. Juglone’s toxic effects have also been observed on *Aedes aegypti* (yellow fever mosquito), *Drosophila melanogaster*, *Manduca sexta* (tobacco hornworm) [49], *Lymantria dispar* (gypsy moth) [37] and its larvae [51], *Callosamia promethea* (saturniid moth) [38], *Trichoplusia ni* [52], *Tetranychus urticae* [53], and *Pieris rapae* and *Helicoverpa armigera* [40]. Therefore, it seems that there are opportunities for using both purified juglone as well as extracts or litter from walnut-producing species for controlling multiple types of insect pests.

2.2. Bactericidal Properties

Several articles have been published on the antibacterial activities of juglone against a number of bacteria ranging from those that affect animal guts to those that contaminate livestock products to others that represent plant pathogens [54–62]. Clark et al. [63], reported that juglone has moderate inhibitory activity against Gram-positive and acid-fast bacteria, and little activity against Gram-negative bacteria. In contrast, strong bactericidal activity of juglone was observed on *Erwinia amylovora*, a Gram-negative bacterium that is the causal agent of fire blight disease in pome fruit [58]. Juglone also inhibits key enzymes in the Gram-negative bacterium *Helicobacter pylori* [64]. Using a proteomics approach, Wang et al. found that in *Staphylococcus aureus*, proteins functioning in the tricarboxylic acid cycle and in DNA, RNA, and protein synthesis are inhibited by juglone [62]. In addition, juglone was found to increase oxidoreductase activity in cells and to create a peroxidative environment, significantly reducing cell wall formation and increasing membrane permeability [61]. Such changes to the bacterial cell biochemical environment likely have the capacity to affect antibiotic resistance activity [60].

Just as there are benefits to the bactericidal properties of juglone, there are examples where caution needs to be taken when introducing juglone into an environment or introducing beneficial bacteria into a juglone-rich environment. Nitrogen-fixing shrubs and trees are sometimes planted in walnut orchards to increase available nitrogen in the soil. This practice is cost effective and environmentally friendly as
it reduces nitrogen fertilizer requirements. However, Dawson and Seymour [65] reported that juglone slightly inhibits growth of *Rhizobium* and completely inhibits growth of *Frankia* species which form associations with actinorhizal plants [66]. In contrast, some bacteria can degrade juglone in soil [67], and certain *Pseudomonas* species can use juglone as their sole carbon source [68]. Thus, the presence of these organisms in the soil could undermine the efficacy of applying juglone or juglone-containing extracts in field or other uncontrolled settings.

### 2.3. Fungicidal Properties

Pathogenic fungi are responsible for damaging crops in both pre- and post-harvest stages, and also for the increased mortality of edible insects. Synthetic chemical fungicides are typically applied to control such pathogenic fungi, though a few natural product-based fungicides are available [69–72]. Clark et al. [63], compared the efficacy of juglone with several commercially available antifungal agents ( clotrimazole, triacetin, tolnaftate, griseofulvin, zinc undecylenate, selenium sulfide, liriodenine, and liriodenine methiodide) and reported that the moderate antifungal activity of juglone was as effective as zinc undecylenate and selenium sulfide. In addition, the antifungal activity of juglone was observed against *Penicillium* spp., *Aspergillus* spp., *Hansenula* spp., and *Saccharomyces carlsbergensis* [55,56].

Higher levels of juglone in pecan cultivars and other species in the Juglandaceae family correlate with increased resistance to pecan scab caused by *Fusicladium effusum* [73]. Foliar application of juglone to bean seedlings was found to confer better protection from rust compared to certain commercial fungicides [74]. On the other hand, Arasoglu et al. [75], compared the antifungal properties of free juglone with its poly (D,L-lactic-co-glycolic acid) [PLGA] nanoparticle formulation against *Aspergillus flavus*, *Candida albicans*, and *Fusarium* spp. Their results indicate that the juglone-encapsulated nanoparticle was more effective than free juglone. Hence, juglone or its PLGA nanoparticle formulations might be useful as a tool for the developing biofungicides.

Comparisons of the antifungal activity of green walnut husk extracts with pure juglone against the plant pathogenic fungi *Alternaria alternata*, *Rhizoctonia solani*, *Botrytis cinerea*, *Fusarium culmorum*, *Phytophthora infestans*, as well as *Ascosphera apis* revealed that juglone is not the only component responsible for inhibiting mycelial growth [76]. Phenolic compounds were also found to synergistically contribute to the activity of the extracts possibly by modifying the antifungal activity of juglone [76]. In another study, Stytkiewicz et al. [77], examined the antifungal potential of methanolic, ethyl acetate, and acid-hydrolyzed methanolic extracts of *J. regia* leaves against pathogenic *Candida albicans* strains and observed that the methanolic extract produced the highest anticanidial activity. Methanolic extracts of *J. regia* leaves contain a range of phenolic acids (e.g., caffeic, chlorogenic, cinnamic, and coumaric acids), tannins, and flavonoids [77]. Interestingly, some fungi are proposed to play a role in the transfer of juglone from plants into the soil, such as the case with arbuscular mycorrhizal fungal hyphae transporting juglone from black walnut roots into the rhizosphere [78,79]. Thus, some fungi have evolved mechanisms to cope with high levels of juglone in the rhizosphere.

### 2.4. Algacidal Properties

Climate change and eutrophication caused by agricultural runoff has promoted the proliferation of “algal blooms” caused by cyanobacteria, diatoms, and green algae that threaten drinking water and aquatic ecosystems [80–82]. Bloom-forming cyanobacteria and nuisance algae shade light for other phytoplankton and reduce water quality by depleting oxygen, producing foul odors [83], and endanger aquatic food webs and human health through released toxins [84–87]. Juglone was shown to inhibit the growth and physiological performance of cyanobacteria including *Microcystis aeruginosa* [88], *Anabaena variabilis*, *A. flos-aquae*, and *Nostoc commune* [89,90]. Growth of Streptophytic (*Closterium acerosum*, *Micrasterias thomasiensia*, and *Spirogyra grevilleana*) and chlorophytic (*Pandorina morum* and *Eudorina californica*) freshwater green algae is also inhibited by juglone at concentrations ranging from 0.1–1 mM [91]. Interestingly, lower concentrations, 0.1–1 mg L$^{-1}$ (0.57–5.7 µM), were found
to stimulate growth of chlorophytic freshwater green algae *Chlorella vulgaris*, *Scenedesmus ecornis*, and *S. quadricauda* and the freshwater diatoms *Asterionella formosa*, *Fragilaria crotonensis*, and *Synedra acus* [92]. Park et al. [92] also found that juglone can inhibit the harmful bloom-forming nuisance cyanobacterium *Microcystis aeruginosa* and the freshwater diatom *Stephanodiscus hantzschii* by up to 93% and 75%, respectively, at 1 mg L$^{-1}$ (5.7 µM). The same study found that even less juglone (0.1 mg L$^{-1}$; 0.57 µM) inhibits growth of the cyanobacterial species *A. flos–aquae*, *Oscillatoria curviceps*, and *Phormidium subfuscum*. Thus, cyanobacteria generally appear to be more susceptible to juglone than do green algae and diatoms. While cellular morphology and anatomy may play a role, given the propensity of juglone to induce ROS formation [93], this is consistent with studies showing that cyanobacteria are more susceptible to hydrogen peroxide than are green algae and diatoms [94,95]. It should be noted that in addition to algae, juglone also acts as a general toxicant to fish and other marine organisms [23,91] and must therefore be used with caution (also see Section 5 and cited references for more information).

### 2.5. Phytotoxic (Herbicidal) Properties

Several articles have been published reporting on the phytotoxic properties of juglone on the germination and growth of different herbaceous and woody crops species (Table 1). Like other 1,4-naphthoquinones, juglone’s phytotoxicity comes from generation of ROS and glutathione (GSH) depletion [93], and from impairing plasma membrane H$^+$-ATPase [96], a mode of action distinct from existing synthetic commercial herbicides [97]. Rapid irreversible growth inhibition in maize coleoptile segments indicates that the impairment of plasma membrane H$^+$-ATPase is via alklylation with juglone [98]. To study juglone phytotoxicity, known concentrations of juglone, most often ranging from µM to mM concentrations, are applied either in hydroponic or soil culture and inhibition is observed [1,99,100]. Nonetheless, little remains known about actual juglone concentrations present in soil [27,28,101], or about the time required to build up sufficient amount of juglone to show toxicity to neighboring species [99]. Dana and Lerner [14] and Strugstad and Despotovski [23], have reported a number of vegetables, fruits, flowers, landscape, and field crop species that are susceptible and tolerant of juglone. Investigation of the effects of juglone on Norway spruce (*Picea abies*) revealed that it has more potent post-germination effects than it does on germination, perhaps suggesting that seeds are more biochemically equipped to neutralize ROS [102]. The seed coats of some species have been proposed to function as barriers to juglone, however, Kocaçaliskan et al. [103], observed no significant differences of juglone’s inhibitory effect on seedling growth and protein content when comparing intact and coatless cucumber seeds. At the same time, differences in germination rate between species with relatively thick (cucumber) versus thin (cress and tomato) seed coats were observed [104]. Interestingly, a recent study found that black walnut extracts increased the height and number of leaves of rice (*Oryza sativa*) but had the opposite effect on height in wheat (*Triticum aestivum*) [105]. At the same time, Chi et al. [21], reported that juglone significantly reduces rice root growth at low concentrations (5–50 µM) and leads to changes in gene transcription associated with cell growth, cell wall formation, chemical detoxification, and abiotic stress responses with rapid induction of ROS. Juglone was also found to induce oxidative damage to the root apical meristem via ROS formation in lettuce [106]. It therefore seems that metabolic differences between species, and perhaps between above- and below-ground organs of the same species, contribute to determining susceptibility of plants to juglone. See Table 1 for additional examples of how juglone affects plant growth and development.
Table 1. Reported effects of juglone or juglone-containing materials on plants. Ref., reference.

| Species | Growth Effect (Solution Tested) | Parts or Processes Affected | Ref. |
|---------|---------------------------------|-----------------------------|------|
| Lonicera maackii, Lespedeza cuneata, Trifolium incarnatum, Alnus glutinosa, Elaeagnus umbellata | Decreased (0.01–1 mM juglone) | Shoot elongation and dry weight accumulation | [1] |
| Cucumis melo cv. Kis Kavunu | Increased (1 mM juglone) | Elongation, fresh and dry weights, and polyphenol oxidase enzyme | [107] |
| Cucumis sativus cv. Beith Alpha | Decreased (1 mM juglone) | Elongation, fresh and dry weights, and protein content of cotyledons | [103] |
| Solanum lycopersicum cv. Rio Grande, Cucumis sativus cv. Çengelköy, Lepidium sativum cv. Bandırma, Medicago sativa cv. Yerli | Decreased (1 mM juglone; 10% (w/v) J. regia leaf aqueous extract) | Seed germination and seedling growth | [104] |
| Cucumis melo | Increased (1 mM juglone; 1/8 of 10% (w/v) J. regia leaf aqueous extract) | Seedling growth | |
| Cucumis sativus cv. Beith Alpha | Decreased (0.01–1 mM juglone) | Germination | [108] |
| Brassica rapa L. | Decreased (2% (w/v) ethyl acetate extract of J. regia rhizosphere and adjacent soil) | Fruit yield per plant, number of fruits per plant, average fruit weight, crowns per plant, number of leaves, leaf area, fresh root weight, total soluble solid, vitamin C, and acidity | [109] |
| Day-neutral Strawberry (Fragaria × ananassa L.) cultivar Fern | Decreased (1 mM juglone; 10% (w/v) J. regia leaf aqueous extract) | Root shoot dry weight and length, and H⁺-ATPase activity | [110] |
| Nicotiana tabacum | Decreased (10–50 µM juglone) | Seedling growth | [111] |
| Triticum aestivum | Decreased (J. nigra leaf aqueous extract) | Plant height and number of leaves | [105] |
| Oryza sativa | Increased (J. nigra leaf aqueous extract) | Plant height and number of leaves | [105] |
| Zea mays and Glycine max | Decreased (10–100 µM juglone) | Root shoot dry weight and length, and H⁺-ATPase activity | [96] |
| Zea mays and Glycine max | Decreased (100 µM juglone) | Shoot and root relative growth rates, leaf photosynthesis, transpiration, stomatal conductance, and leaf and root respiration | [112] |
| Raphanus sativus, C. melo cv. Ananas | Decreased (J. nigra leaf aqueous extract) | Germination rate radical and plumule length, and seedling dry weight | [113] |
| Cucumis sativus cv. Beith Alpha, C. melo cv. Ananas | Decreased (1 mM juglone) | Seedling elongation, fresh and dry weights, catalase and superoxide dismutase activities | [114] |
| Medicago polymorpha, Medicago polymorpha and M. lupulina | Increased (100 µM juglone) | Malondialdehyde (MDA) levels | [114] |
| Lactuca sativa var. angustata | Decreased (180 g J. regia leaf litter per pot with 15 kg soil) | Growth and total protein content | [116] |

Differential regulation of abiotic stress responses also alters susceptibility to juglone. Increased levels of ROS and proline were found in the roots of juglone-inhibited tobacco seedlings [111], and lignification was induced in juglone-inhibited soybean roots [118,119]. Attenuated toxic effects in roots were observed in proline-pretreated tobacco seedlings when subjected to juglone, indicating that juglone toxicity may be countered by preventing ROS accumulation [111]. In another study, Terzi and Kocaçaliskan [120] observed that inhibition of seed germination and elongation, reduction of fresh and dry weights of cress (Lepidium sativum cv. Bandırma) seeds by juglone were alleviated when seeds were pretreated with gibberellic acid and kinetin. In addition, gibberellic acid was found to be more effective than kinetin in alleviation of juglone stress [120].
Juglone is an attractive allelochemical-based herbicide candidate because of its reported efficacy at inhibiting germination and repressing growth of many weeds [19]. In a laboratory study, Sytykiewicz et al. [121] observed higher germination suppression of weed species, *Papaver rheas* (corn poppy) and *Agrostemma githago* (corn cockle) by juglone application (1 µM–10 mM) than the crop species *Triticum aestivum* cv. Nawra (spring wheat) and *Avena sativa* cv. Maczo (spring oat). Similarly, Topal et al. [122], evaluated the herbicidal activity of juglone on the growth of four weed species, *Sinapis arvensis* (wild mustard), *Cirsium arvense* (creeping thistle), *Papaver rheas* (field poppy), and *Lamium amplexicaule* (henbit) along with two crop species, *Triticum vulgare* Vill. cv. Gerek 79 (wheat) and *Hordeum vulgare* L. cv. Kislik (barley) as control. Juglone at higher concentrations (1.15–5.74 mM) completely inhibited the growth of field poppy while a significant amount of reduction on the elongation and fresh weight of all weed species was found with no inhibition on the crops. Higher inhibitory activity on the growth of weeds than crops was also reported by Cachiță-Cosma et al. [123]. From a laboratory, greenhouse, and field trial of a black walnut extract (NatureCur®, Redox Chemicals LLC, Burley, ID, USA) against horseweed (*Conyza canadensis*), hairy fleabane (*Conyza bonariensis*), purslane (*Portulaca oleracea*), and tall annual morning glory (*Ipomoea purpurea*), NatureCur® shows pre- and post-emergent bioherbicide potential [124]. The possibility of juglone derivatives (O-acyl and O-alkyl) and the isomeric 1,4-naphthoquinone, lawsone, also offer promising leads for developing more potent and targeted herbicides [125].

3. Juglone as a Biostimulant

Most plant allelochemicals produce inhibitory effects at higher doses but can function as biostimulants at lower doses [126]. The biostimulatory activity of allelochemicals at lower doses is also known as hormesis [127–131] and may guide discovery of new growth hormones. The inhibitory potential of allelochemicals against target species is the focus of most phytotoxin studies [130], although for herbicides, lower doses have been investigated for hormetic responses [132,133]. This is important to consider for allelochemicals like juglone given that under natural settings soil concentrations may not be sufficient to achieve inhibitory effects observed in vitro or in other controlled conditions, and instead have a biostimulatory effect. Indeed, the presence of *J. nigra* has been reported to improve forage cover in pastures [134] and bioassays have indicated that at low concentrations (typically ≤ 1 µM) juglone exhibits biostimulatory activity e.g., [1,92,118,135]. Other studies (e.g., [136]) have indicated similar effects testing dilutions of extracts from juglone-containing plant materials.

The stimulatory activity of an allelochemical depends on several factors, including the type of allelochemical, the species affected, the trait being measured (e.g., biomass, height, leaf area, protein content, enzyme activity), surrounding environmental conditions (e.g., temperature, moisture, salinity or nutrient content, etc.), plant density, and time of exposure [128,130,131]. Stimulation of a particular trait in one species at a given concentration may not be the same in another species. For example, at 5.7 µM, juglone inhibited the growth of *Stephanodiscus hantzschii* by more than 60%, while at the same time exhibited hormetic activity on three other diatoms, *Asterionella formosa*, *Fragilaria crotonensis*, and *Synedra acus* [92]. Along the same lines, Table 1 summarizes a range of reported inhibitory and stimulatory effects of juglone, juglone-producing species, and juglone-containing materials on various plant species. Examination of the effects of treating cucumber (*Cucumis sativus* cv. Beith Alpha) seeds with juglone found that while elongation, seedling fresh and dry weights, and cotyledon protein content significantly decreased, polyphenol oxidase activity, which offers protection against pathogens, increased [103]. In another study, two different muskmelon cultivars, *Cucumis melo* cv. Ananas and *C. melo* cv. Kis Kavunu, were found to respond oppositely to juglone based on measurements of seedling elongation, fresh and dry weights, catalase and superoxide dismutase activities, and levels of the lipid peroxidation end product malonyldialdehyde (Table 1) [114].

Mechanisms underlying the hormetic activities of allelochemicals, including juglone, are not well understood. Chobot and Hadacek [137], reported that the antioxidant properties of juglone are responsible for the stimulatory activity on the germination of *Sinapis alba* under higher oxidative
stress. In addition to affecting redox cycling, juglone spontaneously forms adducts with the reduced form of the endogenous antioxidant GSH [6]. While at high concentrations juglone depletes GSH levels leading to deleterious effects, at low concentrations, juglone may stimulate expression of genes encoding glutathione S-transferases (GSTs), vacuolar transporters, and/or GSH biosynthetic enzymes. Compounds which induce such effects are called “safeners” [138] and are used to increase crop resistance to herbicides and may confer other types of defensive or xenobiotic detoxification effects. Thus, juglone may also hold potential as a natural product-based safener.

It is important to consider the involvement of several mechanisms in conferring hormetic activity of juglone, or its effect in combination with other compounds. For example, the herbicide glyphosate, which impedes the shikimate pathway (the source of aromatic amino acids and lignin precursors), when administered at low non-herbicidal doses was found to result in more elastic cell walls in soybean [129]. Interestingly, it was only observed in non-transgenic lines indicating the mechanism of hormesis is linked to the herbicide target site [139]. In contrast, soybean root growth is proposed to be inhibited by juglone in part due to the excessive production of lignin. Three-day-old seedlings exposed to 5 µM juglone for 24 h were found to have reduced root length but with increased phenylalanine ammonia-lyase (PAL) activity, which is responsible for the first step of the core phenylpropanoid pathway, and increased levels of lignin [119]. This example illustrates that even targeting the same cellular process can have inhibitory or stimulatory effects depending on the mechanism involved. Thus, more research is needed to identify the potential benefits and drawbacks of hormetic doses of juglone when used alone or in combination with other compounds on crop plants. It is also critical to consider other unintended effects on other types of organisms if it is to be further considered as a biostimulant in cropping systems.

4. Juglone as a Urease Inhibitor

Urea accounts for over half of the world’s nitrogen fertilizer consumption due to its high nitrogen content (46%), its low relative cost per nitrogen unit, its availability in most markets, its high water solubility, its low corrosion capacity, its compatibility across fertilizer formulations, and its high foliar uptake [140,141]. Crops require a steady supply of nitrogen to sustain growth and development compared to other essential plant nutrients. Once nitrogen fertilizer is applied to fields, it is directly absorbed by plants, and the excess amount is lost in ionic or gaseous forms via leaching, volatilization, and the denitrification process, thereby becoming unavailable to plants [142–144].

Urease is an enzyme in plants, fungi, and bacteria that accelerates hydrolysis of urea to ammonia and carbon dioxide at a speed of one-hundred-trillion-fold [145]. Nearly, 79–89% of urease activity in soil derives from extracellular enzymes present in the soil matrix [146]. Depending on environmental conditions, 10–40% of nitrogen applied as urea can be lost as ammonia from the soil surface due to extracellular soil urease activity [147]. This loss of excess nitrogen from crop fields creates air and water (eutrophication) pollution that directly, or indirectly after conversion to other forms, contributes to biodiversity loss, human health hazards, stratospheric ozone depletion, acid rain, and climate change [148–151]. To combat nitrogen losses from soil and to enhance nitrogen use efficiency, various attempts have been made by fertilizer manufacturers to stabilize urea and control nitrogen release attributes [143]. These include surface coatings (e.g., sulfur, polymers etc.), N-(n-butyl) thiophosphoric triamide (BTP/NBPT; Agrotain®, Koch Agronomic Services, Wichita, KS, USA), 25% N-(propyl) thiophosphoric triamide + 75% NBPT (Limus®, BASF USA), phenylphosphorodiamidate (PPD/PPDA), and hydroquinone [140,143,152]. Urease inhibitors are applied to the soil surface or directly to urea granules to slow the action of extracellular soil ureases. Activities of these inhibitors is affected by soil moisture content, pH, and temperature [153]. Delaying urea hydrolysis at the soil surface gives urea an opportunity to penetrate into the soil through precipitation or irrigation [145]. Once infiltrated to a depth of approximately 5–10 cm, released ammonia is trapped and mineralized into other plant usable forms.
A natural product-based ureases inhibitor should function efficiently in all types of soils under various moisture regimes, and at the same time be easy to produce, easy-to-use, less harmful to the crops, and be economical [154]. Kot et al. [155], reported that juglone is a strong, time and concentration-dependent inactivator of urease that irreversibly inhibits via covalent modifications of protein thiols. Conventional urease inhibitors hinder urea hydrolysis at the surface, but do not persist for long periods of time and are weakly mobile in soil. Indeed, juglone is hydrophobic and relatively immobile in soil [14], making it a strong candidate as a natural product-based urease inhibitor. At the same time, juglone is light sensitive and begins to photodegrade within few days [28]. It is also rapidly metabolized by certain soil bacteria that can utilize it as a carbon source [67]. But to date there is a lack of information related to the urease inhibitory activity of juglone under field conditions, though a recent study suggests that soil urease activity is reduced around *J. regia* [156]. This raises the prospect that juglone or walnut extracts applied through either surface drenches or coating of urea granules could be effective at managing urease activity in agricultural settings.

5. Knowledge Gaps and Future Prospects

Considering consumer demand for greener and more sustainable agricultural solutions and the growing number of pests developing resistances to conventional pesticides, natural product-based pesticide and agrochemical development is gaining interest. While natural products have been used for developing certain types of pesticides, they have been vastly underutilized for developing herbicides in particular [157]. Around 20% of conventional pesticides are either natural products or natural product-derived substances, including triketones (herbicides), spinosyn, neonicotinoids and pyrethroids (insecticides), and strobilurin (fungicides) [157]. Structural complexity, costly structure determination and synthesis, obtaining sufficient quantities, labile characteristics of some compounds, and general toxicity are among the obstacle hindering development of natural product-based pesticides and agrochemicals [158]. Below, we have detailed some of the specific limitations presenting barriers to developing juglone-based applications, either through application of pure compound or as part of integrating juglone-producing species or juglone-containing materials into cropping practices:

1. Juglone concentration may vary with species, age of the plant, seasons, and locations. For example, de Scisciolo et al. [27], recorded up to 10-fold variation in juglone concentrations in soils under different walnut trees, while Coder [159], recorded higher juglone levels in the lower parts of the leaf crown. The concentration of juglone appears to be highest during the leaf opening period of walnut and during fruit formation, but it may vary depending on walnut species [3].

2. Batch-to-batch variation and post-harvest effects on juglone content. Carnat et al. [160], found no juglone in extracted *J. regia* dried leaves, while Girzu et al. [161], extracted fresh leaves of the same species and determined juglone accounts for 0.5% of the fresh weight. Juglone concentration also varies across different parts of walnut trees [162], which can lead to unpredictable potencies of mulches derived from litter or unused portions of walnut industry byproducts, for example.

3. Juglone exerts off-target toxicity to beneficial organisms, for example, earthworms [163], N-fixing bacteria [65,66], and fish [91,164,165].

4. The general phytotoxicity of juglone to a variety of specialty crops, like asparagus, cabbage, eggplant, pepper, potato, tomato, apple, blackberry, blueberry, pear, and tobacco limits its use in horticultural production. Nonetheless, there are a number of species that appear to be more juglone tolerant [14].

5. Toxicity may vary depending on the soil types, for example, juglone activity is higher in poor quality soils [28,166] and in moist soil compared to dry soil [167].

6. Oxidized juglone is semi-volatile. While juglone was not detected in headspace collections from intact green husks, it could be detected in collections from blended husks [168]. Thus, while juglone may have low volatility when reduced or in aqueous solution, or be bound as a glycoside in intact tissues, free juglone in pure form or in disrupted tissues (e.g., mulches) has the potential...
to volatilize which could lead to off-target movement and effects on nearby insects, vertebrates, plants, and microorganisms.

7. Juglone is light sensitive and begins to photodegrade within a few days [28]. Surface or foliar applications of juglone therefore may be subject to shortened environmental half-lives that reduce its efficacy.

If the limitations of juglone can be properly addressed, there is great potential to harness it as a natural product-based pesticide, biostimulant, urease inhibitor, and/or other potential agrochemicals. To further develop these potential applications, future research should be directed toward:

1. Investigating the biostimulatory (hormetic) and inhibitory activity of juglone on different crops and weeds at various stages of growth. While most research has focused on studying the phytotoxicity of juglone (Table 1), identifying application rates leading to hormetic doses of juglone at early stages in crops may also contribute to suppressing weed growth by enhancing crop growth [130,169].

2. Understanding the activity of juglone in natural field settings. Most research on juglone has been conducted under strictly controlled environmental conditions, either in laboratory or greenhouse settings [170]. The accumulation of any allelochemical, however, is heavily influenced by environmental conditions [171–174]. In the case of juglone, this further depends on the route by which juglone reaches the environment (Figure 2).

3. Identifying ways to reduce production costs. The cost of chemically synthesizing a natural product, producing it through metabolic engineering in a heterologous system, or of cultivating the producing species and extracting and purifying the target compound must be economically competitive in order to become a practical substitute to conventional synthetic pesticides and agrochemicals. While efficient methods for synthesizing juglone have been reported (e.g., [175]), identifying the remaining unknown genes in juglone biosynthesis [12] should be prioritized to enable biotechnological platforms for producing juglone in engineered biological systems in the field. Moreover, juglone is synthesized in most organs of black and English walnut trees, including the husks, hulls, and leaves [23], which become waste products of the hardwood and food industries. Millions of tons of English walnut shells from walnut kernel processing are generated worldwide but generally end up as waste [176]. Thus, together with other underutilized parts of walnut trees, there is an abundance of inexpensive juglone-containing source material that could be directly used in agricultural applications or for extraction of pure juglone.

4. Exploring the design of novel juglone derivatives [125] that balance alteration of lipophilicity with aqueous solubility [177] and which do not compromise Lipinski’s “Rule of 5” set for physicochemical parameters of pharmaceuticals and fitted for agrochemicals by Tice [178]. Nanoparticle encapsulation is another revolutionary technique that has been shown to increase antimicrobial activity and duration of juglone [179]. Its application in agricultural settings could help reduce off-target movement and toxicity of juglone and improve water solubility of more lipophilic juglone derivatives.

5. Improving basic knowledge about juglone’s mode(s) of action and molecular target sites in insects, vertebrates, plants, and microorganisms, the molecular mechanisms involved in deploying juglone into the environment, the uptake of juglone in target organisms, and the metabolism-based mechanisms that allow juglone-producing plants and other types of juglone-tolerant organisms to counter or resist the effects of juglone.
To further develop these potential applications, future research should be directed toward:

- Investigating the biostimulatory (hormetic) and inhibitory activity of juglone on different crops, including a comparison of its effects on weed growth and crop yield.
- Understanding the activity of juglone in natural field settings. Most research on juglone has been conducted under controlled laboratory or greenhouse conditions. Hence, the transfer of laboratory and greenhouse trials into field conditions is crucial for gaining an understanding of environmental effects on juglone activity and persistence. In this review, we have highlighted significant research findings related to roles for juglone as a novel pesticide and its potential as a candidate for developing other agrochemicals. Despite the opportunities, challenges still exist to adopting juglone for applications related to pest management, to its use as a biostimulant, or for reducing nitrogen losses. It is our intention with this review to not only provide an overview on what has been done, but to identify areas in which research on juglone is still needed in order to integrate it, and perhaps other structurally similar quinones, as components of various sustainable agriculture strategies.

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