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Original Article

Juglans regia L.: Source of Bioactive Compounds with Potential Anticancer Activity

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ABSTRACT

Background: *Juglans regia* L., commonly known as "walnut", belongs to the Juglandaceae family, with antioxidant, anti-inflammatory, and hypoglycemic medicinal properties. **Objective:** Describe the anticancer potential of the bioactive compounds present in *Juglans regia* L. **Method:** Recent scientific studies were reviewed on the effects of bioactive compounds from *Juglans regia* L. on inhibiting tumor growth and cancer development in several experimental models. To do this, a scientific literature search was carried out, using databases such as PubMed, Scopus, and Science Direct. **Results:** Regarding the selected articles, it was found that some bioactive compounds from *Juglans regia* L. exhibit mechanisms of anticancer action, among which the following stand out: induction of apoptosis, suppression of angiogenesis, and modulation of cell signaling pathways related to cell proliferation and survival. **Conclusion:** It is concluded that *Juglans regia* L. contains active metabolites with potential anticancer effects.
Keywords: *Juglans regia* L., Cancer, Antitumor, Apoptosis, Angiogenesis.

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INTRODUCTION

Cancer is one of the most widespread diseases and one of the main causes of death that is continuously increasing, due to the lack of selectivity and resistance induced by chemotherapy drugs[1]. World cancer statistics record 18.1 million new cases of cancer with 9.6 million deaths due to this disease and that the main cause of death is lung cancer followed by breast, colorectal, stomach, and liver[2].

Plant secondary metabolites are important sources of molecules with potential for chemotherapy. These bioactive compounds have been shown to increase anticancer activities and reduce serious side effects of antitumor drugs[3].

Juglans regia L. (*J. regia*) commonly known as "walnut", belongs to the Juglandaceae family, frequently cultivated in China, the United States, Eastern Europe, and Iran[4], this plant species has been used ancestrally to treat various conditions in humans[5].

The phytoconstituents found in this plant vary depending on the geographical location, climatic conditions, and nature of the soil. Thus, in the leaves of *J. regia*, phytochemicals with pharmacological properties are found, among the most common of which are phenolic acids, tannins, essential fatty acids, ascorbic acid, flavonoids such as quercetin, caffeic acid, paracomaric acid and juglone (5-hydroxy-1,4-naphthoquinone) as the most active compound[6,7]. These components not only contribute to its antioxidant activity[8] but have also been shown to have lipid-lowering, antihypertensive[9], antibacterial[10,11], antifungal[12], anti-inflammatory[13], neuroprotective[14], antithrombotic[15]activities, healing activity in incision and excision wounds[16], and hypoglycemic activity[17]. Research supports its medicinal properties, highlighting its anti-cancer potential[6].

The purpose of this review is to provide an overview of the anticancer potential of the bioactive compounds of *J. regia* L. based on the scientific literature found to date and to promote further studies that contribute to finding compounds that contribute to the treatment of cancer.

METHODOLOGY

An exhaustive review of the scientific literature was carried out, the review studies have been compiled from scientific articles published in databases such as Science Direct, Scopus, and PubMed. Original scientific documents were included that covered descriptive and experimental studies related to the potential anticancer activity of the bioactive compounds of *Juglans regia* L. Original articles in preclinical and clinical phases were considered. The keywords in the scientific literature search were obtained from DeCS in Spanish and MeSH in English, which allowed a quick selection of scientific articles related to the thematic field.

Bioactive Compounds of *Juglans regia* L.

Juglans regia L. has found diverse applications in both the cosmetic and pharmaceutical industries due to its bioactive compounds present in its fruits, peels, seeds, bark, flowers, and leaves[18]. *J. regia* L. serves as a significant dietary source of protein, fiber, essential fatty acids, vitamins, and minerals. Additionally, it provides a diverse array of flavonoids, phenolic acids, and related polyphenols[19].

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Walnuts serve as a significant fat source (approximately 74 g/100 g) with a high caloric value of 720 kcal/100 g. Beyond fat content, walnuts also contain valuable polyunsaturated fatty acids and plant proteins rich in essential amino acids and minerals. Proteins, carbohydrates, crude fiber, and minerals constitute approximately 24%, 14%, 2%, and 1.7% of the nut's weight, respectively. Additionally, walnuts harbor bioactive components such as polyphenols and tocopherols, with hydroxybenzoic acids predominantly found in the polyphenolic profile, particularly gallic acid[20]. In the tocopherol spectrum, four forms of tocopherols are identified: α, β, γ, and δ -tocotrienol[21], with α-tocopherol being the one with the highest content and having antioxidant activity, principally in preventing the lipid oxidation process[22].

In *J. regia* nut oil, various bioactive compounds have been identified, including tocopherols, sterols, triterpenic and aliphatic alcohols, carotenoids, and volatile compounds. Among the phytosterols, β-sitosterol is the most abundant, followed by campesterol and Δ-5-avenasterol. The major triterpenic alcohol present is cycloartenol, while hexacosanol serves as the primary aliphatic alcohol. Additionally, the volatile compounds detected include pentanal, hexanal, nonanal, 2-decenal, and hexanol[23].

Naphthoquinones, including juglone and hydrojuglone glycosides, have been identified in various tissues of *J. regia*[24]. Juglona pueden combatir el estrés oxidativo y proteger contra diversas enfermedades y el envejecimiento[25]. Juglone exhibits antioxidant properties, protecting against oxidative stress and age-related diseases. However, as a quinone, juglone can also act as a pro-oxidant, inhibiting cancer cell growth[26]. Additionally, research has investigated polymeric micelles as a delivery system for juglone in pancreatic cancer treatment[27].

J. regia leaves reported several bioactive compounds such as ascorbic acid, juglone[28], phenolic compounds, 3-caffeoylquinic, 3-p-coumaroylquinic, and 4-p-coumaroylquinic acids[29]. Additionally, flavonoids like epicatechin, syringetin-O-hexoside, myricetin-3-O-glucoside, myricetin-3-O-pentoside, esculetin, taxifolin-pentoside, quercetin-3-O-glucuronide, kaempferol-O-pentoside and kaempferol-O-rhamnoside[30]. The acetonic extract from *J. regia* flowers reveals gallic acid, α-tocopherol, and substantial quantities of quercetin hyperoside, quercitrin, and isoquercitrin[31].

Overall, the bioactive compounds identified in *J. regia* have been recognized as potential anticancer agents in the literature. These compounds include ellagic acid[32], quercetin, ascorbic acid[33], tocopherol[34], rutin[35], carotenoids[36], and phytosterols[37].

Anti-Cancer Evaluation of *Juglans regia* L.

Extracts from various parts of *Juglans regia* demonstrate anticancer and antitumor properties by inhibiting proliferation and inducing apoptosis in cancer cells. These plant extracts were evaluated both *in vitro* using cancer cell lines and *in vivo* through animal models. The primary studies assessing the anticancer effects of *Juglans regia* are summarized in Table 1.

Anti-Cancer Mechanisms

The described mechanisms offer a comprehensive understanding of how compounds from *Juglans regia* L. could influence various stages and processes in tumor development, establishing a robust foundation for considering their therapeutic potential in cancer treatment.

Juglone

Juglone inhibits the growth of malignant cells, including HCT-15 cells derived from human colon carcinoma, primarily by blocking the S phase of the cell cycle. Additionally, it induces apoptosis in human leukemia cells (HL-60), human gastric cancer cells (SGC-7901), and SKOV3 ovarian cancer cells through mitochondria-dependent apoptosis pathways and an elevated Bax/Bcl-2 ratio. Furthermore, Juglone significantly inhibits proliferation and induces apoptosis in human bladder carcinoma cell lines (TCC-SUB and RT-4), while in the human breast cancer cell line (MCF-7), it leads to elevated levels of reactive oxygen species (ROS), reduced Bcl-2 expression, increased Bax expression, decreased mitochondrial membrane potential, elevated intracellular Ca^{2+} concentration, rupture of the outer mitochondrial membrane, cytochrome c release, and caspase-3 activation[25]. Research also suggests that juglone significantly inhibits cell proliferation and activates apoptosis in colon cancer. Additionally, juglone negatively regulates the Wnt/β-catenin pathway[50,51] .

Juglone was evaluated on intestinal carcinogenesis in rats by dietary exposure during the initiation phase. Data suggest that juglone could be a promising chemopreventive agent for human intestinal neoplasia. Juglone inhibits tumor progression in mice, triggering oxidative stress leading to apoptosis and cell cycle arrest, suppression of hypoxia-inducible factor 1alpha, and disengagement of glycolytic metabolism.[25].

Ellagic Acid

Ellagic acid may exert an antitumor effect through diverse molecular mechanisms, including inhibition of proliferation, induction of apoptosis, suppression of metastasis and invasion, autophagy induction, and modulation of tumor metabolic reprogramming[32]. Studies demonstrate that ellagic acid reduces cell viability and suppresses tumors in breast cancer. Specifically, it inhibits cell growth and migration by arresting the cell cycle and suppressing metastasis[52], activates pro-apoptotic pathways, and positively regulates p53[32]. Additionally, ellagic acid stimulates apoptosis via the TGF-β/Smad3 pathway and regulates CDK6 during the G0/G1 phase[53]. Furthermore, it reduces cell motility and invasion by binding to and degrading ACTN4 through the ubiquitin-proteasome pathway. Moreover, ellagic acid decreases angiogenesis by reducing VEGFR-2 activity[54] and inhibits proliferation, migration, and invasion by targeting Wnt/β-catenin and PI3K/Akt signaling pathways[55].

Quercetin

In vitro investigations have revealed distinct effects of quercetin on normal prostate cells compared to prostate cancer cells, emphasizing its specific cytotoxic impact on cancer cells. The anticancer mechanism involves Bax dissociation from Bcl-xL[53] and modulation of PI3K/Akt/mTOR, Wnt/β-catenin, and MAPK/ERK1/2 pathways. Quercetin promotes loss of cell viability, apoptosis, and autophagy in cancer by reducing the stabilization of β-catenin and HIF-1. Additionally, it activates caspase-3 and inhibits phosphorylation of Akt, mTOR, and ERK. Furthermore, quercetin prevents metastasis by reducing VEGF and MMP secretion[56].

Similarly, quercetin demonstrates inhibitory effects on cell proliferation and angiogenesis in animal models of prostate cancer, along with a reduction in tumor size[57]. However, the clinical application of this agent faces several challenges related to its bioavailability, absorption, metabolism, stability, and rapid elimination from circulation. Addressing these issues is essential to enhance the clinical utility of quercetin[53].

Tocopherol

In animal models of liver cancer, tocopherol (vitamin E) has demonstrated the ability to suppress angiogenesis, induce apoptosis, and reduce metastasis formation[58].

Carotenoids

Carotenoids have demonstrated protective properties against oxidative stress and reduced cell proliferation in breast cancer studies[59]. Although *in vitro* and *in vivo* research has yielded promising results regarding

Table 1. Studies evaluating the anticancer activity of Juglans regia L.

Plant part	Extract	Doses	Bioactive compounds	Experimental model	Results	Ref
fruit	ethanol-water in a ratio 80:20	50 and 100 mg/kg body weight	gallic acid, caffeoylquinic acids, coumaric acid and flavonoids	prostate cancer in rats	The administration of Juglans regia extract was associated with a reversal of testosterone induced changes in oxidative stress or inflammatory markers	38
husk	ethanolic extract	1 and 10 µM juglone	juglone	HL-60, human leukemia cell line	Apoptosis of HL-60 was detected at 10 µM juglone	6
husk	Extractions were carried out in a Soxhlet apparatus with three different solvents: methanol, chloroform, and n-hexane.	100 mg/mL	omega-3 fatty acids, phytosterols, polyphenols, carotenoids, and melatonin	PC-3 Human Prostate Cancer Cell	The methanol (IC50 66.72 μg/mL), n-hexane (IC50 27.29 μg/mL), and chloroform (IC50 91.14 μg/mL). Green husk extracts suppressed proliferation and induced apoptosis in a dose- and time-dependent manner.	39
fruit	ethanolic extract	8.75 to 140 µg/ml	ellagic acid derivatives and flavanols	human A172 glioblastoma cell line	Extract could decrease cancer cell proliferation and migration	40
fruit	diet	The equivalent of 80 g (approximately 3 ounces) of walnuts in humans	not detected	the transgenic adenocarcinoma of the mouse prostate model	Walnuts as part of a diet reduce tumour growth and size.	41
leaves	Hexane Extract	5, 50 and 100 µg/mL	not detected	PC-3 Human Prostate Cancer Cell	Inhibits growth of human prostate cancer cells by inducing apoptosis with concomitant alterations in cell cycle phase distribution	42
fruit	Methanolic extract and fractions	1, 10, 100, and 500 µg/mL	phenolic compounds	Human cancer cell lines, such as MCF-7 (estrogen receptor positive breast adenocarcinoma), KB (oral and mouth), HepG-2 (liver), Caco2 (colon), and WRL-68 (liver)	Chloroform and ethyl acetate fractions exhibited a high level of antiproliferation against HepG-2, liver cancer cell line (IC50 = 9 and 15 µg/mL, respectively).	43
root bark	Extractions were carried out in a Soxhlet apparatus with three different solvents; methanol, choloroform and n-hexane.	500µg/mL	not detected	MDA-MB-231 breast cancer cells	Suppressed proliferation and induced apoptosis in a dose and time dependent manner	44
root	chloroform extract	100 µM	juglone	Prostate colon (Colo-205 and HCT-116), breast (T47D), prostate (PC-3 and DU-145), skin (A-431) and lung (NCI-H322 and A549).	Exhibited satisfactory cytotoxic activity against a panel of eight different human cancer cell lines	45
seed, green husk and leaf.	mixed with methanol or petroleum ether	31.25, 62.5, 125, 250 and 500 lg extract/mL.	polyphenols	Human renal cancer cell lines A-498 and 769-P and the colon cancer cell line Caco-2.	Showed concentration dependent growth inhibition toward human kidney and colon cancer cells.	46
leaves	hexane, chloroform, ethyl acetate and methanol fractions	0.25 - 1.5 mg/mL	polyphenols, flavonoids and condensed tannins	Human oral cancer, breast adenocarcinoma and colon adenocarcinoma cell lines.	Walnut chloroform fraction may contain effective compounds which can be used as a chemotherapeutic agent.	47
fruit	methanol, ethanol, and hexane solvents	2.0 µg/ml	not detected	MDA-MB-231 cell line	Showed evident apoptotic activity even if it was not as potent as doxorubicin.	48
Leaves	decoction	different concentrations not reported	Malic acid, sucrose, tocopherol, 3-O-caffeoylquinic acids and quercetin O-pentoside	MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), HCT-15 (colon carcinoma), HeLa (cervical carcinoma) and HepG2 (hepatocellular carcinoma)	The methanol extract was most potent against cervical carcinoma cell line (HeLa, GI50= 294.87 µg/mL)	49

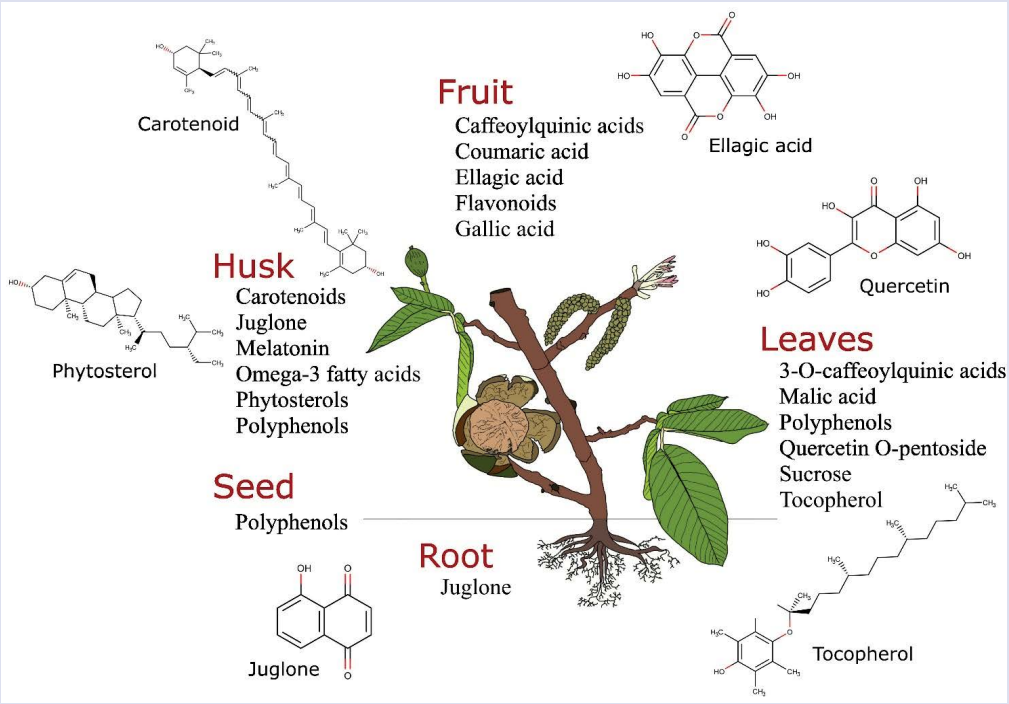

Figura 1. Compuestos Bioactivos de *Juglans regia L.*

the impact of carotenoids on breast cancer, clinical trials have not yet provided definitive conclusions[60].

Phytosterols

Phytosterols can suppress angiogenesis, metastasis, infiltration, and proliferation of cancer cells by regulating the tumor microenvironment through molecular signaling pathways associated with growth factors, chemokines, pro-inflammatory mediators, and pro/anti-apoptotic genes. These compounds have been demonstrated to arrest G_0/G_1 and G_2 cell cycles, promote cell death by upregulating caspases and pro-apoptotic enzymes while downregulating anti-apoptotic enzymes. Additionally, phytosterols enhance immune system function by improving T-cell proliferation and cytotoxicity. Conversely, they also have the potential to inhibit angiogenesis, leading to reduced levels of vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β)[37].

Moreover, they have demonstrated inhibition of cell proliferation and invasion, as well as a reduction in inflammation and oxidative stress by targeting reactive oxygen species (ROS), inhibiting nuclear factor kappa B (NF-κB), and decreasing cell invasion in prostate cancer[61].

FUTURE PERSPECTIVES

This review highlights the potential of bioactive compounds found in *Juglans regia* L. as promising agents against various types of cancer. The included studies demonstrate the effectiveness of these compounds, including juglone, ellagic acid, quercetin, ascorbic acid, tocopherol, rutin, carotenoids, and phytosterols. These bioactive molecules exhibit inhibition of cell proliferation, induction of apoptosis, suppression of angiogenesis, and modulation of cancer-associated signaling pathways in different cellular models and cancer types. However, due to the scarcity of human studies, conclusive results regarding the safety and efficacy of these compounds in cancer treatment remain a challenge for future research.

CONCLUSIONS

The bioactive compounds found in *Juglans regia* L. hold promise as potential anticancer agents, given their ability to inhibit cell proliferation and induce apoptosis. Additionally, several of these compounds demonstrate efficacy in suppressing angiogenesis and modulating cancer-associated signaling pathways. These findings underscore the importance of further exploring the specific molecular mechanisms underlying the therapeutic potential of bioactive compounds derived from *Juglans regia* L. for cancer treatment. Future research should focus on evaluating optimal doses and potential side effects in various cancer types.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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