Review Article

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Juniperus excelsa M.Bieb; a medicinal plant with various pharmacological activities

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Abstract

It is well accepted that medicinal plants are involved with numerous properties that may be considered for new drug discoveries. This review encompasses medicinal and pharmacological activities of *Juniperus excelsa* M.Bieb (Family: Cupressaceae) to draw a frame for further research. Considering the terms "*Juniperus Excelsa*" and "Pharmacological Activity", the databases Scopus, PubMed, Web of Science, and ScienceDirect were precisely searched up to early March of 2017 with the exception of agriculture and genetic-based science papers. Besides various ethnopharmacological properties, different parts of *J. excelsa* are shown to have distinct medicinal activities such as anti-microbial and anti-fungal, anti-parasite and anti leishmania, anti-oxidant and radical scavenging, cardiovascular, anti-diabetes, gastrointestinal, respiratory, wound healing, anti-angiogenic, immunomodulatory and antinociceptive, phytotoxic, cytotoxic activity, and therapeutic effect on cancer.

Keywords: Cupressaceae, *Juniperus excelsa*, Pharmacology, Review.

1. Introduction

Juniperus excelsa M.Bieb (JE), also known as Greek juniper, belonging to the family Cupressaceae, with nearly 70 species, is one of the most well-known species with numerous medicinal properties, duo to the presence of various classes of metabolites (1).

The JE leaf essential oil have around 70 determined volatile chemical compounds, among which cedrol and α-pinene are the major constituents (2, 3). Moreover, other botanical parts of JE such as wood or branches contain essential oils. Around 140 constituents with large amounts of sesquiterpenes were found in a sample from Turkey (4). The number of various constituents obtained from JE fruit is ranged from 30 to 88 through its life span; and α-cedrol and α-pinene were the major compounds (5).

Ethnopharmacological studies have shown that different parts of JE are used by local people to treat rheumatism, backache, diabetes and gastro-intestinal disease (6-8). There are several herbal drugs introduced in Traditional Persian

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medicine (TPM) sources that have become obscure nowadays. This plant is mentioned as *Abhol* or *Urs* in medicinal and pharmaceutical manuscripts of TPM and has been included in a number of medical and medicinal reports. The aim of this study is to add up all proved pharmacological properties of JE as well as those effects prescribed in Persian medicine sources of pharmaceutical manuscripts to outline a viewpoint for further research.

2. Material

Considering the terms "*Juniperus Excelsa*" and "Pharmacological Activity", the databases of Scopus, PubMed, Web of Science, and ScienceDirect were precisely searched up to early March 2017 with the exception of agriculture and genetic-based science papers.

All derived medicinal properties related to JE were divided into 13 different categories; anti-microbial and anti-fungal, anti-parasite and anti-leishmania, anti-oxidant and radical scavenging, cardiovascular, anti-diabetes, gastrointestinal, respiratory, wound healing, anti-angiogenic , immunomodulatory and antinociceptive, memory and neurological activities, phytotoxic, cytotoxic activity, and therapeutic effect on cancer.

3. Results

3.1. Anti-microbial and anti-fungal activity

There are numerous investigation on antimicrobial and antifungal activities of JE using various parts and different extracts of this plant such as aerial parts, fruit, leaf, berries, trunk wood, and twig, as methanol extract, ethanol extract, and essential oil of fruit and leaf. In a study, two isolated diterpenes of JE, ferruginol and sandaracopimeric acid, exhibited significant activities against *Bacillus subtilis*, *Staphylococcus aureus*, and *Streptococcus durans* (with MIC values of 2.50, 4.0, and 2.50 pg/mL for ferruginol and 4.0, 8.0, and 8.0 pg/mL for sandaracopimeric acid). It was shown that ferruginol also has a strong activity against *Mycobacterium smegmatis*, *M. intracellulare*, *M. xenopi*, and *M. cheloni* (9). In another study, all Gram negative and Gram positive bacteria were observed to be susceptible to JE essential oil due to α-pinene as the major component, followed by α-cedral, δ3-carene, and limonene (10).

It is reported that the extract of JE was highly effective against three bacteria: *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus subtilis*, and a fungus *Candida albicans* in a similar study (11). The same study confirmed the antimicrobial activity of the essential oils of fruits and leaves of these plants against *Bacillus subtilis*, *Candida albicans*, *Escherichia coli*, *P. aeroginosa*, and *S. aureus* (12).

In a comparative study for antimicrobial activity of essential oils of JE berries and leaves grown in Macedonia, the most sensitive bacteria to the berries was Haemophilus influenzae (MIC=31 µl/ml), while leaves showed a high activity against *S. aureus*, *Streptococcus pyogenes*, and *H. influenzae* (MIC=125 µl/ml). The constituent α-pinene in the total essential oil was proved to have a moderate effect on *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *S. pyogenes*, *S. aureus*, *Corynebacterium* spp., and *Campylobacter jejuni* (Inhibition>50%). On the other hand, sabinene of the oil revealed a moderate activity against *S. pyogenes*, *H. influenzae*, *Campylobacter jejuni*, and *E. coli* (Inhibition>50%) (13).

In a study on the essential oil of JE growing in Lebanon, it was shown that α-pinene, α-cedrol, and δ-car-3-ene were the main components, which did not reveal any antiradical potential, but caused interesting *in vitro* antimicrobial activities against *S. aureus* and *Trichophyton rubrum* (MICs of 64 and 128 µg/ml, respectively). Related to that study, δ-Car-3-ene is certainly one of the constituents that leads to the antifungal activity of JE essential oil (14).

In a human comparative study, JE berries essential oil showed a similar anti-bacterial efficacy against chlorhexidine for periodontal treatment. In that study, *Aggregatibacter actinomycetemcomitans* and *Streptococcus mutans* were sensitive to the essential oil of JE; and it displayed higher cytocompatibility than chlorhexidine (15).

It is demonstrated that the methanol extract of JE had a significant antibacterial effect on *Nocardia asteroides* and *N. brasiliensis* (16).

An *in vitro* study indicated that methanol extracts of leaves and fruits of all Iranian *Juniperus* species were effective against *S. aureus* using

the whole plat method. Leave extracts of all *Juniperus* species were shown to be potent inhibitor of *Pseudomonas aeroginosa*. In this study, the MIC of the methanol extracts of JE was 0.39 and 0.78 mg/ml for leaf and fruit, respectively. This study revealed that this plant has a good activity against *C. albicans*, *E. coli*, and also *P. aeruginosa* (17).

In another study, fruit of JE showed weak antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus* (MRSA), and *Klebsiella pneumonia*. In that research, JE exhibited no antifungal effect on *Candida albicans* (18). The antifungal activity of JE berries has also been demonstrated (19).

In another study, Fahed *et al*. indicated the antimicrobial activity of different related herbs including JE harvested in Lebanon. It was shown through a broth microdilution method that *S. aureus* and *T. rubrum* were significantly sensitive to the essential oil yielded from the aforementioned JE (MIC of 64 and 128 µg/ml, respectively) (20).

3.2. Anti-parasite effect and activity against leishmania

Among the substances isolated from JE, abieta-7, 13-diene demonstrated *in vitro* antimalarial effect on *Plasmodium falciparum* D6 and W2 strains (IC_{50}=1.9 and 2.0 µg/mL, respectively). However, totarol, ferruginol and 7β-hydroxyabieta-8, 13-diene-11, 12-dione inhibited *Leishmania donovani* promastigotes cell viability with IC_{50} values of 3.5-4.6 µg/mL. Moreover, totarol demonstrated nematicidal and antifouling activities against *Caenorhabditis elegans* and *Artemia salina* at concentrations of 80 µg/mL and 1 µg/mL, respectively. The resinous exudate of *J. virginiana* revealed known antibacterial E-communic acid and 4-epi-abietic acid, whereas the volatile oil from its trunk wood indicated large amounts of cedrol. Using GC/MS, researchers have identified the two known abietanes, totarol and ferruginol, from berries of *J. procera*, JE and *J. phoenicea* (21).

The results of an *in vitro* study demonstrated a significant antileishmanial activity of chloroform fraction of JE berries with ED_{50} value of 14.4 µg/ml. Additionally, diethyl ether fraction of berries revealed lowe antileishmanial activity with ED_{50} value of 60.9 µg/ml than the standard (22).

Another study was carried out to investigate the inhibitory effects of JE on *Leishmania major* promastigotes. The IC_{90} of JE leaf and fruit total extract against *Leishmania major* promastigotes was 1.89+0.03 and 6.96+0.11 mg/ml, respectively. For both fruit and leaf total extracts, petroleum ether fraction exhibited the highest activity compared to chloroform and ethyl acetate, indicating a negative correlation between the polarity of JE fractions and antileishmanial activity. Furthermore, the leaf and respective fractions exerted more antileishmanial activity than those of fruit (23).

3.3. Anti-oxidant and anti-radical activity

According to the previous studies, leaves of JE are rich in ascorbic acid, amino acid proline, and total proteins. Soluble phenols and anthocyanins are in moderate amounts and these components have revealed an exclusively high antioxidant activity (24). Based on a similar study conducted in Mashhad University of Medical Sciences, different parts of JE subspecies essential oils showed antioxidant activity suggesting that very low concentrations might be useful as a natural preservative. However, no activities was reported for α-pinene and limonene; and β-pinene showed a very low activity. The strongest antioxidant activity is referred to oil of female leaves of JE subsp. *polycarpos* in concentration of 4 µL/mL (16.8 %). Besides, low antioxidant activity was determined at a concentration of 4 µL/mL (8.2% and 6.6%, respectively) for leaf and fruit oils of JE subsp. *Excelsa* (25).

Moein *et al*. have revealed the radical scavenging and antioxidant effects of this plant (10). In another research, JE exhibited a moderate antioxidant activity in β-carotene-linoleic acid test method (26). Another study indicated that semi-polar fractions of JE, especially ethyl acetate, possessed more antioxidant activity than other fractions. In inhibition of β-carotene oxidation, ethyl acetate fraction had a remarkable effect (antioxidant activity coefficient, ACC=960±20), which was more than the butanol (ACC=550.7±15.3) fraction; while antioxidant activity of the crude

extract of JE was not detected (27).

According to Orhan *et al*, the leaf aqueous extract of JE has demonstrated lower butyrylcholinesterase inhibition than that of *J. foetidissima*. However, leaf extracts usually exerted higher antioxidant activity (28).

In a research in Shiraz University of Medical Sciences, the highest DPPH radical scavenging was observed in the n-butanol fraction (IC_{50}=135.9±2.5 µg/ml) of JE fruit. Moreover, while phenolic contents (82.9±1.1 mg/g) were determined as responsible ingredients, this fraction possessed the highest reducing power (61.4±2.6 µg/ml)(29).

However, another investigation showed the lowest radical scavenging activity for JE oil among selective Lebanese medicinal plants (30). It is considerable that the effectivness of JE is highly affected by various extracts, essential oil, or type of selected botanical part.

3.4. Phytotoxic effect, and cytotoxic and anticancer activity

A study on phytotoxicity effects demonstrated that JE was extremely toxic for *Lemna aequinoctialis* Welw. In addition, it was observed that brine shrimps at all concentrations are significantly cytotoxic against *Candida albicans* using flow cytometry. It has shown that JE extract may possess high cytotoxicity against brine shrimps at all concentrations. It has also been found to be significantly cytotoxic against *C. albicans* via flow cytometry method, but the extract had no effect against the pests which were tested (11).

In an investigation, the crude methanol extract of JE berries caused 86.6% antitumor activity, which is remarkable as compared to vincristine (100% antitumor activity) (22).

In another research, JE fruit essential oil, with sesquiterpenes as the majority, mainly showed cytotoxic activity against multidrug-resistant p-glycoprotein-expressing CEM/ADR5000 leukemic cells (IC values: (29.46 to 61.54 µg/mL). Multidrug-resistant CEM/ADR5000 cells did not reveal a significant cross-resistance, revealing that the essential oils might be useful to treat otherwise drug-resistant and refractory tumors (31).

Another *in vitro* study on the effect of JE extracts on the cell-cycle phases of MCF-7 breast cancer cell line indicated that JE fruit could reduce the synthesis phase down to 21.97% and block 23.11% of the cell population in G2/M phase. Statistical analysis showed a significant inhibitory effect for JE fruit extract in MCF-7 cell line (32).

3.5. Cardiovascular effect

An *in vivo* study on rabbits revealed that the crude extract of JE exhibited blood pressure lowering effect in cardiovascular diseases through a combination of Ca^{++} antagonism, nitric oxide-modulating, and phosphodiesterase inhibitory mechanisms. The crude extract of JE having anthraquinone, flavonoids, saponins, sterols, terpenes, and tannins showed a dose-dependent fall in the arterial blood pressure of anesthetized rats. In the isolated rabbit aorta, the extract (0.01-5.0 mg/ml) inhibited high K^+ (80 mM) and phenylephrine (1 µM)-induced contractions, as caused by verapamil and papaverine. In endothelium-intact rat aortic preparations, Nω-nitro-l-arginine methyl ester hydrochloride-sensitive vasodilator activity was indicated by JE extract, which also relaxed the endothelium-denuded aorta tissues (33).

3.6. Effect on diabetes

In ethnomedicine of Pakistan, JE is applied for management of diabetes from centuries ago. The ethnopharmacological study in Pakistan has also revealed the anti-diabetic effect of this native plant (8). An *in vivo* study demonstrated that Juniper berries have an acceptable hypoglycemic effect in normoglycemic and diabetic rats (250 mg/kg). The suggested underlying mechanisms for this effect are increase in peripheral glucose consumption and potentiation of glucose-induced insulin secretion (34).

3.7. Gastrointestinal effect

Protective effect of JE has been proved against castor oil-induced diarrhea in mice at 100-1000 mg/kg. In a rabbit model of jejunum preparation, the extract (0.01-1.0 mg/ml) caused relaxation of spontaneous and K^+ (80 mM)-induced contractions at concentrations similar to those of papaverine. However, verapamil was relatively more potent against K^+. The JE extract (0.003-0.01 mg/

ml) caused a leftward shift in isoprenaline-induced inhibitory concentration-response curves, similar to papaverine. This outcome showed that JE can be used as a drug for diarrhea and colic pain (35).

3.8. Respiratory effect

Numerous traditional remedies are being used for treatment of asthma, and JE is one of those remedial agents in some countries (36). According to a relevant study in 2012, JE extract (1.0-30 mg/kg) could cause carbachol suppression (100 µg/kg)-induced increase in anaesthetized rats' respiratory pressure. In guinea-pig trachea, JE extract (0.001-3.0 mg/ml) relaxed the carbachol (1 µM) and high K^+-induced contractions and subsequently, shifted isoprenaline-induced inhibitory curves to the left. According to this investigation, a combination of Ca^{2+} antagonist and phosphodiesterase inhibitory effects of this plant, JE may be a useful drug for the management of asthma (35).

3.9. Immunomodulatory and antinociceptive activities

Several medicinal herbs have potential immunomodulatory effects and antinociceptive activities. In an assessment on some *Juniperus* species in Turkey, anti-inflammatory and anti-nociceptive activities of the leaf and berry extracts of JE was examined for possible anti-nociceptive activity along with two other related species (37). Although the effectiveness of JE was not much considerble compared to that of the others, the outcome of that study might show a promissing point for further investigation on this plant.

3.10. Anti-angiogenic effect

Anti-angiogenic effect of JE berries essential oil has been investigated by researchers (38). In a related study, the effect was assessed on the vascularization system of shell-less chick embryo culture. In a chick chorioallantoic membrane model, 50 µl of the essential oil was applied to the center of the blastodisc; and subsequently, amounts of capillary, branching, and main blood vessels were counted. Among those items, amounts of capillary vascularization was significantly higher than the others (P<0.05). This investigation showed that JE essential oil has a potential effect on extra-embryonic vascular development, thus can be used as an anti-angiogenic agent.

4. Conclusion

This review has compiled medicinal and pharmacological activities of *Juniperus excelsa* M.Bieb to draw a frame for further research. This medicinal plant could have various effective points, pharmacologically and clinically. Many of the related studies have focused on animal models. Thus, conducting an acceptable human study with comprehensive or large and multicenter trials might be a good opportunity to introduce the plant as a new natural medicine with respective activities. Accordingly, it is worthy to consider those promising outcomes for further research.

Conflict of Interest

None declared.

5. References

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