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MEDICAL IMPORTANCE OF *JUNIPERUS COMMUNIS* - A REVIEW

Ali Esmail Al-Snafi
Department of Pharmacology, College of Medicine, University of Thi qar, Iraq.
Cell: +9647801397994. E mail: aboahmad61@yahoo.com

Abstract:
Juniperus communis contained monoterpenes, sesquiteierpenes, essential and volatile oils, wide range of phenolic compounds and many other chemical constituents. It exerted many pharmacological effects included antimicrobial, antiparasitic, antifertility, antioxidant, cytotoxic, hepatoprotective, vessels and trachea protective effects in passive smoking, gastrointestinal, antidiabetic, antihyperlipidemic, anti-inflammatory, analgesic, diuretic, antiurolithiatic, anti-Parkinsonian, memory enhancing, tyrosinase suppressive activity and many other effects. This review will highlight the chemical constituents and pharmacological effects of Juniperus communis.
Keywords: *chemical constituents, pharmacology, Juniperus communis*

Corresponding author:
Ali Esmail Al-Snafi
Department of Pharmacology,
College of Medicine,
University of Thi qar, Iraq
Cell: +9647801397994.
E mail: aboahmad61@yahoo.com

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INTRODUCTION:

Herbal medicine, the oldest form of medicine known to mankind, is still the most widely practiced form of medicine in the world today. Plants produce many metabolites which constitute an important source of many pharmaceutical drugs [1-40]. *Juniperus communis* contained monoterpenes, sesquiteierpenes, essential and volatile oils, wide range of phenolic compounds and many other chemical constituents. It exerted many pharmacological effects included antimicrobial, antiparasitic, antifertility, antioxidant, cytotoxic, hepatoprotective, vessels and trachea protective effects in passive smoking, gastrointestinal, antidiabetic, antihyperlipidemic, anti-inflammatory, analgesic, diuretic, antiurolithiatic, anti-Parkinsonian, memory enhancing, tyrosinase suppressive activity and many other effects. This review was designed to highlight the chemical constituents and pharmacological effects of *Juniperus communis*.

Plant profile:

Synonyms:

Juniperus albanica Pénzes, *Juniperus communis* var.*arborescens* Gaudin, *Juniperus communis* var. *aurea* G. Nicholson, *Juniperus communis* f. *aurea* [G.Nicholson] Rehder, *Juniperus communis* var. *brevifolia* Sanio, *Juniperus communis* subsp. *brevifolia* [Sanio] Pénzes, *Juniperus communis* var. *communis*, *Juniperus communis* var. *compressa* Carrière, *Juniperus communis* f. *compressa* [Carrière] Rehder, *Juniperus communis* f. *crispa* Browicz & Ziel., *Juniperus communis* subsp. *cupressiformis* Vict. & Sennen ex Pénzes, *Juniperus communis* var. *erecta* Pursh, *Juniperus communis* var.*fastigiata* Parl., *Juniperus communis* var. *hemisphaerica* [J.Presl & C.Presl] Parl., *Juniperus communis* subsp. *hemisphaerica* [J.Presl & C.Presl] Nyman, *Juniperus communis* var.*hispanica* Endl., *Juniperus communis* var. *montana* Neilr., *Juniperus communis* var. *oblonga* Loudon, *Juniperus communis* var. *oblonga- pendula* Loudon., *Juniperus communis* f. *oblonga-pendula* [Loudon] Beissn., *Juniperus communis* subsp. *pannonica* Pénzes, *Juniperus communis* var .*pendens* Sudw., *Juniperus communis* var. *pendula* Carrière, *Juniperus communis* f. *pendula* [Carrière] Formánek, *Juniperus communis* var.*pendula- aurea* Sénécl., *Juniperus communis* f. *pendulina* Kuphaldt, *Juniperus communis* f. *pungens* Velen., *Juniperus communis* var.*reflexa* Parl., *Juniperus communis* var. *stricta* Carrière, *Juniperus communis* f. *stricta* [Carrière] Rehder, *Juniperus communis* var. *suecica* [Mill.] Aiton, *Juniperus communis* f. *suecica* [Mill.] Beissn. , *Juniperus communis* var. *variegata-aurea* Carrière, *Juniperus compressa* Carrière, *Juniperus cracovia* K.Koch, *Juniperus dealbata* Loudon, *Juniperus difformis* Gilib., *Juniperus echinoformis* Rinz ex Bolse, *Juniperus elliptica* K. Koch, *Juniperus fastigiata* Knight, *Juniperus hemisphaerica* C. Presl, *Juniperus hibernica* Lodd. ex Loudon, *Juniperus hispanica* Booth ex Endl., *Juniperus interrupta* H. L.Wendl. ex Endl., *Juniperus kanitzii* Csató, *Juniperus microphylla* Antoine, *Juniperus niemannii*E.L.Wolf, *Juniperus oblonga-pendula* [Loudon] Van Geert ex K.Koch, *Juniperus oblongopendula*Loudon ex Beissn., *Juniperus oxycedrus* subsp. *hemisphaerica* [J. Presl & C.Presl] E. Schmid, *Juniperus reflexa* Gordon, *Juniperus saxatilis* Lindl. & Gordon, *Juniperus suecica* Mill., *Juniperus taurica* Lindl. & Gordon, *Juniperus uralensis* Beissn., *Juniperus withmanniana* Carrière, *Sabina dealbata* [Loudon] Antoine, *Thuiaecarpus juniperinus* Trautv[41].

Taxonomic classification:

Kingdom: Plantae; **Subkingdom**: Viridiplantae; **Infrakingdom**: Streptophyta; **Superdivision**: Embryophyta; **Division**: Tracheophyta; **Subdivision**: Spermatophytina; **Class**: Pinopsida; **Subclass**: Pinidae; **Order**: Pinales; **Family**: Cupressaceae; **Genus**: Juniperus; **Species**: *Juniperus communis*[42].

Common names:

Arabic: Arar Adi; Arar shia,a, Arar feniki; English: juniper, common juniper, malchangel; **French**: genévrier, genièvre commun; **German:** gemeine Wacholder**,** Heide-Wacholder; **Hindi:** havuber, havubair; **Italian:** ginepro, ginepro comune; **Portuguese:** zimbreiro; **Spanish**: enebro, ginepro nano ; **Swedish**: en[43].

Distribution:

It was distributed in the Northern Hemisphere, in North America, Europe, Asia as well as Africa. It is the most northerly of the juniper species and one of the most northerly conifers in the world [44].

However, it was found in **Africa** [Algeria, Morocco]; **Asia** [Azerbaijan, Georgia, Russian Federation, China, Japan, Korea, Kazakhstan, Kyrgyzstan, Tajikistan, Afghanistan, Iran, Turkey, Iraq, Nepal, Pakistan]; **Europe** [Belarus, Estonia, Latvia, Lithuania, Moldova, Russian Federation-European part, Austria; Belgium, Czech Republic, Germany, Hungary, Netherlands, Poland, Slovakia, Switzerland, Denmark, Finland, Iceland, Ireland, Norway, Sweden, United Kingdom, Albania, Bosnia

and Herzegovina, Bulgaria, Croatia, Greece, Italy, Montenegro, Romania, Serbia, Slovenia, France, Portugal, Spain]; **Northern America** [United States, Canada]. It was widely cultivated [43, 45-46].

Description:
Shrubs or small trees dioecious, to 4 m, multistemmed, decumbent or rarely upright; crown generally depressed. Bark brown, fibrous, exfoliating in thin strips that of small branchlets [5-10 mm diam.] smooth, that of larger branchlets exfoliating in strips and plates. Branches spreading or ascending; branchlets erect, terete. Leaves green but sometimes appearing silver when glaucous, spreading, abaxial glands very elongate; adaxial surface with glaucous stomatal band; apex acute to obtuse, mucronate. Seed cones maturing in 2 years, of 2 distinct sizes, with straight peduncles, globose to ovoid, 6-13 mm, bluish black, glaucous, resinous to obscurely woody, with 2-3 seeds[47].

Traditional uses:
Juniper has a history of medicinal use dating as far back as 1550 B.C. A remedy to treat tapeworm was found in [The Papyrus of Ani] from ancient Egypt, 240 B.C. It is also known that the branches and berries were burned in temples as a part of purification ceremonies [45].

Aerial parts were used for acute and chronic cystitis, albuminuria, catarrh of the bladder, renal suppression, leucorrhoea, and amenorrhoea. Fruits were used as antiseptic, stimulant, disinfectant, styptic, chronic Bright's disease, migraine, dropsy, rheumatic and painful swellings, piles, and infantile tuberculosis. Bark was used in nephrotic dropsy of children, asthma, gonorrhoea, pulmonary blennorrhoea, arthritis, respiratory affections, diabetes, bladder affections, chronic pyelonephritis, cough, abdominal disorders, and skin affections. The whole plant was used as carminative, urinary antiseptic, diuretic, emmenagogue, sudorific, digestive, and as anti-inflammatory [48-50].

Juniper oil has been used as a carminative, in arthritis, as diuretic and as a steam inhalant in the management of bronchitis [51-52].

Oil of *Juniperus* was also used in aromatherapy, through inhalation, massage, ingestion to create good health and beauty and used in perfume industries [53].

Parts used:
The whole plant, aerial parts, fruits and oil [48-50].

Chemical constituents:
Juniperus communis contained monoterpenes [the highest recorded values were α-pinene, α-cedrol, carene, α-terpinolen, and terpineol-4], sesquiterpenes - beta-caryophyllene, delta-cadinene, farnesol, gamma-elemente, gamma-muurolene, humulene and pregeijerene. Diterpenes - sugiol, xanthoperol, 4-epi-abietic acid, 4-epi-dehydroabietic acid, 4-epi-palustric acid, 4-epi-abietinal, 4-epi-abietinol, isopimaric acid, isocommunic acid, [-] ent-trans communic acid and sandracopimaric acid. Neolignan glycosides - junipercomnoside A and B and icariside E4. it also contained lignans - podophyllotoxin, tannins, gallocatechins and flavonoids [scutellarein, luteolin-7-O-b-D- glucoside, nicotiflorin, kaempferol-3-O-β-D- glucoside, Kaempferol-3-O- a-rhamnopyranoside, Quercetin-3-a-O-L-rhamnopyranoside, Quercitrin, Isoquercitrin, Quercetin-3-O-arabinosyl-glucoside, rutin, quercetin, luteolin, apigenin, amentoflavone, isocutellarein, hypolaetin, kaempferol 3-O-alpha-rhamnopyranoside, nicotiflorin and naringenin]. It also contained diterpene isocupressic acid, the aryltetralin lignan deoxypodophyllotoxin, Imbricatolic acid and dihydrobenzofuran lignan glycoside named juniperoside A [54-64].

In composition analysis, fifteen phenolic compounds were identified in *Juniperus communis*. The main groups of them were flavones, flavonols, phenolic acids, flavanol and biflavonoid including glycosides of quercetin, apigenin, isoscutellarein and hypolaetin [65].

The total polyphenols [Folin-Ciocalteau method] of the berries of *Juniperus communis* were 59.17 ± 1.65 mg GAE/g extract. Flavonoid and biflavonoid content were 25947 ± 0.86 and 4346 ± 3.95 microg/g extract. The HPLC analysis of Jcc allowed the separation of 16 flavonoids; hypolaetin-7-pentoside and quercetin-hexoside were the main compounds [66].

The total phenol content of ethanol extract, hexane fraction, ethyl acetate fraction, and aqueous fraction were found to be 238.78, 189.65, 315.33, and 205.33 mg/GAE/g extract/fraction, respectively [67].

Sesquiterpene identified as longifolene and diterpenes, characterised as totarol, trans-communic acid, isocupressic acid, labdane and communic acid, as well as aryltetralin lignan were isolated from *Juniperus communis* [68-70].

The yield of the oil from the berries and needles of juniper depends on the plant´s geographical location, degree of ripeness and age, as well as meteorological

conditions [temperature, length of sunlight, duration of photoperiod], and other factors [71].

Twenty seven essential oils were detected in *Juniperus communis* from Iran [α–pinene 46.63%, α–fenchene 0.25%,Sabinene 0.58%, β–pinene 1.38%, Myrcene 1.52%, DETA.3-carene 9.85%, Limonene 1.90%, Terpinolene 2.45%, Terpine ol -4 2.86%, α-terpineol 0.94%, Carvone 0.74%, Carvacrol 0.83%, γ-terpinene 0.50%, α-terpinolen 4.64%, α-amorphene 0.99%, β–caryophyllene 1.14%, α–humulene 0.95%, Germacrene-D 1.75%, α–muurolene 0.89%, β–cadinene 1.43%, β–elemene 0.89%, Junipene 0.73%, α–cedrol 12.36%, γ–cadinene 1.25%, δ–cadinene 0.90%, α–cadinene 1.10% and α–cadinol 0.54%], the highest recorded values were α-pinene, α-cedrol, DETA.3-carene, α-terpinolen, and terpineol-4. In this study[45].

Juniperus communis fruits collected from 16 localities in Albania, and their essential oils were analysed by GC/MS. The content of essential oil varies in the range of 1.2 % to 3.8 % and from 34 to 47 substances was identified. The Albanian plants have more geographic types, which were identified on base of the essential oil composition. The first has the dominant compounds β-myrcene [44.5 ± 3.04 %] and α-pinene [19.6 ± 3.35 %]. The second type is characterised by the contents: α-pinene [25.1 ± 1.78 %], β-pinene [13.4 ± 4.41 %] and β-myrcene [21.2 ± 4.79 %] and the third: α-pinene [31.6 ± 1.81 %], β-pinene [13.6 ± 1.78 %] and β-myrcene [18.5 ± 5.60 %]. The last has very high content of α-pinene [37.7 ± 1.92 %], β-pinene [12.4 ± 2.22 %] and β-myrcene [18.6 ± 3.65 %][72].

The needles and berries of the same junipers growing wild in Lithuania produced essential oils of different chemotypes. The dominant compounds in four from investigated needle essential oils were sabinene [34.1–40.8%], α-pinene [11.7–27.8%] and terpinen-4-ol [6.9–9.3%], while in the rest needle oils the main component was α-pinene [41.2–66.5%]. The first major constituent of all berry essential oils was α-pinene [21.0–67.4 %]. The second and third main constituents in unripe berry oils from bushes with needle oils of sabinene chemotype were sabinene [6.3–19.6%], myrcene [4.3–12.8%] and terpinen-4-ol [13.1%] and in the ripe berry oils myrcene [7.8–18.7%] and terpinen-4-ol [3.2–9.6%]. The content of sabinene in all ripe berry oils was only 0.4–2.9%[73].
Analysis of the chemical composition of the essential oils of the aerial parts of *Juniperus communis* from Egypt showed that tthey contained sixty seven [94.32%] components with homogeraniol [36.95%], 10-Epi-elemol [9.45%] and β-Myrcene [5.15%] being the major constituent[74].
Eighty seven compounds accounting for over 96% [micro-distillation and extraction, SDE] and to 94% [supercritical carbon dioxide extraction, SFE] of oils were identified in *Juniperus communis* from Estonian. In the essential oil of the needles and berries of *J. communis* monoterpenes predominated [49.5and 58.0%, respectively], there were differences in composition between the compounds present. So, the juniper-needle oil contained up to 32.6% of sesquiterpenes as against 12.8% in the juniper-berry oil. The amount of oxygenated monoterpenes in the juniper-needle oil was low [2.0%], being 14.7% in the juniper-berry oil. In the juniper-needle oil α-pinene [36.4%], [E]-E-caryophyllene [8.1%], α-humulene [6.3%], β-phellandrene [6.3%], and germacrene D [4.8%] prevailed. The content of α-pinene of the juniper-berry oil was high [47.9%]; the predominant minor constituents were germacrene D [3.7%], myrcene [3.4%], p-mentha-1,5-dien-8-ol [2.9%] and α-campholenal [2.4%][71].

The essential oils of the leaves [needles] of *Juniperus communis* var. *saxatilis* and from three populations of North-West Himalaya were analyzed by GC and GC/MS to determine quantitative and qualitative variation in the oil composition. *J. communis* essential oils characterized with □-pinene, as a main principal component in three investigated oils [31.8-49.5%]. Limonene was the second major constituent [13.7-19.5%], whereas □-3-carene afforded 9.7-14.7%[75].

The essential oils of *Jiniperus communuis* from Sidi-Lakhdar City, Mostaghanem Province-West, Algerian showed that a-pinene [14.2, 9.7%] was the main components, followed by sabinene [12.4, 16.1%], g-terpinene [5.9, 1.7%], terpinene 4-ol [14.1, 9.1%], [*Z*,*Z*]-farnesol [5.4, 6.6%] and manoyl oxide [4.1, 11.7%][76].

The essential oils from needles, berries, wood and roots of *Juniperus communis* L. subsp. *alpina* from Corsica, revealed the presence of 82, 65, 76 and 54 components, respectively. The chemical compositions of the essential oils from needles, berries and wood characterized by a high proportion of monoterpene hydrocarbons. Root oil exhibited a quite different composition. Sesquiterpenes, especially those bearing a tricyclic skeleton [cedrane and longifolane], constituted the main fraction while monoterpenes were present at very low contents[77].
The composition of juniper berry essential oil from Kurt Kitzing GmbH, Wallerstein-

Germany, was dominated by monoterpenes [α-pinene: 35.4%, myrcene: 15.3%, sabinene: 7.6%, limonene: 7.3%], sesquiterpene [α-caryophyllene: 4.2%, germacrene D: 1.8%, δ-cadinene: 1.5%]. The major oxygenated terpenoids were terpinen-4-ol: 2.4%, α- and γ-terpinenes: 0.5 and 1.8%[78].

Analysis of the chemical composition of leaves essential oil of *Juniperus communis* from R. Macedonia revealed four main classes of components: monoterpene hydrocarbons, oxygen-containing monoterpenes, sesquiterpene hydrocarbons and oxygen-containing sesquiterpenes. Diterpenes were present in small amounts as well as some non-terpene components. Monoterpene hydrocarbons were the most abundant fraction in all investigated oils [39.97% - 53.39%], for all samples, followed by Sesquiterpene hydrocarbons [12.27- 28.64%][79].

The main constituents of the essential oil of *Juniperus communis* from the southern part of Serbia were α-Pinene 36.6±0.6- 40.5±0.7%, Sabinene 16.2±0.2- 18.0±0.2%, Myrcene 10.9±0.2-13.5±0.3%,, β-Caryophyllene 5.3±0.1 0-.6±0.0%, D-Limonene.3.9±0.1- 5.1±0.1%, 1-Terpinen-4-ol 2.4±0.1-2.5±0.1% and *p*-Cymene 2±0.1-2.3±0.1%[80].

The essential oil of juniper berries [*Juniperus communis* from Bulgaria., comprised ofmonoterpene hydrocarbons such as α-pinene [51.4%], myrcene [8.3%], sabinene [5.8%],limonene [5.1%] and β-pinene [5.0%] as main constituents [81].
The essential oil composition of the leaves of *Juniperus communis* from Canada were investigated by head space solid phase micro-extraction [HS-SPME] and gas chromatography/mass spectrometry [GC-MS]. Limonene [26.12%], benzene [15.62%], β-mrycene [9.08%] and β-pinene [7.30%] were found to be the main constituents of *J. communis* essential oil [53].

The composition of the essential oil from ripe and unripe berries and leaves of *Juniperus communis* ssp. communis from Sardinia, Italy, analyzed by GC-MS. The major compounds in the essential oils were α-pinene, β-pinene, δ-3-carene, sabinene, myrcene, β-phellandrene, limonene, and D-germacrene [82].

Chemical analysis of the essential oil of *Juniperus communis* from east part of Kosova revealed that the oil composed mainly of monoterpenoids which amounted to 83%, of which 69.4% was monoterpene hydrocarbons. The main monoterpene hydrocarbons were α-pinene [36.2%] and β-myrcene [21.1%]. The sesquiterpene accounted for about 13.4% of the total oil composition. Germacrene D [2.2%], α-cadinol [1.6%], α-humulene [1.5%], spathulenol [1.4%], epi-α-bisabolol [1.3%] and germacrene B [1.1%] were the main constituents of the sesquiterpenes[83].
Juniper berry also contained minerals included N: 0.58-0.60 0.58%, P: 0.18-0.20%, K: 5.72-6.12%, Ca: 1.43-1.45%, Mg: 1.87-1.90 ppm, Fe: 79.32-80.12 ppm, Mn: 15.31-16.58 ppm, Zn: 17.84-18.80 ppm and Cu: 18.91-19.94 ppm[84].

Pharmacological effects:
Antimicrobial effect:
Antimicrobial screening of the essential oils of *Juniperus communis* was studied against 16 bacterial isolates of Gram positive and Gram negative bacteria and one strain of *Candida albicans*. The highest MIC [125 µl/ml] of the essential oils were towards *Staphylococcus aureus* and *Streptococcus pyogenes*, and moderate antimicrobial activity against *Streptococcus agalactiae, Haemophillus influnzae, Corynebacterium* spp. and *Campylobacter jejuni* [MIC > 500 µl/ml]. *Candida albicans, Staphylococcus epidermidis, Acinetobacter* spp., *Salmonella enteritidis, Shigella flexneri, Klebsiella pneumonia, Pseudomonas aeruginosa* and *Proteus mirabilis* were completely resistant to the antimicrobial activity of juniper oil[79].

At concentrations of 20 and 50%, *Juniperus communis* essential oils possessed antibacterial activity against *Staphylococcus aureus* NCIB 6751 [diameter of zone of growth inhibiion 4.8 and 5mm respectively] and *Escherichia coli* NCIB 8879 [diameter of zone of growth inhibiion 7.2 and 8.3 mm respectively][45].

Many fractions as well as essential oil obtained from *Juniperus communis* were investigated for antimicrobial activity [*Escherichia coli* ATCC 8739, *Listeria monocytogenes* IM200, *Corynebacterium* sp. 754, *Pseudomonas aeruginosa* DV5999, *Staphylococcus aureus* ATCC 6538, *Candida albicans* , *Alternaria* sp., *Aspergillus nidulans*, and *Aspergillus niger*], some fractions showed distinct antimicrobial activity with a wide spectrum and wide inhibition zones. Juniper essential oil showed low antimicrobial activity with respect to almost all the investigated species. *B. cereus* was susceptible to all the tested samples, while *E. coli* and *S. aureus* were resistant only to on e fraction. *Corynebacterium* sp. and *P. aeruginosa* DV5999 were the least susceptible to all the oil samples. Five samples as well as juniper essential oil, showed strong inhibitory effects to yeast and fungi [40].

The antibacterial activity of n-hexane extract of *Juniperus communis* roots against Mycobacterium tuberculosis H[37]Rv and *Juniperus communis* aerial parts against Mycobacterium aurum were studied in vitro with isolation and identification of the constituents responsible for this activity. *Juniperus communis* showed antimycobacterium activity, the antimycobacterial activity of *Juniperus communis* was attributed to a sesquiterpene identified as longifolene and two diterpenes, characterised as totarol and trans-communic acid[69].

Antimicrobial activity of the essential oil of *Juniperus communis* was investigated against *Staphylococcus aureus*, *Escherichia coli*, *Hafnia alvei* and *Pseudomonas aeruginosa*. The essential oil showed moderate to high activities against *Staphylococcus aureus*, *Escherichia coli*, *Hafnia alvei* [zone of inhibition 10- 35mm for concentration of 5 mg ml]. *Pseudomonas aeruginosa* was resistant to the essential oil of *J. communis*[83].

The antibacterial effect of crude leaf organic extracts [methanol, ethanol, chloroform and hexane] and aqueous extracts of *Juniperus communis* was studied against five pathogenic multi drug resistant bacteria [*Bacillus subtilis*, *Erwinia chrysanthemi*, *Escherichia coli*, *Agrobacterium tumefaciens* and *Xanthomonas phaseoli*]. All the extracts of *Juniperus communis* showed antibacterial activity except aqueous extract. The hexane extract showed maximum inhibition against the test microorganisms [zone of inhibition, 16 – 21 mm] followed by ethanol, methanol and chloroform extract [zone of inhibition, 6 – 17mm]. The inhibitory activity of these extracts was found very effective as compared to Ampicillin [10 mcg] and Erythromycin [15 mcg] standard antibiotics which were used as positive controls[51].
Diterpenes isocupressic acid, communic acid and the aryltetralin lignan deoxypodophyllotoxin isolated from the *J. communis* extract were tested as antimicobacterium compounds. Isocupressic acid and communic acid displayed MICs of 78 µM and 31 µM and IC50 of 46 µM and 15 µM against M. tuberculosis H37Ra respectively. Deoxypodophyllotoxin was less active, with a MIC of 1004 µM and an IC50 of 287 µM[70].

The essential oils and their major compounds of *Juniperus communis* ssp. communis were tested against Candida albicans, Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa, and the minimum inhibitory concentration and minimum bactericidal concentration were determined. They possessed nonsignificant inhibitory effect [82].

Different concentration of chloroform, methanol, ethanol and petroleum ether of *Juniperus* leaf extract were screened against Aflatoxigenic *Aspergillus flavus* MTCC 2798. Methanolic extract caused maximum percent growth inhibition followed by ethanol [52%], petroleum ether [39%] and Chloroform [27%] at 4000 ppm concentration[85].
Different concentration of methanol, ethanol, chloroform, petroleum ether extracts of *Juniper communis* leaves extracts as well as bark extracts were studied against *A. niger* and aflatoxigenic *A.flavus*. Among all leaf extracts, methanolic extract possessed maximum percentage growth inhibition [57.8%] against *A.flavus*, while ethanolic extract showed maximum percentage growth inhibition [56%] against *A. niger*. Among bark extract, ethanolic extract possessed maximum percentage growth inhibition [48%] against *A. flavus*, and methanolic bark extract showed maximum percentage growth inhibition against *A.niger*[40%][86].

Antifertility effect:
The antifertility mode of action of *Juniperus communis* various extracts were investigated for estrogenic, antiestrogenic, progestagenic and antiprogestagenic properties in laboratory animals. Investigations reveal that the extract possessed only antiprogestational activity which accounts for its antifertility effect[87].

Extract of *juniperus communis* fruits in 50 % ethanol was screened for antifertility activity in female rats. 300 mg and 500 mg per kg bw of the extract was administered orally from day 1 to 7 of pregnancy. The extract possessed dose dependent antiimplantation activity, it also showed abortifacient activity at both dose levels when administered on days 14, 15 and 16 of pregnancy. No evidence of teratogenicity was observed[88].

Antioxidant effect:
The in vitro antioxidant activity of water and ethanol extracts of juniper [*Juniperus communis* fruit was evaluated using different antioxidant assays, including reducing power, free radical scavenging, superoxide anion radical scavenging, hydrogen peroxide scavenging, and metal chelating activities. Both the water and the ethanol extracts exhibited strong total antioxidant activity. The concentrations of 20, 40, and 60 µg/ml of water and ethanol extracts of juniper fruit showed 75%, 88%, 93%, 73%, 84%, and 92% inhibition on peroxidation of linoleic acid emulsion, respectively. Both extracts of juniper possessed effective reducing power, free radical scavenging, superoxide anion radical scavenging, hydrogen peroxide scavenging, and metal chelating

activities at these same concentrations [20, 40, and 60 µg/ml][89].

The antioxidant capacity of the essential oil was evaluated *in vitro* by 2,2-Diphenyl-1-picrylhydrazyl [DPPH] scavenging, 2,2-azino-bis-3-ethylbenzo-thiazoline-6 sulfonic acid [ABTS] radical cation scavenging, hydroxyl radical [OH•] scavenging and chelating capacity, superoxide radical [•O2−] scavenging and xanthine oxidase inhibitory effects, hydrogen peroxide scavenging. The antioxidant activity of the oil attributable to electron transfer made juniper berry essential oil a strong antioxidant, whereas the antioxidant activity attributable to hydrogen atom transfer was lower. Lipid peroxidation inhibition by the essential oil in both stages [hydroperoxide formation and malondialdehyde formation], was less efficient than the inhibition by butylated hydroxytoluene [BHT]. *In vivo* studies confirmed showed that the oil created the possibility of blocking the oxidation processes in yeast cells by increasing activity of the antioxidant enzymes superoxide dismutase [SOD], catalase [CAT], and glutathione peroxidase [GPx][81].

Antioxidant properties of *Juniperus communis* essential oils were evaluated by 7 different *in vitro* models. IC50 for hydroxyl radical [OH] scavenging and for chelating capacity were 0.0235 ig/cm3 and 0.024**6** ig/cm3 respectively. The essential oil exhibited hydrogen peroxide scavenging activity and 2,2'-azinobis[3-ethylbenzothiazoline-6-sulfonic acid] [ABTS+] radical cation scavenging activity – the activity of 10 mg of juniper berry oil is equivalent to 4.77 mM Trolox. The antioxidant activity of the oil attributable to hydrogen atom transfer was lower. IC50 for 2,2-Diphenyl-1-picrylhydrazyl radical scavenging [DPPH] was 944 ig/cm3. Lipid peroxidation inhibition by the essential oil in both stages, i.e. hydroperoxide formation and malondialdehyde formation, was less efficient than the inhibition by BHT[78].

The antioxidant activities of the ethanolic extract [70% v/v] and hexane and ethyl acetate fractions of *Juniperus communis* leaves were investigated by 2,2-diphenyl-1-picrylhydrazyl [DPPH] radical scavenging activity and Fe2+ chelating ability. Total phenol content was found maximum 315.33 mg/GAE/g in EAF. Significant scavenging activity were found for EAF [IC50 = 177 µg/ml] as compared to standard BHT [IC50 = 138 µg/ml], while EAF showed good Fe2+ chelating ability having an IC50 value of 261 mg/ml[67].

Juniperus communis showed antioxidant activity, It was active in the DPPH test with IC50 of 0.63 ±0.09 mg/ml, in reducing power assay 12.82 ±0.10 ASE/mL and in TBA assay IC50 of 4.44 ± 0.70 microg/ml[66].

Cytotoxic effect:

The cytotoxic activities of the ethyl acetate fractions of *Juniperus communis* leaves were investigated by cell viability assay on HepG2 cells. Results obtained from the WST-1 proliferation assay clearly showed that EAF did not affect HepG2 cell viability after treatment for 24 h at all concentration tested [0-10 µg/ml][67].

The cytotoxic activity of *J. communis* was screened using MTT [3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyl tetrazolium bromide] in vitro assay against three cancer cell lines, human prostate cancer cells [PC3], human colon cancer cells [HCT 116] and breast cancer cells [MCF7]. The highest activity with the safest margin of use was recorded for the total methanolic extract against human breast cancer cell line [MCF7][90].

The diterpene isocupressic acid and the aryltetralin lignan deoxypodophyllotoxin from *Juniperus communis*, effectively induced caspase-dependent programmed cell death [apoptosis] in malignant MB231 breast cancer cells. Aryltetralin lignan deoxypodophyllotoxin also inhibited cell survival pathways mediated by the MAPK/ERK and NFκB signaling pathways within hours of treatment[55].

Imbricatolic acid isolated from the methanolic extract of the fresh ripe berries of *Juniperus communis* was evaluated for its ability to prevent cell cycle progression in p53-null CaLu-6 cells. It induced upregulation of cyclin-dependent kinase inhibitors and their accumulation in the G1 phase of the cell cycle, as well as the degradation of cyclins A, D1, and E1[54].

The effect of juniper berry extract [*Juniperus communis* L.] was evaluated on p53 protein, gene expression and DNA fragmentation in human neuroblastoma SH-SY5Y cells. The juniper berry extract activated cellular relocalization of p53 and DNA fragmentation-dependent cell death. Differentially expressed genes between treated and non-treated cells were evaluated with the cDNA-RDA [representational difference analysis] method at the early time point of apoptotic process when p53 started to be activated and no caspase activity was detected. Twenty one overexpressed genes related to cellular stress, protein synthesis, cell survival and

death were detected. They included endoplasmic reticulum [ER] stress inducer and sensor HSPA5 and other ER stress-related genes CALM2 and YKT6 indicating that ER stress response was involved in juniper berry extract mediated cell death. The authors suggested that juniper berry extract induced the p53-associated apoptosis through the potentiation and synergism by several phenolic compounds[65].

Hepatoprotective effect:

The hepatoprotective activities of the of ethyl acetate fraction [EAF] of *Juniperus communis* leaves were investigated against PCM-Paracetamol-induced hepatic damage in Wistar albino rats. It was found that EAF treated group shows remarkable decrease in serum Aspartate aminotransferase, serum Alanine aminotransferase, total bilirubin, direct bilirubin, and alkaline phosphatase level in treatment group as compared to the hepatotoxic group[67].

The combination of ethanolic fruits extract of Solanum xanthocarpum [SX] and *Juniperus communis* [JC] was evaluated against Paracetamol [PCM] and Azithromycin [AZM] induced liver toxicity in rats. Liver toxicity was induced by combine oral administration of PCM [250 mg/kg] and AZM [200 mg/kg] for 7 days in Wistar rats. Fruit extract of SX [200 and 400 mg/kg] and JC [200 and 400 mg/kg] were administered daily for 14 days. A combine administration of AZM and PCM significantly produced liver toxicity by increasing the serum level of hepatic enzymes, oxidative parameters in liver, and histopathological. Chronic treatment of SX and JC extract significantly and dose-dependently attenuated the liver toxicity by normalizing the biochemical factors and histopathological changes in rats[91].

Antidiabetic and antihyperlipidemic effects:

Orally administered juniper decoction showed significant hypoglycemic activity in normal rats after single doses equivalent to 250-500mg juniper/kg and in streptozotocin-induced diabetic rats after 24-day treatment with doses equivalent to 125mg juniper/kg. The effects could be attributed to an increase in peripheral absorption of glucose, independent of plasma insulin levels[92].

Juniperus communis was evaluated for the antidiabetic and antihyperlipidemic activity on Streptozotocin[STZ]-nicotinamide induced diabetic rats. The methanolic extract of *Juniperus communis* [100 and 200mg/kg bw] was administered orally in diabetic rats. The extract showed significant [P<0.01] reduction in blood glucose levels total cholesterol, triglyceride, LDL, VLDL, with elevation of HDL levels in diabetic rats. The effects were dose dependent[49].

Juniperus communis Lynn [JCL] [50, 100, 200 mg/kg JCL oil for 30 days were given to hypercholesterolemic rats to determine their o of hypolipidemic effects. The administration of cholesterol increased the TC level significantly with a significant increase in Ox-LDL levels, but the administration of JCL together with cholesterol prevented these changes[93].

Diuretic and antiurolithiatic effects:

A 10% aqueous infusion of juniper, 0.1% aqueous solution of juniper oil [with 0.2% of Tween 20 solubilizer] and 0.01% aqueous solution of terpinen-4-ol were orally administered to rats at 5ml/100g bw to determine the effect on urine output. Compared to water, the 10% aqueous infusion of juniper and the 0.1% aqueous solution of juniper oil caused reductions of only 6% in diuresis over a 24-hour period, equivalent to the effect of 0.004 IU/100g of ADH, while the 0.01% solution of terpinen-4-ol caused a reduction of 30% in diuresis [p<0.01], equivalent to 0.4 IU/100g intraperitoneal of ADH. Continued daily administration at the same daily dose level, the two juniper preparations and terpinen-4-ol stimulated diuresis on days two and three, although only the 10% aqueous infusion of juniper exerted significant diuretic activity [+ 43% on day two; +44% on day three; p<0.05], suggesting that the diuretic effect is partly due to the essential oil and partly to hydrophilic constituents[94].

However, oral administration of lyophilized aqueous extract of juniper at 1000mg/kg bw to rats, it didnt increase urine volume or excretion of Na+, K+ or Cl- ions over a six-hour period compared to the effect of the same volume of water[95].

The antiurolithiasis and dissolution of urinary stones of *Juniperus communis* fruit extract was studied in vitro. Variable concentrations of some fractions of the extract of *Juniperus communis* fruit [500, 1000 and 2000 µg/ml solutions] were used in vitro on urinary stones brought out from human kidney. Neutral [normal saline], positive [sodium bicarbonate] and negative [acetic acid] control groups were also tested. Significant findings were obtained in urinary stones composed of calcium oxalate [50%], calcium hydrogen phosphate [20%], magnesium ammonium phosphate, [10%] and ammonium urate [20%]. The weight of dry powder of stones in normal saline decreased from 1458 mg to 1162, 1124, 1136, 1144, 1096, 1126, and 1130 mg after exposure to increasing concentrations of some fractions of the extract of Juniperus fruit. In addition, the ratio of

calcium oxalate in normal saline aqueous solution plus stone increased from 70% to 80% after using some fractions of the extract of Juniperus fruit[96].

Effect on Parkinson's disease:
The effect of methanolic extract of *Juniperus communis* [MEJC] leaves on reserpine induced catalepsy was studied in rats. Catalepsy was induced by intra administration of reserpine [2.5 mg/kg, ip]. The methanolic extract at 100 and 200 mg/kg, ip were screened for its efficacy against reserpine induced catalepsy in rats. The MEJC extract reduced catalepsy significantly [$p<0.001$] as compared to the reserpine treated rats, maximum reduction was observed at a dose of 200 mg/kg. Accordingly, *J. communis* possessed a therapeutic effect against Parkinson's disease in reserpine induced animal PD models[97].

The neuroprotective activity of methanolic extrct of *J. communis* [MEJC] was evaluated in chlorpromazine [CPZ] induced Parkinson's model in rats [100 and 200mg/kg, ip]. The neuroprotective activity was evaluated using behavior parameters like catalepsy [bar test], muscle rigidity [rot rod test], and locomotor activity [actophotometer] and its effect on biochemical parameters [TBARS, GSH, nitrite, and total protein] in rats brain. *J. communis* possessed significant [□ <0.001] neuroprotective effect against CPZ induced Parkinson's like symptoms[98].

Effects on memory:
The effects of inhaled juniper volatile oil [1% and 3%, daily, for 21 days] on spatial memory performance were assessed in an Aβ[1-42] rat model of Alzheimer's disease. The Aβ[1-42]-treated rats exhibited decrease of spontaneous alternations percentage within Y-maze task and increase of working memory and reference memory errors within radial arm maze task[99].

Tyrosinase suppressive activity:
The methanolic extract of *J. communis* effectively suppressed mushroom tyrosinase activity, hypolaetin 7-O-β-xylopyranoside isolated from *J. communis* exhibited most potent effect of decreasing mushroom tyrosinase activity with an IC50 value of 45.15 μM. Hypolaetin 7-O-β-D-xylopyranoside-attenuated tyrosinase activity in α-MSH-stimulated B16F10 murine melanoma cell. Hypolaetin 7-O-β-D-xylopyranoside was also effective at suppressing α-MSH-induced melanin synthesis[100].

Anti-inflammatory and analgesic effects:
Anti-inflammatory activity of *J. communis* fruit was determined using isolated cells and enzymatic test. aqueous extract showed 55% prostaglandin inhibition and 78% PAF-exocytosis inhibition[101].
The anti-arthritic effect of amentoflavone isolated from the plant *Juniperus communis* was studied against Freund's adjuvant induced arthritis in rats. The study showed that amentoflavone at a dose of 40mg/kg possessed potentially useful anti-arthritic activity as it gave a positive result in controlling inflammation in the adjuvant induced experimental model[56].

Extracts of *Juniperus communis* were evaluated for inhibitory activity on human platelet-type 12[S]-lipoxygenase. The methylene chloride extracts of Juniperi lignum, Juniperi pseudo-fructus and the ethyl acetate extract of Juniperi pseudo-fructus showed a significant inhibition on the production of [12[S]-hydroxy-5,8,10,14-eicosatetraenoic acid] at 100 microg/ml [54.0 ±6.73, 66.2 ± 4.03 and 76.2 ± 3.36%, respectively]. From the methylene chloride extract of the wood, cryptojaponol and beta-sitosterol were isolated as compounds with inhibitory activity [inhibition at 100 microg/ml = 55.4 ± 2.80% [IC50 = 257.5 microM] and 25.0 ±2.15%, respectively][102].

Methanolic extract of *J communis* [100mg/kg and 200mg/kg] was tested for analgesic activity by different tests like formalin test, acetic acid induced writhing, and tail flick tests. The extract showed significant [□ < 0.01] and dose dependent analgesic activity. The blocking effect of naloxone [2mg/kg ip] to the analgesic activity of the extract of *J communis* confirmed the central analgesic activity[103].

Antiparasitic effect:
The methanolic extracts of *Juniperus communis* was evaluated for schistosomicidal and molluscicidal activities. *Schistosoma mansoni* Sambon worms and *Biomphalaria alexandrina* [Ehrenberg] snails were used. The screening results showed that the extract possessed schistosomicidal activity [LC50 ≈ 91 μg/ml, in 3 days]. *J communis* extract possess potent molluscicidal activity [LC50 = 22.9 ppm, after one day][74].

Vessels and trachea protective effects in passive smoking:
The ability of *Juniperus communis* oil to reverse the vasomotor impairment associated with passive exposure to cigarette smoke was studied in female rats exposed to daily passive smoking for 6 weeks. *Juniperus* aerosols significantly reversed smoking-induced endothelial dysfunction[104].

The effect of cigarette smoking and essential oil of *Juniperus communis* of tracheal contraction and dilatation was studied in female rats. The rats were divided into four lots: smoking, non-smoking, exposed and not exposed to juniper oil. The smoking lot was exposed to 2 cigarettes per day, 5 days a week for 6 weeks. Then, the rats belonging to lots 2 and 4 were exposed to juniper berries oil for 3 weeks, 20 minutes per day. The control lot [lot 1] was not exposed to cigarette smoke. Juniper oil components, administered by nebulization, have had an irritating effect on the airway mucosa in rats and resulted in neurogenic inflammation of the tracheo-bronchial tract, characterized by functional smooth muscle ring tracheal hyperreactivity to acetylcholine and sustained morphological changes characterised by tracheal epithelial lesions and the presence of inflammatory infiltrate. Chronic exposure to juniper oil, administered by nebulization resulted in altered physiological mechanisms of neurogenic regulation of tracheobronchial tone, with the emergence of disbalance component of sympathetic, parasympathetic component bronchodilators, bronchoconstriction, respectively disbalance of the sympathetic component β2 - adrenergic, bronchodilators, and sympathetic component α 1 - adrenergic, bronchoconstriction. On the background of preexisting inflammatory airway lesions induced by chronic exposure to cigarette smoke, oil of juniper, , have boosted the response bronchoconstrictor ring tracheal smooth muscle, and have not influenced the inflammatory infiltrate. Juniper oil also increased the bioactivity of nitric oxide in the pipes of rats, both under normal and of preexisting lesions conditions induced by chronic exposure to cigarette smoke[105].

Gastrointestinal effects:

The anti-ulcer property of *Juniperus communis* was studied in acetyl salicylic acid, serotonin, indomethacin, alcohol and stress-induced gastric ulcerations in rats and histamine-induced duodenal lesions in guinea pigs. The crude leaf extract at doses of 50 mg and 100 mg/kg, ip, significantly inhibited aspirin, serotonin, indomethacin, alcohol and stress-induced gastric ulcerations in rats and histamine-induced duodenal lesions in guinea pigs. The healing rate of acetic acid induced ulcer in rats was also enhanced significantly by the leaf extract. Biochemical analysis of gastric juice revealed that the extract significantly decreased its volume and total acidity, but did not alter its pH and peptic activity[106].

Toxicity and side effects:

The acute toxicity of ethyl acetate fraction of *Juniperus communis* was studied in albino rats. Over the study duration of 14 days, no mortality was seen up to dose of 2 g/kg body weight of the EAF of leaves of *Juniperus communis* orally. During the observation time animals did not produce any changes in the general appearance [67].

CONCLUSION:

The review highlighted the chemical constituent, pharmacological and therapeutic effects of *Juniperus communis* as promising source of drugs because of its safety and effectiveness.

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