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A REVIEW ON THE THERAPEUTIC POTENTIAL AND SAFETY PROFILE OF *JUNIPERUS COMMUNIS* LINN.

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ABSTRACT

*Juniperus communis*is an evergreen shrub or a small tree indigenous to Europe, South Asia and North America. It is widely distributed throughout the northern hemisphere. The plant belongs to the genus juniperus of the Cypress family (cupressaceae). Medicinal plants have historically proven their value as a source of molecules with therapeutic potential, and nowadays still represent an important pool for the identification of novel drug leads. In the past decades, pharmaceutical industry focused mainly on libraries of synthetic compounds as drug discovery source. They are comparably easy to produce and resupply, and demonstrate good compatibility with established high throughput screening (HTS) platforms. This plant is used traditionally in the treatment of various diseases and disorders like anti-inflammatory, anti-diarrhoeal, astringent, menstrual irregularities and some abdominal disorders. In the last few years, this plant has been selected for various research activities. This plant contains various chemical constituents like α-pnene, β- pinene, Apigenin, Sabinine, β-sitosterol, campesterol, limonene, Amentoflavone, Quinic acid, Isocupressic acid, communic acid, deoxypodophyllotoxin, imbricatolic acid, and many others. So why it was reported for various activities like Anticancer, Hepatoprotective, Antifungal activity, Antioxidant, Anti diabetic activity, Antibacterial, Anti Inflammatory activity, Anti-microbial activity, Anticataleptic activity, Antimalarial activity, Antihypercholectroetic activity, Neuroprotective, Anti-arthritic activity and Anti mycobacterial activity. The aim of the present review is to compile its existing research with special reference to its toxicity and biological activity because one major asset of medicinal plant-based drug discovery is the existence or ethno pharmacological information providing hints for compounds therapeutically effective in humans.

KEYWORDS: ***Juniperus communis, Toxicity, Cupressaceae, Pharmacological activity, Safety***.

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INTRODUCTION

Juniperus Communis Linn. belongs to a family Cupressaceae. It consists of 02 subfamilies, 04 tribes, 21 genera and 70 species[1,2]. The juvenile leaves of juniper are needle-likeand awl shaped spreading and arranged in pairs or whorls of three[3]. The plant has great value in traditional medicine in the treatment of various diseases like anti-diarrhoeal, anti-inflammatory, astringent, menstrual disorders and abdominal disorders[4,5]. The main chemical constituents are α-pnene, β- pinene, Apigenin, Sabinine, β-sitosterol, campesterol, limonene, Amentoflavone, Quinic acid, Isocupressic acid, communic acid, deoxypodophyllotoxin, imbricatolic acid, and many others[2]. The aim of the present review is to compile its existing and updated research with special reference to the toxicity profile of *J. Communis.*

SYNONYMS

- Sanskrit – Havusa, Matsyagandha
- Assamese – Arar, Abahal, Habbul
- Bengali – Hayusha
- Eng – Juniper Berry, Common Juniper
- Gujrati – Palash
- Hindi – Havuber, Havubair
- Punjabi – Havulber
- Telugu – Hapusha
- Urdu – Abhal, Aarar

SCIENTIFIC CLASSIFICATION

- Species – *Juniperus communis*
- Class – Pinopsida
- Division – Pinophyta
- Order – Pinales
- Family – Cupressaceae
- Genus – Juniperus

Figure 1
Juniper Comunnis Linn. Plant

DESCRIPTION

Juniperus communis is a shrub or a small tree, variable and is often a low spreading shrub, but occasionally reaching 10 m tall. Common Juniper has needle-like leaves in whorls of three and the leaves are green [6].

OCCURRENCE

It has the largest range of any woody plant throughout the cool temperate Northern Hemisphere from the Arctic south in mountains to around 30°N latitude in North America, Europe and Asia [6].

BOTANY

(i) Whole plant
(ii) Fruits and flowers
(iii) Leaves
(iv) Branches
(v) Bark and stem

CHARACTERS

WOOD MICROSCOPY

Transversal section: Growth ring boundaries distinct, gradual transition from early wood to latewood. Latewood zones generally narrow. No resin canals. Axial parenchyma cells, solitary or arranged in loosely grouped tangential bands, particularly in latewood, contain brown substances [7].

RADIAL SECTION

Uniseriate tracheid pits. Rays homocellular, horizontal ray cell walls smooth, sometimes undulated, tangential walls nodular, at junction of horizontal and tangential walls often indentures. No transversal tracheids in rays. Generally cupressoid pits in early wood. Radial parenchyma cells contain often brown substances [8].

LEAF MICROSCOPY

Stomata were seen in the upper surface and palisade parenchyma was continuous on the upper surface (1-2 layers). Secretary canals were seen bigger than the other taxa, and abundant amounts of starch grains have been observed [9].

STEM MICROSCOPY

The T.S. of stems showed annual rings (xylem growth), medullary rays, phloem, pits with outer layers of cortex, epidermis on staining with phloroglucinol: HCl (1:1)[10].

POWDER MICROSCOPY

J. communis powder: was cleared with chloral hydrate, mounted in glycerine and observed through the microscope. It has shown the presence of xylem vessels, epidermal cells, phloem fibres, cortical cells, calcium oxalate crystals and resins [11].

ETHNO MEDICINAL USES

Table 1
List of traditional uses of J. communis L. plant.

Part	Traditional Use	Reference
Berries	Carminative, urinary antiseptic, diuretic, emmenagogue, sudorific, digestive, anti-inflammatory.	12,13
Aerial parts	Used for Acute and chronic cystitis, albuminuria, catarrh of the bladder, renal suppression, leucorrhoea, amenorrhoea.	
Fruit	used as antiseptic, stimulant, disinfectant, styptic, chronic bright's disease, migraine, dropsy, rheumatic and painful swellings, piles, infantile tuberculosis	14
Bark	nephrotic dropsy of children, asthma, gonorrhoea, pulmonary blennorrhoea, arthritis, respiratory infections, diabetes, bladder infections, chronic pyelonephritis, cough, abdominal disorders and skin infections / diseases	

PHYTOCHEMICAL SCREENING
PHYTOCHEMISTRY/ CHEMICAL CONSTITUENTS

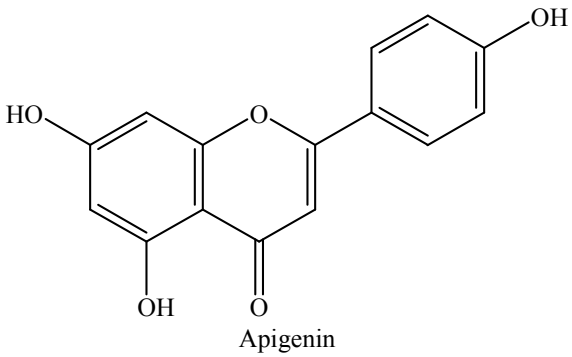
It contains various chemical constituents including flavonoids, volatile oil and coumarins.

FLAVONOIDS
BERRIES

Apigenin, rutin, luteolin, quercetin-3-O-arabinosyl-glucoside, quercetin-3-o-rhamnoside quercitrin,scutellarein, nepetin, amentoflavone, bilobetin.

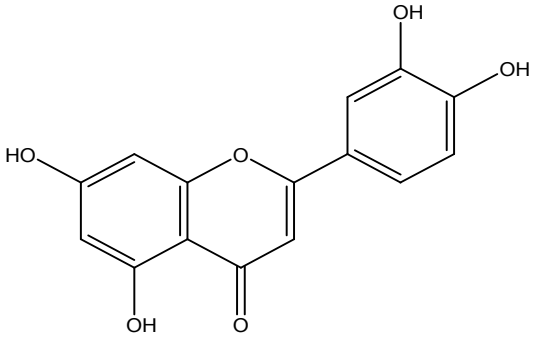
LEAVES

It contains the cupressuflavone, hinokiflavone, biflavones, isocryptomerinamentoflavone, and sciadopitysin. The seeds contain haemagglutinin. Plant also contains several labdanediterpenes and diterpenoids (Methanolic extract) [15].



Apigenin

Figure 2(a)
Apigenin



Luteolin

Figure 2(b)
Luteolin

VOLATILE OIL

The juniper berry oil is largely comprised of monoterpene hydrocarbons such as β-pinene (5.0%), α-pinene (51.4%), sabinene (5.8%), myrcene (8.3%) and limonene (5.1%) [15]. The seeds and fruits of the plant contain d-□-pinene, camphene, pectins, glycolic, malic acid, Formic acid, acetic acid, cyclohexitol, terpene, proteins, fermentable sugars, wax, gum, ascorbic acid, dihydrojunene, □-pinene, hydrocarbon-junene, cadinene, juniper and camphor [16].

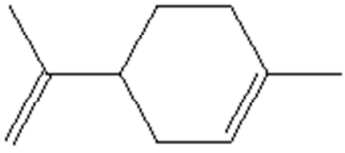


Figure 3(a)
Limonene

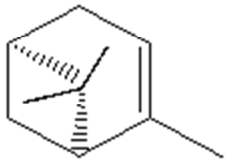


Figure 3(b)
α-pinene

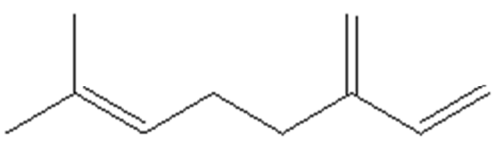


Figure 3(c)
myrcene

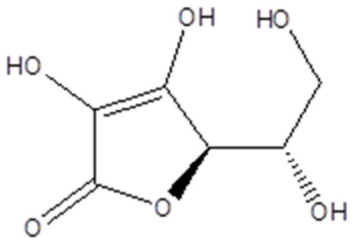


Figure 3(d)
Ascorbic acid

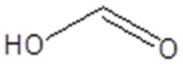


Figure 3(e)
Formic acid

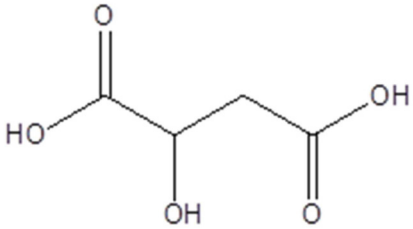


Figure 3(f)
Malic acid

COUMARINS UMBELLIFERONE[16]

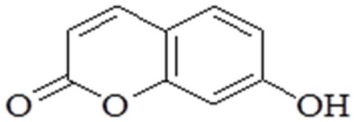


Figure 4
Umbelliferone

BICYCLIC DITERPENES

Imbricatolic acid, Junicedral, *trans*-Communic acid, diterpenes, Isocupressic acid, aryltetralin and lignandeoxy podophyllotoxin[29]. Three new diterpene acids have been identified as 15-dien-18-oic acid, 7-oxo-13-epi-pimara-8, 7α-hydroxysandaracopimaric acid [17].

BIOLOGICAL ACTIVITIES

IN VITRO STUDIES

CELL CYCLE PROGRESSION

Imbricatolic acid was isolated and reported in methanolic extract of fresh ripe berries of *J. Communis*and tested on cell cycle progression in P53-null calu-6—cells. The compound induces the regulation of cyclin dependent kinase inhibitors and prevents the accumulation in G_1 phase of the cell cycle. Hence it may play a role in control of the cell cycle [18].

TUMOUR CELL APOPTOSIS

A study reveals that the effect of Juniper berry extractedwas seen on P53 Protein, Gene's expression and DNA fragmentation in human neuroblastoma SH-SY54 cells. The study showed that its extract activates the cellular re-localization of P53 and DNA fragmentation dependent cell death. It was suggested that juniper berry extracts induced the P53 associated apoptosis through the potentiating and synergism by several phenolic compounds [19].

ANTICANCER ACTIVITY

The methanolic extract of Aerial parts of *Juniperus communis* has been tested along with three more plants in four human cell lines (A549, MCF7, TK6 and U937). Only the extracts of *J. Communis* and *C. Coggygria* showed dose dependent cytotoxic effects by affecting both cell morphology and cell death [20].

CHOLINESTERASE INHIBITION

In vitro, acetyl cholinesterase and butyl cholinesterase inhibiting activity were reported in various parts like leaves, ripe and unripe fruit of *J. Communis* and in four other *juniperus* species. The two extracts, aqueous and ethanol, were selected and found effective against a cholinesterase enzyme [21].

TYROSINASE INHIBITION

The methanolic extract of *J. Communis* fruits was reported as tyrosinase inhibitors. The bio guided isolation of bio flavones was screened against mushroom tyrosinase inhibition. The study concludes that the active compound from *J. Communis* may be useful in treating melanin pigmentary disorders [22].

IN VIVO STUDIES

HEPATOPROTECTIVE ACTIVITY

This activity was accessed with extracts of *Juniperus communis* in CCl_4 induced hepatotoxity. The two ethanol and aqueous extracts were found effective. Both extracts reduced the increased levels of serum SGPT, SGOT, ATP and bilirubin in hepatic cells [23].In another study, juniperus extract showed a synergistic effect with *Solanumxanthocarpus* in paracetamol and azithromycin induced liver injury in rats. Both plant extracts showed a dose-dependent attenuation in liver toxicity by normalizing the biochemical factors [24].

ANTI-INFLAMMATORY ACTIVITY

In-vitro anti-inflammatory activity of juniperus fruits was determined using isolated cells and different enzymatic test. The aqueous extract of juniperus showed 55% prostaglandin inhibition and 78% PAF exocytosis inhibition [25].*Juniperus communis* also evaluated for their inhibitory activity on human platelet type 12(5)-lipoxygenase inhibition. Fruits and wood extract of J.C were used in the study, in which ethyl acetate extracts showed a significant inhibition on the production of

12(5)-HETE [12(5) hydroxyl 5,8,10,14 ecostetraenoic acid [26].

ANTIOXIDANT ACTIVITY

In-vitro antioxidant activity of J. Communis plant was done using different assays like DPPH scavenging, SOD scavenging and hydroxyl scavenging, further the activity was confirmed in vivo in yeast cells. The results showed that it decreased the further oxidation process [27]. In another study, protective effects of amentoflavone (AF), isolated from six species of *Juniperus*(AF1-AF6) (Cupressaceae) *Juniperus communis*L. (AF1)*,Juniperus wallichiana*L. (AF2)*, Juniperus indica*L. (AF3)*, Juniperus macropoda*L. (AF4)*,juniperusrecurva*L. (AF5)and *Juniperus polycarpos*L. (AF6) against H2O2 induced oxidative damage in human erythrocytes and leukocytes. Among all plant extracts, *Juniperus communis*L. (AF1B) showed the highest activities on CAT (13.79±1.832 AU mgG1 protein) and SOD (820±14.50 U mgG1 protein) while *Juniperusindica*L. (AF3B) showed significant effects on Gpx (152.72±3.70 U mgG1 protein), GSH (25.93±1.560 µg mgG1 protein) and LPO (10.54±2.90 nmol mgG1 protein) enzyme systems of leucocytes. The study concludes that isolated fractions of AF from *Juniperus*species (among six species), has a potential source of natural antioxidants for treatment and prevention of diseases in which oxidative stress takes place [28].

ANTIDIABETIC&HYPERLIPEDEMIC

Methanolic extract *Juniperus communis*was tested in streptozocin- nicotinamide induced diabetes in rats. The two doses 100 and 200 mg/kg, p.o. were tested. The extract imparts a significant reduction in blood glucose and increase in HDL levels in diabetic rats [29].

ANALGESIC ACTIVITY

The analgesic activities of methanolic extracts of *J. communis* were performed in various models of analgesia like formalin test; acetic acid induced writhing response and inhibition in late phase of standard drug (Asprin) in rats. The extract was tested with two doses (100 and 200 mg/kg). Both doses showed a significant inhibition of writhing response and blocking effect of naloxone proved its central analgesic activity. So the inference from the study was J. Communis acts by peripherally and centrally[30].

ANTIBACTERIAL ACTIVITY

Different leaf extracts like methanol, chloroform, hexane and aqueous extract of *J. communis* were tested against five multidrug resistance bacteria. The effectiveness of antibacterial activity was higher in methanol extract and order were hexane>ethanol>methanol>chloroform. All results were compared with standard antibiotics (Ampicillin 10µg and Erythromycin 15µg) [31].

ANTIMICROBIAL ACTIVITY

The isolated volatile oil from J. communis was reported as antimicrobial against different species like E. coli, StaphyllococusAureus, Hafniaalvei and Pseudomonas aeruginosa. The oil at concentration, 1, 3, 5mg/ml showed maximum zone inhibition in a medium disc, which proved its potency against tested microorganism [32].

ANTIFUNGAL ACTIVITY

The essential oil from Arial parts of J. *Communis*was tested against two fungi, i.e. *RhizoctoniaSolani* and *RhizopusStolonifer*. The oil from *J. Communis* showed a maximum (EC50:0.554) at 0.704mg/ml against both fungi. The study concluded that its antifungal activity was due to presence of oxygenated monoterpenes[33].

ANTI-CATALEPTIC ACTIVITY

Themethanolic extract of *J. Communis*leaves was reported as protective in reserpine induced catalepsy in rats. The extract was administered to rats at two doses 100 and 200 mg/kg, p.o. and the higher dose (200mg/kg) were observed with marked reduction in Catalepsy [34].

ANTIMALARIAL ACTIVITY

The leaves and twigs (stems) of eight plants (*Juniperus communis, Artemesia vulgaris, Myrtus communis, Lavandula angustifolia, Eucalyptus globus, Rosemarinus officinalis* and *Salwia officinalis*) were tested against *Plasmodium falciparum*. The two plants, *Myrtus communis* & *Rosemarinus officinalis* showed best results at two concentrations, 150 and 270µg/ml [35].

ANTIHYPERCHOLETROLEMIC ACTIVITY

The isolated fruit oil was reported as hypo cholestrolemic in rats against high-cholesterol diet. The oil was tested at three concentrations, 50, 100, 200 mg/kg with addition of 2% cholesterol pellet diet. The dose at 200mg/kg showed a significant increase in blood urea nitrogen, creatinine levels and with reduction in Ox-LDL levels in samples of blood and tissues [36].

NEUROPROTECTIVE ACTIVITY

This activity was carried out in chlorpromazine induced Parkinson models in rats. The methanolic extract of *J. Communis* leaves was selected and administered in two doses, 100 and 200 mg/k, p.o. in rats. The extract was evaluated for various behaviors (locomotor activity, muscle rigidity, etc.) and biochemical parameters estimation in rats' brain tissues. The extract at concentration 200mg/kg, showed a significant neuroprotection in a rat brain. The study concludes that this plant may be a better choice to treat Parkinson's symptoms[37].

ANTI-ARTHRITIC ACTIVITY

This activity was reported on isolated compounds (Amentoflavone) from methanolic extract of *J. Communis.* The isolated fraction at two doses (20 and 40mg/kg, p.o.) was tested against Freund's adjuvant arthritis in rats. The 40mg/kg dose was found to be more effective results in controlling inflammation and consider being as promising anti-arthritic agent from plant origin [38].

ANTIMYCOBACTERIAL ACTIVITY

The methanolic extract of *J. Communis* needles, and branches were subjected to bioassay guided fractionation using a Microplate resazurin assay (MRA) to access inhibitory activity against *Myobacterium tuberculosis* strain H37Ra. The different constituents

were isolated and confirmed by NMR, Mass and Polarimetry analysis. Isocupressic acid, communic acid and Deoxy Podophyllotoxin were identified as the principal constituent responsible for anti-mycobacterial activity of arial parts of *J. Communis*[39].

TOXICOLOGY

The oil from J. Communis was not phototoxic in animal tests. JuniperusOxycedrus Tar was genotoxic in several assays. No genotoxicity data were available for any of the extracts. *Juniperus communis* Extract did affect fertility and was abortifacient in studies using albino rats. Clinical tests showed no evidence of irritation or sensitization with any of the tested oils, but some evidence of sensitization to the tar [40].

SAFETY ISSUES CONTRAINDICATIONS

Juniper is contraindicated in those patients with reduced renal function.

PREGNANCY/NURSING

Documented adverse effects include allergenic, catharsis in large doses, diuretic, and increases uterine tone (ie, possible anti-implantation, abortive, and emmenagogue/stimulating menstrual flow effects). Nursing women and women planning pregnancy should avoid use. Juniper should not be ingested by pregnant women.

INTERACTIONS

None well documented.

SIDE EFFECTS

Skin and respiratory allergic reactions may occur.

TOXICITIES

Applied juniper may cause potentially carcinogenic DNA damage and, in large doses, convulsions and renal damage. Juniper should not be ingested by pregnant women [41].

CONCLUSION

It is concluded from the literature and reported activities that the plant has significant medicinal value but monitoring is required as per the safety and contraindications reported from its use during pregnancy and patients with renal disease.

AUTHORS CONTRIBUTION STATEMENT

Souravh Bais designed the model and the computational framework and analysed the data. Also carried out the implementation, performed the calculations, wrote the manuscript with input with guidance of Dr. N. J. Patel, They conceived the study and were in charge of overall direction and planning.

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CONFLICT OF INTEREST

Conflict of interest declared none.

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