IOSR Journal Of Pharmacy *www.iosrphr.org*
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 6, Issue 6 Version. 2 (June 2016), PP. 66-76

Medical importance of *Cupressus sempervirens*- A review

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Abstract: The preliminary phytochemical analysis showed that the plant contained alkaloids 0.7%, flavonoids 0.22%, tannin 0.31%, saponins 1.9% , phenols 0.067%, essential oils, and many other biologically active constituents. The previous pharmacological studies revealed that *Cupressus sempervirens* possessed antibacterial, antifungal, antiviral, antiparasitic, insecticidal, antioxidant, wound healing, anticancer, estrogenic, anticoagulant and many other effects. This review was designed to highlight the chemical constituents and pharmacological importance of *Cupressus sempervirens*.

Keywords: *constituents, pharmacology, medical, Cupressus sempervirens*

I. INTRODUCTION

During the last few decades there has been an increasing interest in the study of medicinal plants and their traditional use in different parts of the world[(1)]. Plants generally produce many secondary metabolites which were constituted an important source of many pharmaceutical drugs[(2)]. Many previous reviews revealed the wide range of the pharmacological and therapeutic effects of medicinal plants[(3-69)].

The preliminary phytochemical analysis showed that the plant contained alkaloids 0.7%, flavonoids 0.22%, tannin 0.31%, saponins 1.9% , phenols 0.067%, essential oils, and many other biologically active constituents. The previous pharmacological studies revealed that *Cupressus sempervirens* possessed antibacterial, antifungal, antiviral, antiparasitic, insecticidal, antioxidant, wound healing, anticancer, estrogenic, anticoagulant and many other effects. This review will highlight the chemical constituents and pharmacological importance of *Cupressus sempervirens*.

II. PLANT PROFILE:

Synonyms:

Cupressus sempervirens L. subspecies *horizontalis* (Mill.) A. Camus, *Cupressus sempervirens* L. variety *sphaerocarps* (Parl.) Parl., *Cupressus sempervirens* L. variety *umbilicata* (Parl.) Parl., *Cupressus sempervirens* L. Forma *stricta* (Aiton) Rehder, *Cupressus sempervirens* L. subspecies *indica* (Parl.) Silba, *Cupressus sempervirens* L. variety *atlantica* (Gaussen) Silba, *Cupressus sempervirens* L. variety *dupreziana* (Camus) Silba, *Cupressus sempervirens* L. variety *globulifera* Parl., *Cupressus sempervirens* L. variety *horizontalis* (Mill.) Loudon, *Cupressus sempervirens* L. variety *indica* Parl., *Cupressus sempervirens* L. variety *numidica* Trab., *Cupressus sempervirens* L. variety *pendula* (Endl.) A. Camus, *Cupressus sempervirens* L. variety *stricta* Aiton[(70-71)].

Taxonomic classification:

Kingdom: Plantae, **Subkingdom**: Viridiplantae, **Infrakingdom**: Streptophyta, **Superdivision**: Embryophyta, **Division**: Tracheophyta, **Subdivision**: Spermatophytina, **Class**: Pinopsida, **Subclass**: Pinidae, **Order**: Pinales, **Family**: Cupressaceae, **Genus**: Cupressus, **Species**: *Cupressus sempervirens*[(72)].

Common names:

Arabic: Saro, Shajarat el-Saro, Saro al-bahr al-abiadh; **Chinese**: di zhong hai bai mu; **English:** Common cypress, Graveyard cypress, Italian cypress, Mediterranean cypress, Tuscan cypress, Pencil pine; **French**: Cyprès commun, Cyprès de Montpellier, Cyprès de Provence, Cyprès d'Italie, Cyprès méditerranéen, Cyprès ordinaire, Cyprès pyramidal, Cyprès sempervirent, Cyprès toujours vert; **German**: Echte Zypresse, Italienische Zypresse; **Italian**: Cipresso commune; **Spanish:** Ciprés común, Ciprés italiano; **Swedish**: kretacypress[(73)].

Distribution:

It was native to the Mediterranean basin. However, the plant was distributed in North Africa, Asia (Iran, Palestine, Jordan, Lebanon, Syria, Iraq, Turkey), Southern Europe (Greece and Italy) and Northern America[(73-76)].

III. DESCRIPTION:

Cupressus sempervirens is a tree that grows up to 30 m tall. The leaves are 0.5 to 1 mm, dark green and obtuse. The male cones are 4 to 8 mm, the female are 25 to 40 mm. They are elliptical-oblong (rarely globose),

green when young and shining yellowish-gray when ripe, with 8 to 14 short and obtusely spiked scales. There are 8 to 20 seeds on each scale[77].

Traditional use:

The drug was used externally for head colds, coughs and bronchitis[77]. A decoction of the cones and leaves of *Cupressus sempervirens* was used in a sitz bath three times a day for one week for haemorrhoids**.** The cones and leaves were used internally as an astringent. Externally, the extract of the cypress was incorporated in preparations (ointments and suppositories) and used to treat haemorrhoids, varicose veins and venous circulation disorders. The essential oil was used as antiseptic and an antispasmodic for stubborn coughs[78]. Cypress was also described as deodorant, and diuretic, to promote venous circulation to the kidneys and bladder area, and to improve bladder tone and as a co-adjuvant in therapy of urinary incontinence and enuresis[79].

Parts used: The parts of the plant used medicinally were the leaves and cones[78].

IV. PHYSIOCHEMICAL CHARACTERISTIC

The essential oil of *Cupressus sempervirens* was extracted by steam distillation with a yield of 0.50%. The specific gravity, refractive index, acid value, and ester value of the essential oil of *Cupressus sempervirens* were 0.825, 1.341, 0.22, and 24.60, respectively[80].

V. CHEMICAL CONSTITUENTS

The preliminary phytochemical analysis showed that the plant contained alkaloids 0.7%, flavonoids 0.22%, tannin 0.31%, saponins 1.9% and phenols 0.067%[81-82].

It appeared that the essential and volatile oils of the plant were differ according to the plant location and variety. Selim *et al*., isolated 20 compounds from the oil of Mediterranean cypress (*Cupressus sempervirens*), included: tricyclene, α-thujene, α-pinene, camphene, sabinene, β-pinene, myrcene, δ-3-carene p-cymene, limonene, γ –terpinene, α-terpinolene, camphor, bronyl acetate, carvacrol, β-caryophyllene, α-humulene, germacrene-D, δ-cadinene and α-cedrol. However, the major components were included α-pinene which represented (48.6%), δ-3-carene (22.1%), limonene (4.6%) and α-terpinolene (4.5%)[83].

The essential oils isolated from Tunisian *Cupressus sempervirens* were ranged from 0.1 to 0.65% depending on the part of the plant analyzed. The greatest yields were in cones and leaves (0.65 and 0.43%, respectively) and the oil was lowest in the branches (0.1%). 52 compounds were identified accounting for 93.7, 94.82 and 95.8% of the total oil in leaves, cones and branches, respectively. The monoterpene fraction amounted 48.1 to 65.9%, sesquiterpenes accounted 27.3 to 45.01%, with low amount of diterpenes (less than 2.6%). In monoterpene fraction, hydrocarbon compounds were the major constituents, accounting 43.21 and 42.7% respectively in cones and leaves, and 60.4% in branches. The main monoterpene hydrocarbons were α-pinene 27.5% in leaves, 28.91% in cones and 35.8% in branches and δ-3-carene (5.8, 7.2 and 13.2%), respectively in cones, leaves and branches. In sesquiterpene fraction, sesquiterpene hydrocarbons were the major constituents 21.9% in leaves, 18.26% in cones and 14.9% in branches. However, the percentage content of the individual components in the leaves, cones and branches (%) respectivily were: tricyclene 0.1, - and 0.1; α-thujene 0.1, 0.1 and -; α-pinene 27.5, 28.91 and 35.8; α-fenchene 0.6, 0.2 and 0.7; sabinene 0.2, 0.6 and 1.3; β-pinene 0.8, 0.9 and 2.5; β-myrcene 1, 1.5 and 1.9; α-phellandrene 1.4, 1.8 and -; δ-3-carene 7.2, 5.8 and 13.2; 1.8.cineole 1, 0.6 and; *p*-cymene 0.2, 1.7 and 1.1; limonene 2.2, 0.6 and 1.9; β-phellandrene 0.1, 0.2 and -; α-terpinolene 1.3, 0.9 and 1.9; linalool 0.1, 0.3 and - ; α-campholenal 0.2, 0.2 and 0.9; camphre 0.1, - and 0.1; borneol 0.2, 0.3 and - ; δ-terpineol 0.1, 0.7 and 1.7; myrtenal 0.1, - and -; myrtenol 0.2, - and 0.1; terpen-4-ol 1.8, 1.9 and 1.5; α-terpineol 1.1, 0.8 and -; *iso*-bornyl acetate 0.3, 0.4 and 0.7; α-terpenyl acetate 0.2, 0.4 and 0.5; longifolene 0.6, 1.2 and 0.6; (*Z*)-caryophyllene 2.2, 1.9 and 1.1; α-cedrene 0.6, 1.8 and 1.3; α-humulene 2.1, 2.4 and 1.9; ermacrene D 12.1, 6.36 and 3.9; β-selinene 0.6, 1 and 1.8; α-murrolene 0.5, 0.1 and 0.5; *epi*-zonarene 0.2, 0.3 and 0.6; β-bisabolene 0.5, 1.1 and 0.4; cubebol 0.1, 0.6 and 0.3; *Cis*-calmanene 0.2, - and - ; δ-cadinene 0.2, 0.4 and 0.6; α-copan-11-ol 0.3, 0.3 and 0.1; α -calacorene 0.2, 0.2 and 0.1; elemol 0.1, 1.4 and - ; germacrene B 1.5, 0.9 and 1.2; β-calacorene 0.6, 0.8 and 1; caryophyllene oxide 0.3, 0.6 and 1.1; α-cedrol 19.3, 18.55 and 7.7; T-cadinol 0.5, 1.1 and 1.3; T-murrolol 0.6, 1.7 and 0.1; manoyl oxide 0.9 , 2.3 and 1.7; abietatriene 0.4, 0.1 and 0.8; abietadiene 0.4, 0.3 and 0.5; nezukol 0.3, 0.2 and 0.6; sempervirol 0.1, 0.4 and 0.4; *(Z)*- tartarol 0.2, - and 0.3[84].

The essential oils obtained from fresh fruits and terminal branchlets with adherent leaves of *Cupressus sempervirens* L cv cereiformis growing in Iran, were analyzed by GC-MS. Thirteen components were identified in the essential oils. The main constituents of both fruits and leaves were α-pinene, Δ -3-Carene, α-terpenyl acetate and terpinolene. However, the volatile oil isolated from *Cupressus sempervirens* L cv cereiformis. fruits and leaves % respectively were: α-pinene 30.0 and 39.0, sabinene 2.0 and 3.0, β-pinene 2.6 and 2.2, myrcene 4.1 and 3.9, Δ-3-carene 24.0 and 24.0, limonene 4.0 and 3.0, terpinolene 6.6 and 4.3, bronyl

acetate trace and 1.7, α-terpenyl acetate 6.6 and 5.6, β-caryophyllene 1.2 and trace, α-humulene 1.3 and trace, germacrene D 4.0 and 1.7, while grouped compounds: (monoterpene hydrocarbons 73.3 79.4); (oxygen-containing monerpenes 6.6 and 7.3); (sesquiterpene hydrocarbons 10.5 and 1.7); (oxygen-containing sesquiterpenes 4.0 and trace)[85].

Glycosides from fresh cypres cones, *Cupressus sempervirens* were isolated by cold and hot ethyl acetate extraction. After enzymatic hydrolysis by means of β-glucosidase, 18 aglycones were released. The glycosidically bound volatile compounds amounted to 7-8 mg/ kg. The main aglycones were 3-hydroxybenzoic acid methyl ester (15.5%) and thymoquinone (5-isopropyl-2-methyl-1,4-benzoquinone: 3.7-9.7%). Other important aglycones were perilla alcohol (3.6-8.2%), *p*-cymen-8-ol (5.3-6.4%), 2-phenylethanol (2.7-6.9%) and carvacrol (2.5-6.3%). There was no similarity between the glycosidically bound aglycones and the corresponding free compounds found in the essential oil[86].

Diterpenes, 6-deoxytaxodione (11-hydroxy-7, 9(11), 13-abietatrien-12-one), taxodione, ferruginol, sugiol, trans-communic acid, 15-acetoxy imbricatolic acid and imbricatolic acid were isolated from *Cupressus sempervirens*[75].

The total phenols content of *Cupressus sempervirens* fresh leaves was 4.35 (mg gallicacid/g extract) and the total flavonoids was 9.5 (mg quercetin/g extract)[87].

VI. PHARMACOLOGICAL EFFECTS

Antibacterial and antifungal effects:

The antibacterial activity of the methanol, ethanol and ethyl acetate extracts of the aerial parts of *Cupressus sempervirens* were studied against *S. aureus* (ATCC6538), *B. subtilis* (ATCC6633), *P. aeruginosa* (ATCC6643), *E. coli* (ATCC15224), *K. pneumonia* (MTCC618) and *S. typhimurium (*ATCC13048). The extracts were used in 8 concentrations (1, 2, 3, 5, 7.5, 10 , 12.5 and 15 mg/ml). All *Cupressus sempervirens* extracts induced dose dependent bacterial growth inhibition against all the tested bacteria[88].

The antibacterial and antifungal activities of water and chloroform extracts of *Cupressus sempervirens* were carried out against six bacterial strains *Bacillus subtillis, Proteus vulgaris, Staphylococus aureus* (Gram-positive), *Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi* (Gram-negative), and fungal species *Aspergillus niger and Candida albicans*. *Cupressus sempervirens* showed high activity against Gram positive bacteria (zone of inhibition 9-14 mm for water extract and 9-12 mm for chloroform extract), low activity against Gram negative bacteria (zone of inhibition 1-6 mm for water extract and 1-5 mm for chloroform extract). However, water extract showed no activity against fungi, but chloroform extract showed mild activity against *Candida albicans* (3mm)[81].

The antibacterial activity of methanolic, ethanolic and ethyl acetate extracts of leaf of *Cupressus sempervirens* was determined against six bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae* and *Salmonella typhimurium*) using agar well diffusion method. Among the plant extracts, a significant antimicrobial activity was obtained by methanolic extracts followed by the ethyl acetate and ethanol extracts. The methanolic extract exhibited maximum inhibitory activity against *K. pneumonia*, *B. subtilis* and *S. aureus*. The ethanolic extract showed higher activity against *P. aeruginosa*. Greater inhibitory activity against *S. typhimurium* and *E. coli* was possessed by ethyl acetate extract of *Cupressus sempervirens*[74].

Essential oil exerted moderate *in vitro* antimicrobial activity against all tested bacteria, including Gram positive (*Bacillus cereus , Enterococcus feacalis, Serratia marcescens, Staphlococcus aureus*), and Gram negative (*Aeromonas hydrophila, Escherichia coli, Klebsiella pneumonia, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella indica*) with diameter zones of inhibition 4 to 12 mm, with MIC and MBC values ranging from 62.5 to 250 µg/ml. However, the methanol extract of *Cupressus sempervirens* was strongly inhibited the growth of all tested bacteria[83].

The antimicrobial activity of *Cupressus sempervirens* essential oil was studied against ten bacteria and fungi (*Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Halomonas elongate, Salmonella typhimurium, Enterococcus hirae, Aspergillus niger, Candida albicans* and *Trichoderma reesei*). The results revealed that the oil of *Cupressus sempervirens* inhibited the growth of susceptible bacteria, filamentous fungi and yeasts. The MIC and MCC values indicated that *Cupressus sempervirens* essential oil was highly effective. In addition, MIC/MCC ratio confirmed a bactericidal and fungicidal activity of the essential oil. However, the antimicrobial activity of the *Cupressus sempervirens* essential oils was more pronounced against Gram-positive than Gram-negative bacteria[89].

The zone of inhibition of 2 and 4 µl/disc of essential oil of *Cupressus sempervirens* against the tested microorganisms were (respectively): *Micrococcus luteus* 10 and 13; *Staphylococcus aureus* 7 and 8; *Mycobacterium simegmatis* 10 and 11; *Pseudomonas pyocyaneus* 9 and 11; *Yersinia enterolitica* 8 and 9; *Aeoromonas hydrophila* 7 and 10; *Enterococcus faecalis* 7 and 9; *Bacillus megaterium* 7 and 9;

Streptococcus faecalis 7 and 9; *Bacillus brevis* 7 and 8; *Saccharomyces cerevisiae* 9 and 10; and *Klyveromyces fragilis* 15 and 17 mm[90].

The essential oil of *Cupressus sempervirens* was tested against three bacteria (*Escherichia coli, Micrococcus luteus,* and *Bifidobacterium lactis*) and seven fungi *(A. niger, A. flavous, A. fumigatus, F. solani, F. oxysporium, P. digitatum,* and *C. terus*). The zone of inhibition of essential oils after 96 hr incubation against *Escherichia coli* was 16.11 mm, *Micrococcus luteus* 11.90 mm and *Bifidobacterium lactis* 24.05 mm. Regarding antifungal effect of the essential oil, the zone of inhibition ranged from 5.7 mm against *F. solani* to 29 mm against *P. digitatum* after 96 hr of incubation[80].

Diterpenes, 6-deoxytaxodione (11-hydroxy-7, 9(11), 13-abietatrien-12-one), and taxodione isolated from *Cupressus sempervirens* cones (fruits) showed potent antibacterial activities (IC_{50} 0.80 and 0.85 µg/ml) against methicillin-resistant *Staphylococcus aureus*[75].

The *in vitro* antifungal activity of the essential oil samples of *Cupressus sempervirens* were evaluated against 8 cultivated crop fungi (*Fusarium culmorum*, *Fusarium oxysporum*, *Fusarium equisiti*, *Fusarium verticillioides*, *Fusarium nygamai*, *Botrytis cinerea, Microdochium nivale* var. nivale and *Alternaria* sp), and all samples of essential oil of *Cupressus sempervirens* have shown a significant antifungal activity against all tested fungi[84].

Essential oils isolated from *Cupressus sempervirens* var. *dupreziana* leaves were tested for antifungal activity against 10 agricultural fungal species (*Gibberella avenacea, Fusarium culmorum, Fusarium oxysporum, Fusarium subglutinans, Fusarium verticillioides, Fusarium nygamai, Rhizoctonia solani, Microdochium nivale, Alternaria alternate*n and *Fusarium culmorum*). Results of *in vitro* antifungal test assays showed that oils significantly inhibited the growth of 10 plant pathogenic fungi[91].

VII. ANTIVIRAL EFFECT

Ethanol extracts of *Cupressus sempervirens, C. semipervirens* var. *horizontalis* and *Cupressus sempervirens* var. *cereiformis* were used to test their influence on herpes viruses (HSV-1). HeLa cells monolayers were infected with herpes viruses (HSV-1). Antiviral activity of the plant extracts assessed using Hematoxylin & Eosin method and observed under a light microscope. All tests were compared with a positive control, acyclovir. Results showed that all three plants have antiviral activity against HSV-1 virus. The most active extract was the extract obtained from *C. semipervirens.* Among the different parts tested, the fruit's extract possessed the strongest anti- HSV activity[92].

A proanthocyanidin polymer fraction (MW 1500–2000 daltons) isolated from *Cupressus sempervirens* L. exhibited true antiviral activity *in vitro* against two retroviruses, HIV and HTLV III B. No toxicity was observed at concentrations of 50 µg/ml which exceeded the IC_{50} values (1.5 to 15 µg/ml for HIV and 5 to 25 µg/ml for HTLV)[93].

VIII. ANTIPARASITIC AND INSECTICIDAL EFFECT:

The ethanol extract of the powdered cones of *Cupressus sempervirens* , collected from Oxford, Mississippi, exhibited potent antiparasitic activities. Bioassay-guided fractionation using a centrifugal preparative thin-layer chromatography led to isolation of many diterpenes, 6-deoxytaxodione (11-hydroxy-7, 9(11), 13-abietatrien-12-one), taxodione, ferruginol and sugiol. 6-deoxytaxodione (11-hydroxy-7, 9(11), 13-abietatrien-12-one) and taxodione, displayed potent antileishmanial activity with half-maximal inhibitory concentration (IC_{50}) values of 0.077 µg/ml and 0.025 µg/ml, respectively, against *Leishmania donovani* promastigotes, compared to those of the standard antileishmanial drugs, pentamidine (IC_{50} 1.62 µg/ml) and amphotericin B (IC_{50} 0.11 µg/ml)[75].

Ethanolic, acetone and petroleum ether extracts of leaves from the Egyptian *Cupressus sempervirens* were tested against 3rd instar larvae of the mosquito *Culex pipiens*. The obtained results indicated that petroleum ether extracts were more efficient than ethanolic and acetone extracts. The toxicity, based on LC_{50} values, were: ethanolic (LC_{50} 263.6ppm) > acetone extract (LC_{50} 104.3ppm) > petroleum ether extracts (LC_{50} 37.8 ppm). A remarkable reduction in both the pupation percent and adult emergence was obtained. Moreover, all extracts exerted a delayed toxic effect on the pupae and adults after treatment of larvae. Furthermore, various degrees of morphogenic abnormalities were observed in the immature and adult stages[94].

IX. ANTIOXIDANT EFFECTS:

The chloroform and methanol leaf extracts of *Cupressus sempervirens* were tested for antioxidant activity using the DPPH assay. Antiradical activity of the chloroform extract (50 µg/ml) was 6 %, while that of methanol extract (50 µg/ml) was 65 % [95].

The antioxidant activities of *Cupressus sempervirens* fresh leaves by nitric oxide scavenging assay was 1.17 (mg quercetin /g extract), by reducing power assay was 2.85 (mg ascorbic acid/g extract), by metal chelating

assay was 2.70 (mg EDTA /g extract) and by phospho molbdenum antioxidant assay was 16.5 (mg Ascorbic acid/g extract)[87].

Antioxidant activity of the extracts of two varieties was determined using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and *N*,*N*-dimethyl-*p*-phenylendiamine (DMPD) radical scavenging activity, metal-chelation capacity along with ferric- (FRAP) and phosphor-molibdenum reducing antioxidant power (PRAP) tests. Antioxidant activity of the extracts was screened at 2000 µg/ml. In general, antioxidant activity of the extracts was observed to show a discrepancy according to the method used. For instance; the cone ethyl acetate extract of *Cupressus sempervirens* var. *horizantalis* displayed the highest DPPH radical scavenging activity (87.53±0.17%), while only six of the extracts had ability to scavenge DMPD radical varying from 6.06±0.23 to 30.34±0.69%. In the FRAP assay, the cone acetone extract of *Cupressus sempervirens* var. horizantalis exhibited the highest absorbance value, which was indicative of the highest antioxidant activity, although the extracts had generally low activity in the PRAP assay. The leaf methanol extract of *Cupressus sempervirens* var. horizantalis was the most active one. Concerning the results obtained from the metal-chelation assay, the cone and leaf methanol extracts of both varieties did not possess metal-chelation capacity. However, the leaf ethyl acetate extracts of *Cupressus sempervirens* var. *horizantalis* (75.86±0.33%) and *Cupressus sempervirens* var. *pyramidalis* (77.07±3.22%) showed the highest activity in this assay[76].

The antioxidant activity of *Cupressus sempervirens* essential oil was evaluated by measuring the radicals-scavenging effect on 2, 2-diphenyl-1-picrylhydrazyl (DPPH) and by using the 2, 2'-azinobis(3-ethylbenzothiazoline-6-sulfonate) (ABTS) assay. Essential oil showed high antioxidant activity (7.7 µg/ml and 2.14 mM Trolox for DPPH and ABTS assays, respectively) when compared to BHT[89].

The antioxidant and anti-glycation properties of branchlet and fruit oils of *Cupressus sempervirens* var. horizontalis were studied after extraction of essential oils. Essential oils were extracted from the branchlets and fruits of *Cupressus sempervirens* var. horizontalis using the steam distillation method. A gas chromatography-mass spectrometry method was employed for the compositional analysis of essential oils. In order to evaluate antioxidant activities of oils at different concentrations (180, 220 and 260 µg/ml), linoleic acid peroxidation test and peroxyl radical mediated hemolysis of red blood cells (RBC) assay were used. Linoleic acid peroxidation was monitored for 4 h and determined during each hour of incubation. Antiglycation effects of oils at 200, 400 and 600 µg/ml were assessed using hemoglobin and insulin glycation assays. Hemoglobin glycation was inhibited by both branchlet (44.8, 62.6 and 54.0%) and fruit (41.0, 62.8 and 48.5%) at 200, 400 and 600 µg/ml of oil respectively. Insulin glycation inhibitory rates were (66.1, 69.2 and 73.8%) for branchlet oil, and (80.0, 76.9 and 81.5%) for fruit oil at 200, 400 and 600 µg/ml, respectively. RBC hemolysis was also inhibited by both branchlet oil (49.9, 38.5 and 15.0%) and fruit oil (45.9, 38.6 and 25.0%) at 180, 220 and 260 µg/ml, respectively. Finally, the oils mitigated linoleic acid peroxidation which was peaked after 4 h for both branchlet (39.5, 35.6 and 53.4%) and fruit (47.5, 58.6 and 59.8%) at 180, 220 and 260 µg/ml of oil respectively [96].

The antioxidant activities of hydroethanolic extract of leaves of *Cupressus sempervirens* was studied *in vitro* in comparison with ascorbic acid, and their correlation with *in vivo* hepatoprotective activity in rat model of paracetamol-induced hepatotoxicity. *In vitro* study revealed that the tested extracts contained abundant amount of phenolic and flavonoids compounds attributed to their effective antioxidant potential in different models. In *in vivo* study, the pre-treatments with extract (250 mg/kg/day, po) or silymarin (100 mg/kg/day, po) for 4 weeks have good safety profile in normal rats and exhibited a marked hepatoprotection against single toxic dose of paracetamol (4 g/kg bw, po), significant preserving the normal liver function parameters, maintenance the hepatic redox status as evident from significant increase in antioxidant enzyme activities and reduced glutathione with inhibition of lipid peroxidation and protein oxidation, decreasing nitric oxide and tumor necrosis factor alpha, membrane stabilizing effects as confirmed from significant increase in the hepatic Na^+-K^+-ATPase activity and decrease in lysosomal enzyme activities which were changed in the untreated paracetamol-intoxicated rats[97].

Anticancer effect:

Antiproliferative activity of *Cupressus sempervirens* ssp. pyramidalis essential oils was tested on amelanotic melanoma C32 cells and on renal cell adenocarcinoma cells, using the sulphorhodamine B assay. *Cupressus sempervirens* ssp. pyramidalis leaf oil exerted the highest cytotoxic activity with an IC_{50} value of 104.90 microg/ml against C32[98].

The ethanolic fruit extract of *Cupressus sempervirens* (CS), inhibited proliferation of human BPH-stromal cells and the activity was localized to its chloroform-soluble, diterpene-rich fraction. Eight major diterpenes isolated from this fraction exhibited moderate to potent activity and the most active diterpene (labda-8(17),12,14-trien-19-oic acid) exhibited an IC_{50} of 37.5 µM (antiproliferative activity against human BPH-stromal cells). It significantly inhibited activation (phosphorylation) of Stat-3 in BPH-stromal cells and prevented transactivation of androgen sensitive KLK3/PSA and TMPRSS2 genes in LNCaP cells. Labda-

8(17),12,14-trien-19-oic acid-rich CS fraction prevented prostatic hyperplasia in rat model and caused TUNEL labeling of stromal cells with lower expressions of IGF-I, TGF-ß and PCNA, and bcl-2/bax ratio. Human BPH tissues exhibited precise lowering of stromal component after incubation in labda-8(17),12,14-trien-19-oic acid, ex vivo[99].

Taxodione isolated from *Cupressus sempervirens* cones (fruits) showed potent cytotoxic activity[75].

The antihepatotoxic and antimutagenic activities of hydroethanolic extract of *Cupressus sempervirens* was studied in experimental rat model of paracetamol-induced liver toxicity in rats, comparing with silymarin as reference agent. The results revealed that the pre-treatment with either hydroethanolic extract (250 mg/kg/day, po) or silymarin (50 mg/kg/day, po) for 4 weeks has good safety profile in normal rats and exhibited a marked hepatoprotection against single toxic dose of paracetamol (4 g/.kg bw, po) as proved from marked decline in the DNA fragmentations and inhibition in the percentage of chromosomal aberrations in bone marrow cells[100].

X. HYPOLIPIDEMIC EFFECT:

The effects of *Cupressus sempervirens* cone extract (CSE) on the lipid profile was studied in Wistar rats. The oral administration of the extract resulted in a substantial decrease of serum total cholesterol, which was significant even after 6 weeks of treatment. Moreover, these animals exhibited lower total cholesterol levels compared to the controls after the initiation of treatment ($p<0.001$). The administration of the extract also led to a substantial reduction in serum triglycerides ($p<0.05$) , comparing 0 week to 6-24 weeks. However no significant differences in triglyceride levels were observed between CSE animals and controls during the entire study period. No significant changes in HDL-cholesterol level[101].

Protective effect:

The *Cupressus sempervirens* extract was investigated for its therapeutic effect against CCl_4 hepatotoxicity by biochemical (serum total proteins, albumin**,** urea, creatinine, LDH) and histopathological evaluations. A single intraperitoneal dose of 10% CCl_4 in olive oil (1 ml/kg body weight) was administered to a group of female Wister rats as the injury group. The other group was given CCl_4 and administered with *Cupressus sempervirens* extract three times per week for six weeks and a further group administered CCl_4 was left for six weeks to allow self-recovery. At the end of experiment, the rats from all groups were sacrificed for sampling for biochemical and histological analysis. Remarkable disturbances were observed in the levels of all tested parameters. On the other hand, rats injected with the toxic agent and left for one and a half month to self recover showed moderate improvements in the studied parameters. Treatment with herbal extract ameliorated the levels of the disturbed biochemical parameters. The *Cupressus sempervirens* group also showed histopathological liver & kidney profiles close to those of the control group[102].

Pre-treatment with either hydroethanolic extract (250 mg/kg/day, po) or silymarin (50 mg/kg/day, po) for 4 weeks has good safety profile in normal rats and exhibited a marked hepatoprotection against single toxic dose of paracetamol (4 g/.kg bw, po) as proved from marked decline in the DNA fragmentations and inhibition in the percentage of chromosomal aberrations in bone marrow cells[100].

The possible protective effect of *Cupressus sempervirens* and its flavonoids (quercetin and rutin) against the toxicological effect of lead acetate to the liver was evaluated. 30 Male albino rats and divided into five groups (six per group). Group I, served as control, group II exposed to 0.5 mg/g concentrations of lead acetate in diet for 60 days. Group III was received daily doses of 8 mg/100g bw of *Cupressus sempervirens* (liophilized from methanol extract of seeds) two weeks prior to lead acetate administration. Group IV received daily doses of 0.3 mg/100g bw of the flavonoid quercetin two weeks prior to lead acetate administration; Group V was received daily doses of 0.1 mg/100g bw of the flavonoid rutin two weeks prior to lead acetate administration. Lead acetate caused a significant increase in serum and tissue AST, ALT, ALP, bilirubin, serum and tissue MDA, plasma and tissue NO, in addition to, highly significant increase in serum cholesterol, LDL, triglycerides and HDL. On the contrary, lead induced a significant decrease in serum and tissue total protein, albumin, globulin, albumin/globulin ratio, blood and tissue SOD and GPx compared to control group. Administration of *Cupressus sempervirens* methanol extract, quercetin and rutin two weeks prior to lead acetate prevented the elevation of these parameters. Accordingly, the treatment with *Cupressus sempervirens* methanol extract and its flavonoids may provide a partial protection against the toxic effect induced by lead acetate[103].

Anti acetylcholinesterase effect:

The dichloromethane, acetone, ethyl acetate, and methanol extracts of the cones and leaves of *Cupressus sempervirens* var. *horizantalis* (CSH) and var. *pyramidalis* (CSP) were screened for their inhibitory activity against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and tyrosinase (TYRO). The extracts displayed weak to moderate cholinesterase inhibition at 200 µg/ml. The cone dichloromethane extract of CSP showed the highest inhibition (36.10±1.45%) against AChE, while the best inhibition (40.01±0.77%) against BChE was caused by the leaf acetone extract of CSH[76].

The antiacethylcholinesterase study of *Cupressus sempervirens* essential oil was investigated. It showed that essential oil inhibitory concentration (IC_{50}) was 0.2837 ± 0.0115 mg/ml[104].

XI. OSTEOGENIC EFFECT:

Four diterpenoids (sugiol, trans-communic acid, 15-acetoxy imbricatolic acid) and imbricatolic acid) were evaluated for esteogenic effect by using validated models including alkaline phosphatase assay, mineralization assay and expression of osteogenic genes-bone morphogenetic protein-2 and osteoblast transcription factor, in primary calvarial cultures harvested from neonatal mice. Among them, sugiol at a dose of 1.0 mg/kg bw exhibited significant osteoprotective effects and did not show uterine estrogenicity at the same dose. Additionally, sugiol treatment led to improved biomechanical properties as exhibited by increased power, energy and stiffness in femoral bones compared to untreated Ovx animals. Because, osteoporotic compression fracture was correlated with the mechanical characteristics of trabecular bone, so sugiol could effectively reduce the risk of this type of fracture by improving trabecular micro architecture in postmenopausal women[105].

XII. ANTICOAGULANT AND EFFECT ON VIABILITY OF ISCHEMICALLY CHALLENGED FLAPS:

In vitro assessment of endothelial cell function in isolated aortic rings of rats pretreated with cypress cones water extract showed increased production of endothelium-derived nitric oxide. Additionally, it possessed anticoagulant properties. Based on these effects, its effect on survival of random extensions of ischemic axial flaps was investigated. The pretreated group received 30% of cypress cones water extract treatment orally 7 days before flap elevation and for 3 days afterward. The ischemic target was a 6 × 7 cm islanded epigastric artery flap based on the right inferior epigastric pedicle. After the observation period, hemodynamic variables including mean arterial pressure and heart rate were assessed. Flap survival and perfusion rates were determined by microangiography and laser doppler flowmetry. *In vitro* isometric tension of the aortic segments isolated from the control and pretreated groups was monitored to reflect vascular responsiveness. The dose response relations to acetylcholine was determined and compared with control group. There were no significant differences between the hemodynamic variables. In the pretreated group, microangiograms revealed increased angiogenesis and capillary density and enhanced flap perfusion (as blood perfusion units) in the right distal and proximal parts ($p<0.05$). Endothelium-derived nitric oxide – dependent maximal relaxation (E_{max}) and the EC_{50} value to acetylcholine were significantly greater in the pretreated group compared to that of the controls. Accordingly, the data suggest that pretreatment with cypress water extract enhances the viability of ischemically challenged flaps[106].

XIII. WOUND HEALING EFFECT

The essential oils obtained from cones of *Cupressus* were evaluated for their wound healing and anti-inflammatory effects. *In vivo* wound healing activity was evaluated by linear incision and circular excision experimental wound models, assessment of hydroxyproline content, and subsequently histopathological analysis. The healing potential was comparatively assessed with a reference ointment Madecassol. Additionally acetic-acid-induced capillary permeability test was used to test the oil anti-inflammatory activity. The essential oils of *Cupressus sempervirens* var. *horizontalis* and *Cupressus sempervirens* var. *pyramidalis* did not show any significant wound healing effect[107].

Toxicity and side effects:

Health risks or side effects following the proper administration of designated therapeutic dosages are not recorded. Kidney irritation was likely with intake of larger dosages[77].

Many studies showed that *Cupressus sempervirens* pollen was the major aerospore component in winter and early spring. A personal series of patients encountered in 1994-96 in Rome revealed a 9.33% incidence of positive prick-test responses to cypress pollen among a population with atopical status. That series included 16 (19.05%) single and 68 (80.95%) multiple allergy sufferers. Among the former the symptoms encountered were rhinitis (62.5%) and asthma (37.5%)[108].

XIV. CONCLUSION

This review discuss the chemical constituent, pharmacological and therapeutic effects of *Cupressus sempervirens* as promising herbal drug because of its safety and effectiveness.

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