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PHYTOCHEMICALS AND BIOACTIVITIES OF *CEDRUS LIBANI* A. RICH

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Cedrus libani (Pinaceae) is a species native to the Mediterranean area. It was traditionally used to cure a wide range of illnesses, including inflammatory and respiratory conditions, as well as to relieve toothache pain. The purpose of this review is to deepen our understanding of both the composition and the bioactivities of this plant by providing a survey of the information that is currently available on numerous electronic databases about botanical aspects, traditional uses, phytochemistry, and biological activities. This review demonstrated that various plant parts have a wide range of bioactivities and active phytochemicals, suggesting that they might be used as a source of natural antioxidants and antimicrobials for industrial and medical applications. Human blood-related illnesses may also be treated with Cedrus libani. Moreover, it exhibits promising analgesic and anti-inflammatory properties. However, more toxicological and clinical research is required to determine its applications' safety and efficacy in treating human ailments.

Keywords: *Cedrus libani, Essential oil, Tar, Phytochemistry, Biological activities*

INTRODUCTION

The Pinaceae family, also known as the pine family, includes 12 genera and approximately 225 species of monoecious, resinous conifer trees (rarely shrubs) that are native to northern temperate regions. *Cedrus*, the second-oldest genus after *Pinus*, is one of the significant genera[1,2]. The essential oils from this genus, which is indigenous to the mountains of the Mediterranean and Himalayan areas, have been used in traditional medicine for centuries as an anti-cancer, anti-inflammatory, and antimicrobial agent[3]. The genus contains four species: *Cedrus libani*, *Cedrus atlantica*, *Cedrus deodora*, and *Cedrus brifolia*.

Cedrus libani is a mountain evergreen conifer tree that grows mainly on stony ground at an altitude of 1,500–1,800 m. Its name combines the Latin term libani, which means "of Lebanon," and the Greek word kédros " κέδρος" which means "cedar"[4].

C. libani is native to Syria, the Lebanese mountains, the southwest of Turkey, primarily between 800 and 2200 metres in the western Taurus Mountains, where it can live up to 1000 years, Cyprus, and the Atlas Mountains[5]. Moreover, Asia and Africa are home to this tree[1,6]. Since ancient times, it has also been planted in numerous locations all around the Mediterranean basin[6].

The majestic tree, *C. libani*, can reach a height of 40 meters and has a flat crown and a hard leading shoot **(Fig. 1)**. The young, smooth branches have spiral arrangements of 20 to 30 mm long, dark green, needle-like leaves[6]. The trees are monoecious; the female cones are 7 to 12 cm long, gray-brown in colour, and nearly umbilicate or cylindrical-truncate at the apex, while the male cones are 3 to 5 cm long and pale brown in colour when mature[6].

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a b c

Fig. 1: *C. libani* A. Rich. tree (a), leaves (b) and cones (c) from Aleppo parks in Aleppo (Syria), where it is planted as an ornamental tree.

The Old Testament of the Holy Bible contains over 75 mentions of *C. libani*, and the Epic of Gilgamesh, the oldest documented legend, also contains mentions of *C. libani*[7]. Ancient civilizations made extensive use of this tree to build boats, temples, and palaces[8]. The Egyptians also employed this tree's essential oil during the mummification process[9,11]. It is also employed as a representation of power and stability[12].

This review, which is the first of its type, provides a thorough explanation of recent findings regarding the chemical composition, biological effects, and pharmacological activities of such unique naturally occurring matrices. The goal of the manuscript is to highlight the significance of extending research past the *in vitro* stage in order to obtain natural compounds that might be used to treat human and animal illnesses as well as for use in the food and cosmetic sectors. The manuscript's scope also includes consideration of the toxicity and safety of *C. libani*.

Methodology

Scientific data for *C. libani* was gathered from different internet resources, including Scopus, Google Scholar, PubMed/MEDLINE, the Web of Science, ResearchGate ScienceDirect, and standard Google search tools like Google Books, without respect to a specific time limit.

The terms "*Cedrus libani*" and "Cedar" associated with the terms "biological activity," "health benefits," "pharmacology," "natural products and extract," "phytochemicals," or "essential oil" were used in the literature search, as well as the terms "homoeopathy," "traditional use," "ethnopharmacology," "clinical studies," "toxicity," and "safety". Articles that didn't have a practical focus, as well as those that looked at ecosystems, economics, and environmental horticulture, were excluded.

Ethnomedicinal uses of *Cedrus libani*

Several preparations from the plant, *C. libani*, are employed in traditional medicine because they are believed to treat or manage a wide range of human diseases. In Lebanon, cedar has a long history of use in the treatment of numerous infectious diseases[13]. In Turkey, in order to treat or prevent a variety of human ailments, villagers use katran "as medicine." For instance, they consume tar syrup (also known as "katran syrup"), which is created by drizzling a few drops of katran into a glass of water[14]. The villagers claim that this syrup treats internal wounds like ulcers, eradicates gastrointestinal bacteria, and inhibits endodermal parasites[15]. In contrast, tar is applied externally as a thin film to bruises, cuts, and wounds on the body[15]. In order to stop the spread of colds and flu, it is also placed around the nostrils since it is thought that "the devil keeps away from its sharp and sacred fragrance." Those with upper respiratory illnesses, such as asthma, often find relief by inhaling tar[14]. Moreover, the wood oil had a number of traditional applications, including the treatment of leprosy[16] and catarrhal respiratory tract disorders[6]. Toothaches were also treated with cedar[10].

From a veterinary perspective, katran, which is derived from the resinous root and wood of cedar, is also used in Turkey to cure ailments in domestic animals, including skin issues[12].

In southern Turkey, wooden structures are protected against insects, fungi, parasites, and bacteria using tar made from a plant in the Taurus Mountains[14]. Moreover, it is applied both internally and externally to treat various ailments in both humans and pets[12]. The tar is also used to kill insects and parasites like aphids[12,14].

Moreover, cedar essential oils were utilised in the manufacturing of perfume compounds for cosmetics and as a flavouring agent for food and beverages[12,17,18].

Classification

C. libani belongs to the Plantae Kingdom, Pinophyta Division, and Pinopsida Class. The order is Pinales[19]. The plant is known under several common names, such as Lebanese cedar, Cedar of Lebanon, and Kamalak in southern Anatolia[10,20,21]. Other, less common names are *Abies cedrus* (L.) Poir., *Cedrus cedrus* (L.) Huth, *Cedrus effusa* (Salisb.) Voss, *Cedrus elegans* Knight, and *Cedrus patula* K.Koch[22].

Phytochemical composition

Various studies have been conducted on the chemical composition of *C. libani*. The abundance of essential oils and other chemical compounds has made it a valuable source of natural products with medicinal properties. The composition of essential oils and other constituents will be discussed in the paragraphs that follow:

Essential oils (EOs)

The cones, and wood of the cedar tree, as well as other parts, all contain EOs. In several published articles, the yield and composition of EOs displayed variations because of environmental variables and genetic factors. The quantity and quality of EOs are directly influenced by ecological conditions, which also have an impact on plant development and vegetative growth. These external factors include geographical elements like altitude and agricultural conditions (temperature, sunshine duration, wind regime, rainfall, humidity, etc.).

Cedar wood and seeds had high yields of EOs; the EOs yield for the wood was around 0.7% w/w[16,26,27] while the yield for the seeds ranged from 0.8 to 2.75%[28,29]. The main components in seed oil are α-pinene and β-pinene, whereas sesquiterpenes compose the majority of wood oil[27].

Cones had an average oil production of between 0.16 and 0.54%, with 51% of the oil being composed of α-pinene. The oil from the leaves had a yield of 0.21% w/w and contained a high amount of the sesquiterpene germacrene D (29.40%)[30]. The yield and composition of EOs in various cedar parts will be discussed in the sections that follow:

Cones' EOs yield and composition

Studies showed that cones **EOs'** yield and composition can vary depending on geographic location, environmental conditions, and extraction method. Several studies showed that the yield of EOs was between 0.16 and 0.54 %[15,16,24,31].

A study in Lebanon reported a yield of 0.41 % (w/w)[16] for EOs obtained by hydrodistillation. However, in another study the average EO yields of plants from different regions in Lebenon were between 0.16 ± 0.02 and 0.54 ± 0.1 % after 3h extraction using Clevenger apparatus (**Table 1**)[24,31]. In Fahed *et al.*, a yield of 0.34 % was reported after three hours of hydrodistillation using a Clevenger-type apparatus[32].

Table 1: EO yields and main compounds from cedar cones grown in Lebanon.

The region in Lebanon[24]	Bsharri	Ehden	Chouf	Tannourine	Qartaba
Yeild of EO from cones (%)	0.25	0.29	0.54	0.24	0.16
Chemical compounds & percentage					
α – Pinene %	27.7 ± 0.4	27.7 ± 0.3	37.3 ± 0.4	25.1 ± 0.8	26.0 ± 1.8
β – Pinene%	21.4 ± 0.4	35.6 ± 1.8	26.1 ± 0.1	16.0 ± 0.5	6.4 ± 0.4
Myrcene%	ND	ND	ND	ND	30.6 ± 0.7
Limonine%	9.8 ± 0.1	7.5 ± 0.2	5.6 ± 0.2	5.9 ± 0.2	14.1 ± 0.1
δ -3- Carene%	0.5 ± 0.3	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.0	0.5 ± 0.0
Abieta -8,11,13-triene%	7.0 ± 0.2	7.7 ± 0.3	3.0 ± 0.2	10.2 ± 0.7	2.2 ± 0.5
Kaur-16-ene%	7.1 ± 0.1	4.7 ± 0.5	7.1 ± 0.1	7.5 ± 0.1	3.5 ± 0.1
Abieta -7,13-diene%	3.4 ± 0.0	1.9 ± 0.1	3.2 ± 0.1	7.5 ± 0.3	4.7 ± 0.8

ND: not determined.

Analysis of EO and ethanolic extract (4% w/w) from dried cones by gas chromatography/mass spectrometry (GC-MS) revealed the presence of 19 compounds. The main compound was α-pinene (51%). Other compounds were β-myrcene (13%), 7,13-abietadiene (3.2%), terpinolene (3.1%), α-limonene (2.25%), camphene (2.15%), trans-α-bisabolene (1.42%), abietatriene (1%), and less than 1% was for α-terpineol (0.74%), Δ-3-carene (0.72%), ρ-cimene (0.68%), β-phellandrene (0.67%), γ-terpinene (0.61%), E-β-fernesene (0.58%), α-terpinene (0.55%), α-terpineol (0.35%), bormyacetate (0.35%), 8(14),13(15)-abietadiene (0.27%) and longifolene (0.15%)[13,16].

It is worth noting that β-pinene was absent in the above-mentioned studies[13,16].

Contrary to this, as shown in **Table 1**, the composition of EO revealed the presence of α-pinene and β-pinene in different percentages according to the geographical area in Lebanon, where the content ranged from 25.1 to 37.3% and from 16.0 to 35.6% for α-pinene and β-pinene, respectively. Moreover, some samples were distinguished by the dominance of myrcene (30.6%) and limonene (14.1%)[24,28].

In Fahed *et al*[32]., GC analyses with a flame ionization detector (FID), and GC-MS analyses revealed that the oil was rich in α-pinene (39.7%). Other identified compounds were: Terpinen-4-ol (20.7%), β-pinene (14.7%), Citronellol (10.3%), Citronellal (4.9%), Camphor (3.1%), α-Terpineole (1.6%), Myrcene (1.4%), Limonene (1.3%), Farnesol (0.9%), Camphene (0.5%), Citronellic acid (0.5%), *trans*-*p*-Mentha-2-en-1-ol (0.4%), trans-Pinocarveol (0.4%), Isophyllocladene (0.4%), p-cymene (0.3%), trans-Piperitol (0.3%), Terpinolene (0.2%), cis-Piperitol (0.2%), 2-Undecanone (0.2%), alpha-phelandrene (0.1%), δ-3-Carene (0.1%), ɣ-terpinene (0.1%), α-fenchone (0.1%), and cis-p-Mentha-2-en-1-ol (0.1%)[32]. α-terpinene was absent in this oil[32].

Leaves EOs yield and composition

Although the overall yield was lower than that from the cones, the oil from the leaves included more components. According to Loizzo *et al*.[16], the hydrodistillation yield of dried leaves EO from plants grown in Lebanon was 0.21% w/w[16]. According to GC-MS analysis, the sesquiterpene germacrene D (29.40%) was found to be the major component of this EO. Other 36 identified compounds were: 1-epi-cubenol (6.30%), trans-α-bisabolene (5.90%), β-caryophyllene (5.60%), δ-cadinene (5.60%), γ-muurolene (4.83%), 4 (14)-salvialene-1-one (4.00%), trans-cadinol (3.40%), γ-cadinene (2.87%), α-pinene (2.20%), α-himachalene (1.74%), dodecanoic acid (1.72%), α-humulene (1.3%), α-muurolene (1.17%), β-copaene (1.01%), β-bourbounene (0.79%), α-copaene (0.73%), β-myrcene (0.73%), 4β-10β-1(5),6guiadiene (0.56%), β-pinene (0.54%), γ-amorphene (0.53%), α-cubebene (0.46%), cadina-1,4-diene (0.44%), α-limonene (0.44%), β-himachalene (0.29%), α-ylangene (0.26%), bormyacetate (0.26%), muurola-4(5) 5-diene (0.26%). The content of γ-terpinene, terpinolene, trans-pinocarveol, cis-verbenol, terpinen-4-ol, 7,15-isopimaradiene, 8,15-isopimaradiene, and manool was less than 0.1%[16,33,34].

The same compounds with the same percentage were identified by GC-MS in the leaves ethanolic extract (95% ethanol for two weeks (3X), yield: 5% w/w)[13].

Wood EOs yield and composition

The yield of EO obtained by hydrodistilling plants cultivated in Lebanon for 3 hours using a Clevenger apparatus was 0.68 and 0.7% w/w, indicating that woods were particularly rich in EO[16,26,27]. GC/MS analysis revealed the presence of 13 compounds. The most characteristic compounds were himachalol (22.50%) and β-himachalene (21.90%) **(Fig. 2)**. Other compounds included the following: α-himachalene (10.50%), γ-himachalene (9.1%), allohimachalol (3.20%), *Z*-α-Atlantone (2.10%), *E*-γ-atlantone (1.73%), *Z*-γ-atlantone (1.72%), manool (1.70%), *E*-α-atlantone (0.82%), longiborneol (0.8%), γ-dehydro-*ar*-himachalene (0.4%) and traces of *Ar*-himachalene[16,33].

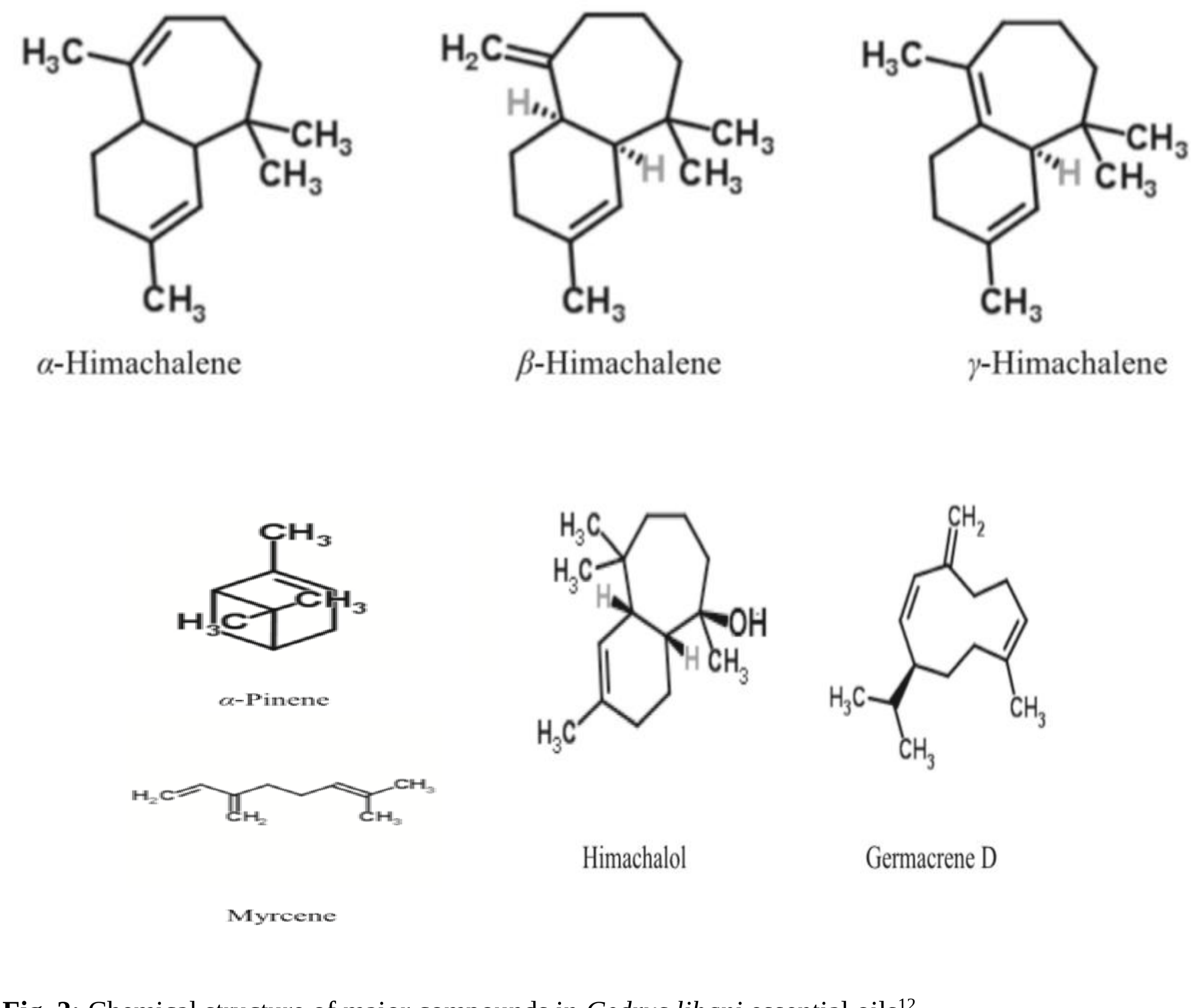

Fig. 2: Chemical structure of major compounds in *Cedrus libani* essential oils[12].

In Venditti *et al.,* 34 compounds were found to account for 85.8% of the overall composition after EO was analyzed using GC-FID and GC-MS. In contrast to the previously described study[12], the composition of this oil revealed considerable variances, with percentages of 43.8 and 39.2 for oxygenated sesquiterpenes and sesquiterpene hydrocarbons, respectively. The proportion of oxygenated monoterpenes, however, was 0.5. Contrarily, monoterpene hydrocarbons were only detected in traces, whereas other substances accounted up 0.8% of the EO[27].

The main representative compounds with their percentage were (*E*)-α-atlantone (19.3), β-himachalene (19.0), α-himachalene (9.6), (*Z*)-α-atlantone and α-acorenol (both 7.0), γ-himachalene (5.9), (*Z*)-γ-atlantone (4.4), (*E*)-γ-atlantone (3.6) and allo-himachalol (2.1). Other components with a percentage less than 1 were manool and (*E*)-α-bisabolene (both 0.5), cis-cadina-1(6),4-diene (0.6), and limona ketone and longifolene (both 0.4)[27,35].

On the other hand, the cedar wood oil coming from Turkey showed a similar composition as in Venditti *et al.*[27], where the main constituents were himachalenes (α-, β-, and γ) and (*E*)-α-atlantone which accounted for 58.6 and 32.23% of the oil, respectively[35].

In Saab *et al.,* 13 compounds in the wood oil of the *C. libani* plant growing in Lebanon were found[25]. While oxygenated sesquiterpenes such as (*E*)-α-atlantone, (*Z*)-α-atlantone, α-acorenol and (*Z*)-γ-atlantone were not found, the oil had fewer components than the oil in Venditti *et al.*[27]. The major components with percentages were himachalol (22.50), β-himachalene (21.90), α-himachalene (10.50) and γ-himachalene (9.10). It is important to highlight that the oil of Venditti *et al.*[27] was devoid of himachalol, which was the primary ingredient in Saab *et al.*[25].

In Saab *et al.*[36], 23 components were detected, although several substances discovered in earlier research[16,27] such as the two α-atlantone isomers, α-acorenol, limona ketone, longifolene, manool, (*E*)-α-bisabolene and cis-cadina-1(6), 4-diene were not recognised. However, in this study[36], the oil has 3.8% of α-caryophyllene which was not present in Venditti *et al.*[27]

In Elias *et al.*[3], woods were extracted (72 h) using warm hexane to yield 1.95% of a dark oil. GC-MS analysis of the oil extract showed that 30 compounds constituting around 83% of the extract with the remaining 17% constituting several unidentified compounds, of which none were found to be present in excess of 2%[3,25]. The identified compounds with percentage were: 2-himachalen-7-ol (40.22), gamma sitosterol (7.80), dodecyl acrylate (7.44), β-himachalene (3.36), γ-himachalene (3.18), α-himachalene (2.96), (Z)-9-octadecenamide (2.74), 1H-benzocycloheptene (2.72), 3β-ergost-5-en-3-ol (2.31), stigmast-4-en-3-one (1.37), dibutyl phthalate (0.94), (S)-phenol, 2-methyl-5-(1,2,2-trimethylcyclopentyl) (0.91), 4,4-dimethyl-3-(3-methylbut-3-enylidene)-2-methylenebicyclo[4.1.0]heptane (0.84), δ-himachalene (0.84), methyl 2,7,13 – abietatrienoate (0.55), abietadien-18-al (0.51), (24 R)-ergost-4-en-3-one (0.44), methyl levopimarate (0.43), butylated hydroxytoluene (0.42), tetracosane (0.36), 1,1,2,2,3,3-hexamethylindane (0.34), tricontamethyl cyclopentadecasiloxane (0.32), octadecane (0.31), methyl isopimarate (0.27), tetracosamethyl-cyclododecasiloxane (0.23), eicosane (0.20), methyl abietate (0.12), eicosane (0.12), β-pinene (0.069)[3,25].

Seeds EOs yield and composition

In Turkey, the seeds' mean EO contents ranged from 0.8 to 2.75% after being hydrodistilled for two hours with a Clevenger-type apparatus[28,29].

The EO of *C. libani* seeds has been less commonly studied and reported in the literature compared to the wood and cone oils. However, a study by Saab and coworkers (2011)[37] analyzed the chemical composition of EO obtained from the seeds of *C. libani* collected from Lebanon. Seeds were extracted through ultrasound assisted maceration (20 min at 25°C, 3X) with chloroform and ethanol. The yields were 13.8 ± 1.2 and 35.8 ± 2.8 %, respectively. The study identified the following 24 major chemical components in the chloroform extract when analyzed by GC and GC/MS: α-pinene (34.42%), β-pinene (33.28%), trans-verbenol (3.16%), trans-pinocarveol (2.82%), abieta-7,13-diene (2.58%), myrtenol (1.99%), β-phellandrene (1.98%), β-cis-farnesene (1.89%), abieta-8,11,13-triene (1.50%), limonene (1.18%), α-bisabolene (1.16%), verbenone (1.15%), myrcene (1.10%), myrtenal (0.89%), pinocarvone (0.53%), p-cymene (0.48%), 6-camphenol (0.48%), cis-limonene oxide (0.46%), p-cymen-8-ol (0.43%), camphene (0.38%), 4-terpineol (0.37%), borneol (0.34%), trans-carveol (0.54%), and bornyl acetate (0.75%)[37]. On the other hand, in ethanol seed extract 22 compounds have been checked by GC and GC-MS. The most abundant compounds were fatty acids and ethers such as oleic acid (17.26 ± 1.34 %), methyl oleate (7.77 ± 0.42 %) and ethyl oleate (5.27 ± 0.48 %). Diterpenes, such as neo-abietol (11.81 ± 0.98 %), abieta-7,13-diene (7.99 ± 0.46 %), abieta-8(14),13(15)-diene (7.92 ± 0.66 %), abietol (6.04 ± 0.55 %), abieta-8,11,13-triene (2.05 ± 0.13 %), abietal (2.75 ± 0.21 %), dehydroabietal (1.07 ± 0.09 %) were also checked[37]. The other 12 compounds were: Methyl linoleate (1.43 ± 0.12 %), α-bisabolene (0.57 ± 0.03 %), methyl stearate (0.54 ± 0.04 %), palmitic acid (0.53 ± 0.03 %), trans-pinocarveol (0.71 ± 0.04 %), thuja-2,4(10)-diene (0.54 ± 0.03 %), verbenone (0.46 ± 0.02 %), methyl palmitate (0.46 ± 0.01 %), β-cis-farnesene (0.41 ± 0.02 %), manoyl oxide (0.35 ± 0.01 %), bornyl acetate (0.34 ± 0.02 %), myrtenal (0.29 ± 0.01 %)[37].

Essential oil composition from the oleoresin of the female cones

The EO composition of cones grown in Turkey was examined using GC and GC-MS[38]. By using these techniques, certain high boiling compounds could not be recognised, and around 91% of the compounds in the oil were identified. According to the findings, there were approximately 38.48% monoterpenes, 33.70% diterpenes, 11.77% oxygenated monoterpenes, 4.67% sesquiterpenes, and 0.33% sesquiterpene alcohols in the EO. The oil's major constituents in percentage were α-pinene (24.78), abieta-7,13-diene (16.67), abieta-8,11,13-triene (6.85), manool (5.73), terpinen-4-ol (3.74), α-terpineol (3.42), p-cymene (2.89), and limonene (2.69)[38].

Tar (*Katran*) from *C. libani* wood

Many factors, such as the types of plant tissues and the extraction procedure, might affect the chemical makeup of tars[14]. In Kurt *et al*.[14], *katran* was produced from wood and analyzed through GC/MS. 20 to 60 % of the weight of dry wood is the range of *katran* yield. Analyses revealed that *katran* was composed of 83 distinct components, with 17 accounting for 86% of the compounds. Sesquiterpenoids made up 47.6% of the sample, with β-himachalene accounting for 21.17, α-himachalene for 5.9, γ-himachalene for 5.46, α-atlantone for 7.40, tumerone for 4.50, and chamigran-9-one for 2.18%. From monoterpenoids, m-cymene could be detected with a percentage of 1.10. The percentage of sub-total hydrocarbons was 47.55: heptane (15.38%), cyclohexane (3.92%), benzene (1.27%), hexane (1.23%), heptacosane (5.29%), eicosane (4.31%), cyclotrisiloxane (1.13%), and nonacosane (2.18%)[14]. The percentage of sub-total aziridines was 34.71, with 2.55% for 2-aziridinedicarboxylate. The percentage of other compounds was 14.09[14,39,40].

Other compounds

The cedar of Lebanon contains a range of constituents in addition to the EO, such as phenolic compounds and alkaloids. The phenolic content in cones methanolic extract was 220 mg GA/100g, while it was 103.65 μg/g in shoot aceton extract and 101.67 μg/g in needle aceton extract[41,42]. The shoot and needle EtOAc extracts had total flavonoid contents of 66.85 ± 4.42 and 64.73 ± 5.57 μg/g extract, respectively[41]. On the other hand, using HPLC, the amounts of rutin, quercetin, kaempferol, and resveratrol in the leaf and fruit of *C. libani* in Turkey were respectively 154.33, 2, 5, and 20 μg/g[30].

Tannins were extracted from waste wood barks of Taurus cedar trees, and their yield was 8.99%, whereas the total phenol content, proanthocyanidin (condensed tannin) content, and reducing sugar were 27.77, 7.61, and 41.77 mg/g, respectively[43].

In Karrat *et al*.[44],a qualitative analysis of the phytochemicals of ethanolic leaves extracts of *C. libani* from Syria showed that the leaves contained carbohydrates, tannins, flavonoids, phenols, and coumarins. However, alkaloids and cyanogenic glycosides weren't present[44]. Nevertheless, in another study, a significant amount of the alkaloid piperidine was found in the shoots' aceton extract[41].

In general, there have been fewer investigations on the constituents of cedar than on the composition of EOs; this could be related to the widespread use of oil in traditional medicine.

Regardless of the focus of research on volatile oil components, cedar phytochemicals have a wide range of biological activities[3,25].

Pharmacology: Preclinical Evidence

A number of pharmacological activities of *C. libani* have been reported in the literature, which justifies some of its ethnomedicinal uses. Several plant parts, including cones, leaves, bark, wood, and resins from stems and roots, have been the subject of pharmacological studies. The following is a discussion of these activities:

Antimicrobial activity

Several studies were conducted regarding the antibacterial, antifungal, antiviral, and antileishmanial activities of different parts of cedar, such as cones, leaves, and barks, as well as the crude oleoresins from stems and roots[21,32,42,45,46].

Antibacterial and antifungal activity

In Kizil *et al.*[21], the antimicrobial activity of resins obtained from the stems and roots of *C. libani* grown in Turkey was evaluated using the disc diffusion method against clinical isolates (*Staphyococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa, Escherichia coli , C. albicans*) and *(Bacillus brevis* ATCC, *Bacillus megaterium, Bacillus thuringiensis, and Bacillus cereus).* The results indicate that crude extracts of the resins have low activity against *C. albicans* (zone diameter: 12 mm), but are more active against *S. pyogenes, E. coli (*pUC9, pBR322*), B. brevis* ATCC, *B. megaterium, B. thuringiensis,* and *B. cereus* (zone diameter of 16–24 mm), at a concentration of 80 µg/ disc. The activity was found to be more or similar to that of the standard antibiotic amoxicillin[21].

In Semerci *et al.*[42], the methanolic extract of female cones from Turkey showed a broad spectrum of activity on various microbial stains. The extract was evaluated against seven gram positive and gram negative bacteria (*B. subtilis* ATCC 6633, *E. coli* ATCC 8739, *Enterecoccus faecalis* ATCC 29212, *S. aureus* ATCC 29213, *Staphylococcus epidermidis* ATCC 12228, *Salmonella typhimurium* ATCC 14028, *Pseudomonas aeruginosa* ATCC 9027) and one yeast (*C. albicans* ATCC 1029) using the disc diffusion method. The extract exerts no inhibitory effect against *S. typhimurium* or *C. albicans.* However, the inhibiton zones were determined to be 10.5–13 mm against the rest of the microorganisms. However, the activity of the cones against the test microorganisms was found to be lower than that of gentamycin[42].

In Fahed *et al.*[32], EOs from cones from *C. libani* in North Lebanon were tested against the gram (-) bacterial strain *P. aeruginosa* CIP 82118, gram (+) bacterial strain *S. aureus* ATCC 29213, yeast *C. albicans* ATCC 10231, and the clinical isolates of the dermatophyte *Trichophyton rubrum* SNB-TR1, *T. mentagrophytes* SNB-TM1, *T. soudanense* SNB-TS1, *T. violaceum* SNB-TV1, and *T. tonsurans* SNB-TT1. A broth microdilution method was used to assess the EOs' antimicrobial activity. Although *C. libani* EOs were ineffective against *P. aeruginosa* or *C. albicans* (MIC: 512 µg/ml), *S. aureus* and *T. rubrum* were noticeably susceptible to them (MIC of 64 µg/ml)[32]. This investigation came to the conclusion that the activity was not caused by α-pinene[32].

In Diğrak *et al.*[45] , the antimicrobial activities of several parts of cedar from Turkey were investigated by the disc diffusion method. Chloroform, acetone, and methanol extracts of leaves, resins, barks, cones, and fruits were prepared and tested against *Bacillus megaterium* DSM 32, *B. subtilis* IMG 22, *B. cereus* FMC 19, *E. coli* DM, *Klebsiella pneumoniae* FMC 3, *Enterobacter aerogenes* CCM 2531, *S. aureus* Cowan 1, *Mycobacterium smegmatis* RUT, *Proteus vulgaris* FMC 1, *Listeria monocytogenes* Scoot A, *Pseudomonas aeruginosa* DSM 5007, *C. albicans* CCM 314, *C. tropicalis* MDC 86, and *Penicillium italicum* K. The extracts were inactive against *E. coli* and possessed no antifungal effects, but they inhibited the growth of the other studied bacteria[45].

In Venditti *et al.*[27], wood EOS from Lebanon were tested against *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *E. faecalis* ATCC 29212, and *C. albicans* ATCC 24433 by the paper disc diffusion method, and the diameters of the inhibition zone were determined. In this study, ciprofloxacin (5 µg/ disc) and nystatin (100 units/disc) were used as reference agents. The results indicated that *P. aeruginosa* and *E. coli* were not susceptible to the EOs. *E. faecalis* and *S. aureus* were affected by the EO with inhibition zone diameters (IZD) of 8 and 9.5 ± 0.5mm, respectively. The oil showed less effective inhibition (IZD: 8.3mm ± 0.6) against *C. albicans*[27].

In contrast, in Abd Rashed *et al*.[46], the EO exerted remarkable activity against the yeast *C. albicans*. Moreover, (E)-α-atlantone exhibited antifungal activity against several *Aspergillus* species[47]. On the other hand, it was shown in Daoubi *et al.*[48] that β-himachalene possessed interesting properties as a fungicide[48].

Taken together, cedar can be included in antimicrobial formulations intended for both the treatment and avoidance of superficial infections.

Antiviral activity

C. libani is widely used as a traditional medicine in Lebanon for the treatment of different i*nfectious disease*. In Loizzo *et al.*[13], the antiviral activity of wood EO and ethanolic (95%) extracts of cones and leaves from plants grown in Lebanon was studied against herpes simplex virus type 1 (HSV-1) in infected Vero cells. The EO and ethanolic extracts exhibited interesting activity with TC_{50} of 0.87 and 1.92 mg/ml, respectively. HSV-1 growth was partly inhibited, and the IC_{50} of cones and leaves ethanolic extracts was 0.50 and 0.66 mg/ml, whereas the EO showed better activity with an IC_{50} of 0.44 mg/ml[13].

Antileishmanial activity

The 90% methanolic extracts of leaves didn't show antileishmanial activity *in vitro* against *Leishmania major* promastigotes[49].

Insecticidal effect

In Abdel-Maksoud *et al*.[50], wood oil of cedar showed *in vitro* an insecticidal effect on *Dermestes maculatus*. The concentration of 1011.2 ppm killed the larvae after one hour, while the concentration of 31.6 ppm was less effective even after 12 days[50].

In Cetin *et al.*[29], EO of seeds showed a larvicidal effect on *Culex pipiens* in the third and fourth instar larvae. The mortality increased by increasing the oil concentrations; the concentration 400 ppm showed 100% larvicidal activity, and the concentration of 100 ppm of the oil killed more than 45% of the fourth and third instars. Moreover, there was no significant difference in mortality between the reference temephos 1 ppm and the high concentration of 400 ppm. It is worth mentioning that many mosquito species have been resistance to temephos[29]. In Singh *et al*.[51], β-himachalene showed also interesting insecticide properties[51].

Antiproliferative activity or cytotoxic activity

In Saab *et al.*[37], human chronic mylogenous leukaemia K562 cells were used to test the antiproliferative activity and erythroid differentiation capabilities of chloroform and ethanolic extracts from seeds of *C. libani*, grown in Lebanon. Results demonstrated that the antiproliferative effects of the ethanol and chloroform extracts were distinct, with IC_{50} values of 40.57 ± 1.16 and 69.20 ± 1.69 µg/ml, respectively. Compared to the chloroform extract, the ethanolic extract significantly decreased cell proliferation (41.37%). At a concentration five times lower than that displayed by the chloroform extract, the ethanolic extract similarly demonstrated a strong ability to induce differentiation (16.00 ± 1.52 % at 10 µg of ethanolic extract/ml and 12.00 ± 1.25 % at 50 µg of chloroform extract/ml). The ethanol extract's ability to inhibit cell proliferation was related to palmitic acid (0.53 ± 0.03 %) and methyl linoleate (1.43 ± 0.12 %), two less common compounds, as well as abietane diterpenoids[37]. Whereas α- and β-pinene were responsible for the chloroform extract's activity. In contrast to the positive control, both extracts exhibited a low biological incidence because arabinose cytosine inhibited cell growth by 92.00 ± 2.70 % at 250.0 ± 0.2 nM[14].

In Saab *et al.*[52], wood EOs exceeded seed extracts in terms of their ability to inhibit the proliferation of K562 cells. The K562 cell growth was inhibited by the EO at an IC_{50} of 23.38 ± 1.7 µg/ml. Furthermore, at a concentration of 5 µg/ml, this oil caused erythroid differentiation (15 ± 2 %)[52]. Moreover, the oil showed noteworthy activity against the multidrug-resistant P-glycoprotein-expressing CEM/ADR5000 leukaemia cells and the drug-sensitive CCRF-CEM (human leukemic lymphoblasts) (IC_{50} values: 29.46 to 61.54 µg/ml). Interestingly, cross-resistance was not present in multidrug resistant CEM/ADR5000 cells, suggesting that this EO may be effective in treating drug-resistant and refractory tumours[53].

According to Venditti *et al.*[27], wood EOs have high cytotoxic activity against three human cancer cell lines, including A375 (human malignant melanoma cells), MDA-MB 231 (human breast adenocarcinoma cells), and HCT116 (human colon carcinoma cells), especially against HCT116 cells with an IC_{50} value of 8.38 µg/ml[27].

In Elias *et al.*[3], the cytotoxic properties of 2-himahcalene-7-ol, 7-HC, the main component of wood EO from North Lebanon, as well as the simultaneous administration of cisplatin (5 and 10 µg/ml) and 7-HC (2.5 and 5 µg/ml) against four human cancer cell lines; Caco-2 (human colon cancer cell line), SF-268 (human astrocytoma cell line), Sk-OV-3 (human ovarian cancer cell line), and HT-29 (human colon cancer cell line) were evaluated. In SF-268, HT-29, and Caco-2 cell lines, the results demonstrated potent cytotoxic activity and a dose-dependent reduction in cell survival (IC_{50}: 8.1, 10.1, and 9.9 µg/ml, respectively), with almost complete inhibition of proliferation at 25 µg/ml. For Caco-2 and SF-268 cells, comparable IC_{50} values of cisplatin and 7-HC were found. While HT-29 exhibited resistance to cisplatin, 7-HC had an IC_{50} value of 9.1-10.1 µg/ml and was 8–10 times more effective than cisplatin. With an IC_{50} value greater than 50 µg/ml, SK-OV-3 cells were the most resistant to 7-HC. Also, it was discovered that Sk-OV-3 cells are resistant to cisplatin treatment (IC_{50} > 100 g/ml)[3,25,37,54].

Co-treatment with combinations of 7-HC:cisplatin (2:1 and 4:1 ratios) showed a significant synergistic anti-proliferative effect against SF-268, HT-29, and Caco-2 cells. SF-268 cells were found to be the most sensitive to this combined treatment. However, the synergistic inhibitory effect of both drugs was not observed on Sk-OV-3 cells. Therefore, 7-HC exerts selectivity against certain cancer cell lines[3,37,54,55].

On the other hand, 7-HC showed a minor cytotoxic effect on isolated rat monocytes due to its insignificant cytotoxicity against these cells. The reduction in cell survival at concentrations of 10, 25, and 50 µg/ml was 7.7, 11.5, and 12.7 %, respectively. This result confirms the selectivity of 7-HC for cancer cells relative to normal cells[3].

It is suggestive that cedar and 2-himahcalene-7-ol can be utilized as medical supplements in the treatment of cancer and human blood related diseases.

Antioxidant effects

Antioxidants are chemicals that keep cells free of reactive species, or free radicals, and are essential for maintaining good health. The antioxidant properties of EOs and extracts from various plant parts were evaluated[27,42]. Using the $ABTS^+$ and DPPH tests, the antioxidant activity of Lebanon-grown cedar wood EO was evaluated *in vitro*. The activity was lower than that of the positive control, trolox, whose IC_{50} values were 0.74 µg/ml in the $ABTS^+$ test and 1.89 µg/ml in the DPPH assay, whereas the IC_{50} values of EO were 502 µg/ml (in the $ABTS^+$ assay) and 1532 µg/ml (in the DPPH assay). Moreover, the total reduction power was assessed by the FRAP assay, and it was 39.8 µmol trolox equivalent/g[27]. In Semerci *et al.*[42], the antioxidant activity of a methanolic extract of female cones in Turkey was tested using a DPPH assay. The IC_{50} was 0.58 µg/ml, which was more than that of ascorbic acid (IC_{50} :3.20 µg/ml)[42]. On the other hand, in Senol *et al.*[41], the antioxidant activity of acetone (Ace), ethyl acetate (EtOAc), and ethanol (EtOH) extracts of the needles and shoots was tested using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and N,N-dimethyl-p-phenylendiamine (DMPD) radical scavenging, Fe^{+2}-Ferrozine metal-chelation capacity, ferric-(FRAP) and phosphomolibdenum-reducing antioxidant power (PRAP) assays. The best result in DPPH scavenging activity was for the aceton needle extract, which was 63.83% at 1000 µg/ml but still less than the positive reference of gallic acid, which had a scavenging activity of 94.08 ± 0.13%. The shoot ethanolic extract had a marked scavenging effect on the DMPD radical (30.08%), while the scavenging activity of the positive reference, quercetin, was 68.32 ± 0.67%[41]. In the Fe^{+2}-Ferrozine test, the most active extract was the shoot ethyl acetate extract, with an inhibitory effect of (58.04 ± 0.70)%[41], but also less than the positive reference (EDTA), which had an inhibitory effect of 78.71 ± 1.86%. In FRAP and PRAP assays, the most active extract was shoot aceton extract, but with less activity than chlorogenic acid (positive reference) in FRAP and a comparable effect to quercetin in PRAP[41,56].

The terpenes in oil, as well as phenols and flavonoids, may play a role in the recognized antioxidant properties of cedar. These studies used *in vitro* tests to assess antioxidant activity. Antioxidant properties *in vivo* and their methods of action are still being researched. In particular, oxidative stress-related disorders can be treated with cedar, making it a suitable candidate.

Anti-inflammatory activity

There are several *in vivo* and *in vitro* tests to evaluate the anti-infammatory activity of EOs and ethanolic extracts of different parts of *C. libani*. In Tumen *et al.*[23], the anti-inflammatory activity of cone EO was investigated by an acetic acid-induced increase in capillary permeability test in mice. 30.5% inhibition was achieved using 200 mg/kg, whereas 10 mg/kg of the positive control (indomethacin) showed 49.7% inhibition[23]. In Elias *et al*.[3], 7-HC significantly inhibited the chronic inflammation in rats, which was produced by a subplantar injection of 20 µL of 2% formalin in the right hind paw, in a non-dose-dependent manner, in comparison with diclofinac [10mg/kg (i.p.)][3]. The dose 100 mg/kg (i.p.) showed inhibition of 63.1% of paw edema. It was proposed that the activity was partially mediated through the suppression of COX-2 expression[3].

In Karrat *et al*.[44], the anti-inflammatory effects of *C. libani* leaves ethanolic extract from Syria were investigated using the human red blood cells (HRBC) membrane stabilization assay and albumin denaturation assay, and sodium diclofenac was the positive control. The inhibition of hemolysis was observed at concentrations of 2.5–25 µg/ml. Moreover, the albumin denaturation test showed a protection effect with an IC_{50} of 47.74 µg/ml[44].

It was suggested that the observed effect could be due to phenolics such as flavonoids and tannins. This ultimately suggested that the extract could be a potential new therapeutic tool for the treatment of inflammatory disorders.

The analgesic effect

In Karrat *et al.*[44], the analgesic effects of leaves ethanolic extracts of *C. libani* from Syria were evaluated using a formalin test at a dose of 30 mg/kg and a tail flick test using a gel containing 2% (w/v) of ethanolic extract. Diclofenac sodium, diclofenac gel 1%, and lidocaine gel 2% were used as positive controls. In the formalin test, the extract could significantly reduce paw licking time and inhibit paw edema, and the effect was better than the positive control. In the tail flick test, plant extract gel showed greater efficacy than diclofenac gel by calculating the maximum possible effect (MPE%)[44]. It was suggested that the observed effect could be due to phytochemicals such as flavonoids and tannins.

Hair growth promoting *activity*

The hair growth activity *of cedar wood oil* was studied *in vivo* and clinically. Uronnachi *et al.* tested the enhancing effects of wood oil (oleogel 10%) on hair growth in albino rats. The oil induced remarkable hair growth and increased hair density, but less than the positive control (Minoxidil 2%)[57].

In a clinical study, the hair growth of people with alopecia areata was significantly improved when using combinations of cedar wood, thyme, rosemary, and lavender EOs as a daily scalp massage[58]. To enhance hair growth, four to five drops of cedar wood oil may also be added directly to the shampoo[58].

Wound healing activity

Ethnobotanical surveys revealed that *C. libani* has been used to promote wound healing in Turkish folk medicine. In Tumen *et al.*[23], the effect of the EO of *C. libani* cones grown in Turkey on wound healing using excision and incision wound models was studied. Madecassol ointment® (1% extract of *Centella asiatica*) was used as a positive control. The EO (1%) demonstrated high activity in both wound models[23].

Antiulcerogenic activity

In Turkey, *C. libani* is used in traditional medicine for the treatment of ulcers. To verify this traditional use, methanolic and aqueous extracts of cones from turkey were tested using a water immersion-stress ulcer model in rats[59]. The aqueous extract (300 mg/kg oral) showed orally significant antiulcerogenic activity, whereas the methanolic extract was inactive[59]. In Yeşilada *et al*.[60], the anti-*Helicobacter pylori* activity of the extracts and fractions obtained from *C. libani* cones, which are used in folk medicine to treat gastric conditions, including peptic ulcers, was examined against one standard strain and eight clinical isolates of *H. pylori* using the agar dilution method[60]. Findings revealed that 50% of the clinical isolates examined as well as the standard stain with a MIC of 31.2 µg/ml were both sensitive to the chloroform fractions' anti-*helicobacter* activity[60].

In conclusion, water woody stem extracts as well as the chloroform fraction from methanolic cone extract have revealed anti-ulcerogenic properties.

Other activities and uses

α-amylase inhibitory activity

Alpha amylase inhibition is crucial for enhancing glucose tolerance in diabetic individuals. A study on the effects of cedar EOs from leaves, wood, and cones revealed that the wood oil was more potent than the cone oil, with IC_{50} values of 0.14 mg/ml and > 1 mg/ml, respectively[16]. While the oil from the leaves was inactive. It was assumed that the sesquiterpene himachalol, which is primarily found in wood but missing in cones and leaves, was responsible for the α-amylase inhibitory activity[16].

Cedar wood oil has a promising α-amylase inhibitory effect related to diabetes. However, more *in vivo* research is still needed, as well as a thorough understanding of the molecular mechanism through which it combats hyperglycemia.

Cholinesterase inhibitory activity

Cholinesterase inhibition is an important drug treatment strategy against Alzheimer's disease. In Senol *et al*.[41], the possible *in vitro* neuroprotective effects of the aceton, ethyl acetate, and ethanolic extracts of the needles and shoots of *C. libani* grown in Turkey were evaluated through their inhibition of acetylcholinesterase (Type –VI-S, EC 3.1.1.7) and horse serum butyrylcholinesterase (EC 3.1.1.8) at 100 µg/ml. The substrates were acetylthiocholine iodide and butyrylthiocholine chloride. The inhibition of ACHE activity of shoots ethanolic extract was 44.07%, and the inhibition of BCHE activity of needles aceton extract was 67.54%, but less than galantamine. It was proposed that the activity was related to the piperidine alkaloid[41,56].

Others

Cedar wood oil has been reported to be antidepressant and sedative when inhaled[61,62], and because of its anti-inflammatory, antiseptic, antioxidant, and antimicrobial effects, it could be beneficial for skin conditions like acne, seborrhea, eczema, and dry skin[63].

The homoeopathic medicinal product *C. libani* featured unexpected therapeutic properties during a multicentre pathogenetic trial performed in 2016 concerning the treatment of vascular congestion in the upper part of the body for patients with a specific psychological profile[64].

Mutagenic effect & Safety

Toxicological studies on cedar are rare. In Takci *et al.*, the mutagenic properties of cedar tar were tested using the *Salmonella typhimurium* T98 and TA100 strains in the presence and absence of S9 metabolic activation. The results indicated that the tar has no mutagenic activity till a concentration of 200mg/plate[65]. In Çelìk *et al.*, cedar was classified as non-toxic[66].

Conclusion

Most of the traditional uses of *C. libani* in cosmetics, foodstuffs, flavouring agent, and traditional medicine were verified. Also, a variety of pharmacological actions, including anti-inflammatory, antibacterial, antioxidant, and anticancer activity, have been studied. In addition, the chemical composition of *C. libani* has also been extensively studied, alkaloids, polyphenols, and terpenoids are thought to comprise this plant's main chemical components. The results of all previous research should be used for the therapeutic use of this plant in a scientifically correct manner, rather than relying on folk medicine. They also provide an opportunity for pharmaceutical companies looking to manufacture new alternative therapeutic products.

Possible future research ideas on *C. libani*

Despite these encouraging findings, many studies have used solely *in vitro* models to investigate the therapeutic application of these findings. Future research should concentrate on studies in both animals and humans.

Moreover, most of the conducted studies did not thoroughly explore the molecular mechanisms of action of *C. libani* extracts, which reduced their applicability. Future research should therefore try to study the mechanisms of action of these extracts and their phytochemicals.

To increase the capability of manufacturing, marketing, and consumer acceptance of this plant's products, its known components should be standardized, and appropriate safety studies should be conducted. Possible areas of interest include the drug formulation from this plant to treat pain and inflammation, in addition, *C. libani* is a suitable candidate for the development of pharmaceuticals and nutraceuticals for the management and prevention of cancer.

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المكونات الفعالة و الفعالية الحيوية لنبات الأرز اللبناني
Cedrus libani A. Rich

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يعد الأرز اللبناني (الفصيلة Pinaceae) نوعاً نباتياً موطنه منطقة حوض البحر الأبيض المتوسط. استخدام العقار شعبياً لعلاج العديد من الأمراض، بما في ذلك الحالات الالتهابية وأمراض الجهاز التنفسي، وكذلك لتخفيف آلام الأسنان. تهدف هذه المراجعة إلى تعميق المعرفة عن كل من التركيب الكيميائي والفعالية الحيوية لهذا النبات من خلال مسح المعلومات المتوفرة حاليًا في العديد من قواعد البيانات الإلكترونية حول الجوانب النباتية والاستخدامات التقليدية والكيمياء النباتية والفعاليات الحيوية .

أظهرت هذه المراجعة أن لأجزاء النبات المختلفة مجموعة واسعة من التأثيرات الحيوية وتحتوي على العديد من المركبات الكيميائية الفعالة، مما يشير إلى امكانية استخدام هذا العقار كمصدر لمضادات الأكسدة الطبيعية ومضادات الميكروبات للتطبيقات الصناعية والطبية. يمكن أيضًا علاج الأمراض المرتبطة بالدم عند الإنسان باستخدام نبات الأرز. علاوة على ذلك ، للعقار خصائص واعدة مسكنة للألم ومضادة للالتهاب. ومع ذلك ، هناك حاجة إلى مزيد من الأبحاث المتعلقة بالسمية والأبحاث السريرية لتحديد سلامة وفعالية التطبيقات العملية لهذا النبات في علاج الأمراض التي تصيب الإنسان.