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Review article

# Genus *Thuja*: A comprehensive review on botany, traditional uses, pharmacological activities and phytochemistry

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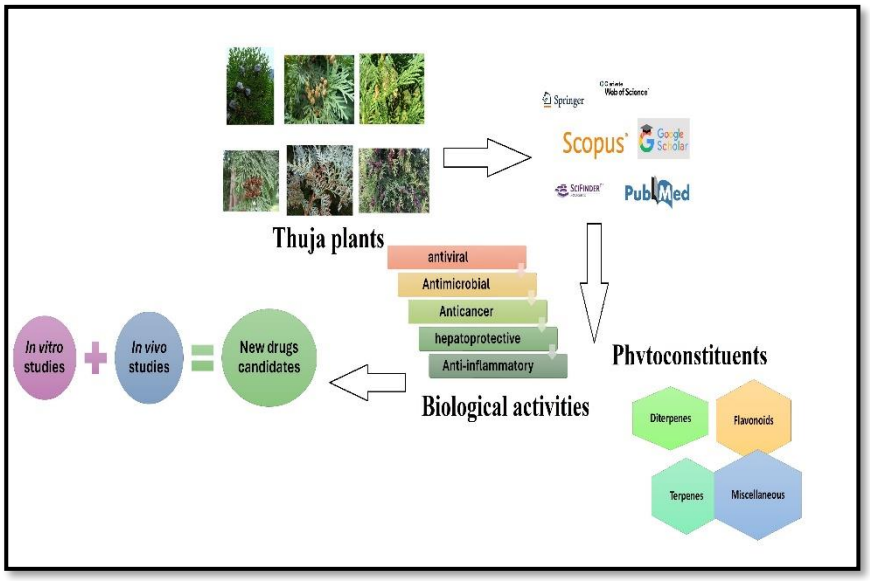
## Abstract




*Thuja* is one of Coniferous trees (family Cupressaceae). It comprises five species: *Thuja occidentalis*, *Thuja koraiensis*, *Thuja plicata*, *Thuja standishii* and *Thuja sutchuenensis*. This review aimed at gathering the botany, traditional uses, biological activities and phytoconstituents of *Thuja* species from 1984 until 2020, as they are considered generous sources of numerous phytoconstituents that may be used as scaffolds for new drugs with diverse pharmacological activities. Online bibliographies were searched using popular search engines, such as Google Scholar, PubMed, Springer, and Web of Science, in order to cover the botany, folk uses, biological activities and phytochemistry of *Thuja* plants. The review revealed that *Thuja* plants have diverse biological effects, and economic and folk uses. Moreover, the review showed the different phytoconstituents classes in *Thuja* plants. It can be concluded that *Thuja* plants are good candidates for intensive research to prove their biological activities by *in vivo* and clinical trials in order to get evidence-based drugs and discover new drugs for the treatment of several ailments.

**Keywords:** *Thuja occidentalis*, *Thuja koraiensis*, *Thuja plicata*, *Thuja standishii*, *Thuja sutchuenensis*, *Thuja orientalis*

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## 1. Introduction

*Thuja* is a genus of coniferous trees belonging to the family Cupressaceae. It contains five species; two of them are native to North America and the other three are native to east Asia (**Table 1**). Plants of this genus are commonly called arborvitaes which is a Latin word that means tree of life or Thujas. Meanwhile, they are usually known as cedar but, they are not true cedars (Cedrus), so it is suggested to name them red-cedars or white-cedars. The five species that belong to this genus are *Thuja occidentalis*, *Thuja koraiensis*, *Thuja plicata*, *Thuja standishii* (Gordon) and *Thuja sutchuenensis* Franch (**Fig. 1**). *Thuja orientalis* is considered as distinct and distantly related species that is now treated as a monotypic genus under the name *Platycladus orientalis* [1, 2] (**Fig. 1**). Literature showed the high economic and medicinal values of *Thuja* species. Moreover, these plants are characterized by having diverse biological activities. Furthermore, these plants are considered as important sources of numerous and different phytoconstituents that could be further used as candidates for new drugs with diverse biological activities. In this review, the botany, folk uses, biological activities and phytoconstituents of *Thuja* plants; *Thuja orientalis* L. (syn, *Platycladus orientalis* L. Franco and *Biota orientalis* (L.) Endl) and five *Thuja* species were gathered and collected. It is worthy to mention that this is the first comprehensive review of genus *Thuja*.


**Fig. 1:** (A) *Platycladus orientalis*, (B) *Thuja occidentalis*, (C) *Thuja koraiensis*, (D) *Thuja plicata*, (E) *Thuja standishii* and (F) *Thuja sutchuenensis*



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**Table 1:** Species of genus *Thuja* and *Platycladus* and their geographical distribution

| Botanical origin | Geographical distribution |
|---|---|
| ***Thuja occidentalis*** | North America and Europe |
| ***Thuja koraiensis*** | North and South Korea, as well as the southern portion of the adjacent Jilin province in China, Changbai Mountain area of China |
| ***Thuja plicata*** | USA: Alaska, Montana, Idaho, Washington, Oregon and California, Canada: British Columbia, Alberta |
| ***Thuja standishii*** | Japan: mountains of Honshu and Shikoku |
| ***Thuja sutchuenensis*** | Southern side of the Daba Shan near Chengkou, Chongquing (China) |
| ***Thuja orientalis* L. (syn, *Platycladus orientalis* L. Franco and *Biota orientalis* (L.) Endl)** | Northwestern China, Korea, India, Japan, Eastern Russia, and Iran and in Europe as an ornamental plant since 18th Century |

## 2. Methodology

To get more detailed insights into the ethnopharmacology, botany, phytochemistry, and pharmacology of the *Thuja* plants, online bibliographies were searched using popular search engines, such as Google Scholar (http://scholar.google.com), PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Springer (http://www.springer.com/gp ), and Web of Science (http://apps.webofknowledge.com), SciFinder and Scopus search engines in order to cover the botanical description, folk uses,biological activities and phytochemistry of *Thuja* plants. The chemical structures of *Thuja* phytoconstituents were drawn using Chembiodraw Ultra (Version 12.0). The structures of Thuja phytoconstituents were drawn using Chembiodraw Ultra (Version 12.0).

## 3. Botanical description

### *3.1. Thuja occidentalis* Linn.

*Thuja occidentalis* (Arbor vitae or white cedar) is native to Eastern North America and in Europe is used as a tree for ornamental purposes [3]. Its common names are Northern white-cedar and eastern white cedar. White cedar is an evergreen monoecious tree that reaches high up to 25 m tall with 100 cm trunk diameter. The plant is usually with a single straight stem and a conical crown. On the other hand, it may yield multiple stems as it can reproduce by layering. The bark is red-brown which turns gray with age. Branchlets are flattened, bearing foliage in flattened, fan-shaped sprays. Leaves are scale-like, 1-4 mm long and 1-2 mm wide, pointed. Leaves' color is dull yellow-green on both top and bottom. Pollen cones are 1-2 mm long and reddish. Meanwhile, seed cones are ovoid, 9-14 mm long, green turning into brown, with two pairs of woody fertile scales yielding a total of 8 seeds. Seeds are winged, red-brown and 4-7 mm long [4].

### *3.2. Thuja koraiensis* Nakai

*Thuja koraiensis* (Korean arborvitae, Korean thuja) is an endangered conifer of high economic and ecological value. It is an evergreen, coniferous species of broad shrub or small tree, distributed in North and South Korea, as well as China. It is an evergreen tree that grows to mature heights of (6 - 10 m) tall. The bark is reddish-brown colored and smooth, but it turns with age into grayish-brown and becomes fissured, and flaking. Branches are ascending or spreading, forming a pyramidal crown. The facial leaves are triangular-ovate and bright green colored, while lateral leaves are as long as or shorter than the facial leaves, with incurved apex. Pollen cones are purplish in color and 2 - 3 mm long. On the other hand, seed cones are oval, yellowish green and 7 - 11 mm long [5].



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### *3.3. Thuja plicata* Donn ex D. Don

*Thuja plicata (*Syn: *Thuja gigantean* Silba*)* is also known as Western or giant red cedar. It is a large evergreen Coniferous tree of 50-70 m tall and 200-600 cm dbh. It is characterized by a pyramidal habit, horizontal branches, and flattened twigs. The color of the bark is red-brown or gray-brown especially when exposed to sunlight, 10-25 mm thick, fibrous with shallow longitudinal fissures and it is easily peeled. Shade leaves are scale-like, decurrent, arranged oppositely in 4 ranks, green-coloured, glabrous, and acute to abruptly acuminate. On the other hand, sun foliages are characterized by more flexible and less planar sprays, with smallest shoots upturned and nearly round. Pollen cones are 1-3 mm long and they are formed in a cup designed by two leaf pairs at the tips of lateral spray branchlets, and they are most abundant on sun foliage. Meanwhile, seed cones are formed in the medial region of lateral spray branchlets, ellipsoid, consisting of 4 pairs of scales arranged in 4 ranks, 10-12 mm long and they are characterized by the presence of a nearly terminal dentate projection. Seeds are reddish-brown colored, winged, 8-14 per cone and 4-7.5 mm [6].

### *3.4. Thuja standishii* (Gordon.)

*T. standishii* which is known as Nezuko, kurobe and Japanese arborvitae is a threatened evergreen tree with a height up to 18 m. Leaves color is deep green. Facial leaves have subacute apex are without abaxial gland. Meanwhile, lateral leaves are slightly shorter than or as long as facial leaves and they have an incurved apex. Pollen cones are black colored and 1.5-2 mm long. On the other hand, seed cones are terminal, deep brown- colored, obovoid and 8-10 mm diameter. Seeds are 5-6 mm long and winged. Generally this *Thuja* species is very similar to other *Thuja* species regarding foliage and bark characters, but it can be easily distinguished distinguished according to its cones shape [7].

### *3.5. Thuja sutchuenensis* Franch

*Thuja sutchuenensis* Franch which is commonly named Ya Bai and Sichuan Arborvitae is a critically endangered plant. It is an evergreen tree or shrub up to 20 m tall, characterized by a pyramidal crown of spreading, and ascending branches. The bark is fibrous, orange-brown colored when young, but it turns gray-brown upon maturity. Leaves are imbricate, decurrent, appressed and dimorphic; facial leaves shape is rhombic to diamond-shaped while lateral leaves are slightly larger, bilaterally flattened, incurved and obtuse. Pollen cones are terminal, subglobose and yellow-green colored and turn brown upon maturity. Meanwhile, seed cones are terminal and ellipsoid. Seeds are ovoid-oblong and winged [8].

### *3.6. Thuja orientalis* L. (syn, *Platycladus orientalis* L. Franco and *Biota orientalis* (L.) Endl)

*Thuja orientalis* L. (syn, *Platycladus orientalis* L. Franco and *Biota orientalis* (L.) Endl) is a genus of evergreen monoecious coniferous trees that of family Cupressaceae [9]. The meaning of *Platycladus* is "with broad or flattened shoots". This genus contains only one species, *Platycladus orientalis* which has common names, such as Chinese arborvitae, biota, oriental cedar or oriental Thuja [10]. It is native to northwestern China but now also found in Korea, India, Japan, Eastern Russia and Iran [11] *Platycladus* was formerly included in *Thuja*, but due to morphological and embryological issues it was separated from this genus [12]. *Platycladus* is distantly related to *Thuja*, as there are many differences, such as its distinct cones, wingless seeds, and it's almost scentless foliage [12]. *P.orientalis* is a small,



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slow-growing tree which upon maturation reaches heights of 15 - 20 m tall with a 0.5 m wide trunk diameter. Leaves are scale-like, 2 to 4 mm long and decussately opposite. The cones are 15 to 25 mm long, newly formed cones are green, but upon ripening they turn brown in about eight months after pollination and become woody horn-like, male cones are terminal, while female cones are axillary with 6–10 fleshy scales arranged in opposing pairs. The seeds are 4 to 6 mm long and wingless [13].

**4. Traditional uses of *Thuja* species**

In traditional practices, *Thuja* is widely used for the treatment of many ailment such as cough, bronchial catarrh, gout, rheumatoid arthritis, flu, gastric ulcers, enuresis, cystitis, psoriasis, uterine carcinomas, amenorrhea pain and inflammation disorders [14,15]. *Thuja orientalis* leaves is widely used as a Chinese medicine. In China, it is used in treatment of acute vaginal bleeding, baldness, bacillary dysentery, chronic tracheitis, diarrhea, hemorrhoid bleeding, gonorrhea, *Herpes zoster*, insomnia, skin lightening [16]. In Japan it is used to alleviate arthralgia, while in Korea it is used to help in case of excess phlegm([16]. The essential oil is also used for fungal and bacterial infections treatment, body care products as well as perfume industry in western countries [17].

Meanwhile, *T. occidentalis* (white cedar) is traditionally used for the treatment of numerous disorders such as: bronchial catarrh, psoriasis, uterine carcinomas, amenorrhea, and rheumatism. Nowadays, the mother tincture or dilution is mainly used in homeopathy. On the other hand, *T. occidentalis* is combined with other immunostimulant herbs, such as *Echinacea* species. At the same time, *Thuja occidentalis* is widely used in homeopathy and evidence based phytotherapy. Its immunopharmacological potential has been demonstrated in numerous *in vitro* and *in vivo* test models showing its immunostimulating and antiviral activities [4]. Furthermore, *T. occidentalis* has been used for numerous gynecological disorders, such as; amenorrhoea and uterine carcinoma [18, 19]. *Thuja occidentalis* is prescribed in Homoeopathy in treating rheumatoid arthritis [20]. Besides, it is used as homeopathic mother tincture for treatment of moles and tumors [21]. Moreover, *T. occidentalis* results in stimulation of blood circulation and secretion of hormones, enzymes, gastric juices, acids, and bile, in addition to its effect on peristaltic motion, the nerves, heart, and brain [18].

*T. koraiensis* possess an important role in the protection of the environment because it possesses a high adsorption ability of fluorine. Its wood is widely used in construction and handicrafts. Furthermore, its different plant parts are traditionally used with diverse biological activities, such as antiviral, anti-inflammatory and anticancer activities [22].

*Thuja plicata* was used for treatment of a wide range of complaints [23]. Leaves infusion has been used to treat GIT complaints. Meanwhile, leaves decoction has been used in the treatment of colds. Externally powdered leaves decoction is used for treatment of rheumatism [23]. Chewing leaf buds is used to treat toothaches and sore lungs, while its decoction is used as a gargle. Meanwhile, twigs decoction has been used as a wash to cure venereal disease sores. Furthermore, the bark and twigs decoction has been used to treat kidney complaints, while the infusion of the seeds and twigs has been used in case of fevers [23]. Chewing the bark or its decoction is used to induce menstruation. Because of its insecticidal and antimicrobial effect, western red cedar



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essential oil is widely used as a natural insect repellent and a preservative of wood [24].

*T. standishii* wood is highly prized and is used for special building intentions, such as ceilings in addition to its use for furniture [25]. Furthermore, it is widely grown in Japan for ornamental purposes.

*T. sutchuenensis* has various medicinal values such as its capablility of improving insomnia and dreaminess. Moreover, the fragrance of the *T. sutchuenensis* has the capability of improving oxygen content in blood that is responsible of feeling pleased upon smelling its fragrance. Furthermore, it can be placed around the patient in order to improve patient's mood and boost immunity. Furthermore, the aromatic smell of the *T. sutchuenensis* can help in resisting inflammation and relieving swelling as this smell can purify air and kill bacteria and viruses. There is an invention that relates to *Thuja sutchuenensis* wood medicinal pillow for treating cervical spondylosis [26].

*T. orientalis* essential oil is traditionally used in order to treat fungal and bacterial infections, and because of its insecticidal and antimicrobial effect, western red cedar essential oil is traditionally used as a natural insect repellent and wood preservative [24].

## 5. Biological activities of *Thuja* species

### 5.1. Anti-inflammatory activity

The effect of *Thuja orientalis* on airway inflammation was assessed in ovalbumin (OVA) -induced allergic asthma and RAW264.7 murine macrophage cells. The plant showed inhibitory effect on the production of pro-inflammatory mediators in LPS-stimulated RAW264.7 cells [27]. The topical application of the extracts of *T. orientalis* (syn, *Platycladus orientalis* L. Franco and *Biota orientalis* (L.) Endl) relieved the symptoms of atopic dermatitis through the reduction of the activity of pro-inflammatory mediators in addition to suppression of the over-activated immune responses. These suggested that such combination can be used as alternative for the management of atopic dermatitis [28].

The effect of *T. plicata* essential oil on seventeen proinflammatory markers and tissue remodeling was assessed using a pre-inflamed human dermal fibroblast culture model. Results showed that tested oil has anti-inflammatory activity through inhibiting pro-inflammatory markers and it has beneficial effects on human skin cells [24]. All these results displayed the anti-inflammatory potential of *Thuja* plants and eliciting the need for more clinical trials to get evidence-based drugs and to isolate phytoconstituents that are responsible for such activity.

### 5.2. Antimicrobial activity

Many studies were conducted in order to evaluate the antimicrobial activities of *Thuja* plants extracts and essential oils against different strains of bacteria and fungi aiming at finding new antimicrobial agents with new mechanisms of action to overcome bacterial resistance problem.

Leaves' methanol extract of *Thuja orientalis* was evaluated against MRSA (methicillin-resistant *staphylococcus aureus*), the extract showed potential for controlling both hospital- and community-acquired MRSA [29]. *Thuja orientalis* leaves extracts alone and in combination with ciprofloxacin were evaluated against *Pseudomonas aeruginosa* using disc-diffusion susceptibility assay. Results showed that the combination of methanolic crude extract, chloroform and butanol fractions showed a pronounced antibacterial activity against *Pseudomonas aeruginosa* at all tested levels, while ethyl acetate and aqueous fractions showed synergistic effect against *P. aeruginosa* (Kirby Bauer method) [30]. The



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antibacterial activity of wild and planted *Thuja orientalis* essential oils exhibited that both tested essential oil possessed activity [31].

The effect of *T. occidentalis* extract against *Pseudomonas aeruginosa* was assessed *in vitro* and *in vivo* and results revealed that the test extract is able to reduce *Pseudomonas aeruginosa* infections [32]. The antimicrobial activity of *Thuja occidentalis* seeds extracts were investigated against the isolated skin infecting microorganisms. Results revealed that the test extract exhibited a considerable level of antibacterial activity [33].

The antibacterial activity of *T. koraiensis* extract was assessed in *Staphylococcus aureus, Bacillus subtilis* (gram-positive bacteria), *Escherichia coli, Salmonella typhimurium* (gram-negative bacteria) using paper disk diffusion assay and the results showed the activity of the extract against all tested bacteria [5].

The antibacterial activity of eight sesquiterpenes isolated from stems and roots of *T. sutchuenensis* was evaluated against *Staphylococcus aureus* (CMCC 26003), methicillin-resistant *Staphylococcus aureus* (JCSC 4744), *Bacillus cereus* (ATCC 10876), and *Staphylococcus epidermidis* (ATCC 12228).

**5.3. Antiviral activity**

The antiviral activity of *Thuja occidentalis* polysaccharides was investigated against human immunodeficiency virus (HIV)-dependent. Results showed a dose-dependent inhibition of HIV-1-specific antigen expression on freshly infected MT-2 cells [34].

The antiviral activity of *T. koraiensis* extract was assessed against Bovine viral diarrhoea virus which is an RNA virus in Madin-Darby bovine kidney cells. Results unveiled that the extract had antiviral activity against Bovine viral diarrhoea virus especially at lower concentrations [5].

The antiviral activity of *Thuja* plants needs much deeper studies against different strains of different viruses that invade humans and plants or animals to help cure different human diseases and to make economic benefits by protecting and curing plant and animals from viral invasions.

**5.4. Antidiabetic and antihyperlipidemic activities**

Diabetes is a metabolic disorder that is managed by different antihyperglycemic drugs. Due to the side effects of synthetic drugs there is an emerging need to get hypoglycemic drugs with minimal side effects [35]. *Thuja* plants are important sources of numerous active constituents and there are studies that were conducted in order to evaluate their antidiabetic and hyperlipidemic effects.

*T.occidentalis* extract decreased levels of serum glucose, total cholesterol, triglycerides, low density lipid cholesterol, very low density lipid, alanine amino transaminase, aspartate amino transaminase, lactate dehydrogenase, alkaline phosphatase, acid phosphatase, albumin, creatinine, urea and uric acid and increased levels of serum insulin, HOMA-$\beta$, high density lipid cholesterol, total protein and impairment in pancreatic $\beta$-cell functioning [36]. Bioassay-guided fractionation or targeted metabolomics studies of *T. orientalis* and *T. occidentalis* are required to isolate the compounds that are responsible for the antidiabetic activity.

**5.5. Anticancer activity**

The volatile oil of the flowering parts of *Thuja orientalis* was evaluated against different tumor cell lines. Results showed that the oil displayed the highest cytotoxic activities against MCF7, followed by PC3



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and, Hep-G2, respectively, while it showed the least activity against lung carcinoma cell line [37].

The anticancer activity of the crude extract of the *T. occidentalis* seeds was evaluated and results revealed that the test extract has a considerable anti-proliferative effect allowing further studies to discover lead molecules for anticancer therapy [38].

### 5.6. Hepatoprotective activity

The hepatoprotective activity of *Thuja orientalis* and *T. occidentalis* leaves extract were assessed and results showed that the aqueous and petroleum ether extracts possessed high hepatoprotective activity as they significantly decreased the elevated serum aspartate aminotransferase (AST), alkaline phosphatase (ALP) and alanine aminotransferase (ALT) activities and the reduced serum total protein (TP), albumin (Alb) and globulin (G) accompanied by liver intoxication [39].

### 5.7. Analgesic activity

Petroleum ether, chloroform, methanolic and aqueous extract of leaves of *Thuja orientalis* were assessed for their analgesic activity. Results showed that petroleum ether and aqueous extracts showed significant analgesic activity [40]. In another study, the ethanol extract of *T. occidentalis* leaves showed a significant analgesic activity [41].

### 5.8. Hair growth promoting effect

A study was conducted to evaluate the effect of *T. orientalis* extract on the telogen to anagen transition. Results suggested that *Thuja orientalis* extract induces the hair follicles' anagen phase, thus it may be a candidate to be a hair growth-promoting agent [42].

### 5.9. Gynecological activity

A study aimed at determining the effect of *T. occidentalis* oil and its active terpene α-thujone in the treatment of polycystic ovary syndrome (PCOS). Results showed that they can be used for the treatment of PCOS with no osteoporosis [18].

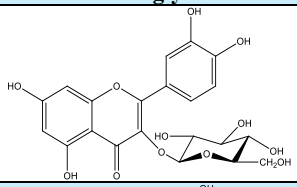
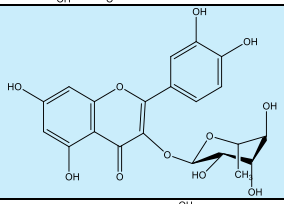
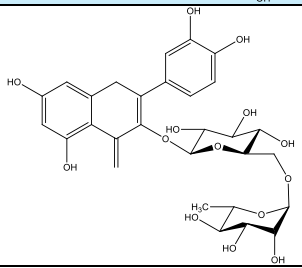
## 6. Phytochemistry of Genus *Thuja*

Several studies showed that there are different classes of secondary metabolites are isolated from *Thuja*, these compounds include monoterpenes, diterpenes, flavonoids, lignans and coumarin in addition to their essential oil [43].

### 6.1. Flavonoids

Flavonoids are phenolic compounds which have several pharmaceutical, pharmacological and clinical properties in addition to their contribution to several biological activities of *Thuja* plants, such as: anti-inflammatory [44], antimicrobial [45] and anticancer activities[46]. Flavonoids and bioflavonoids isolated from different *Thuja* species are listed in **Table 2.**

**Table 2:** Flavonoids isolated from *Thuja* species

| Compound | Structure | Species |
|---|---|---|
| **Flavonoid glycosides** | | |
| **Isoquercetrin** |  | *T. orientalis* |
| **Quercetrin** |  | *T. orientalis* *T. occidentalis* |
| **Rutin** |  | *T. orientalis* |



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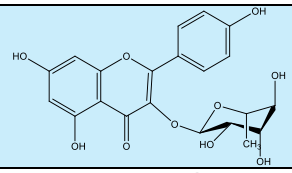
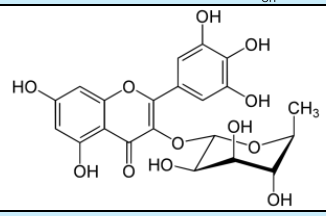
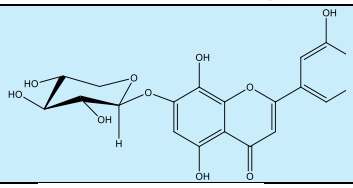
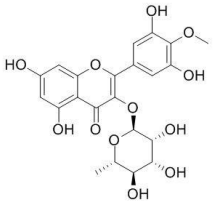
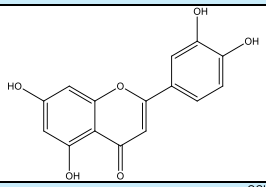
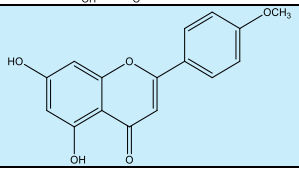
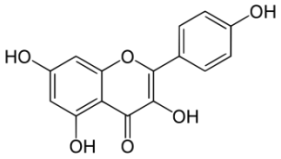
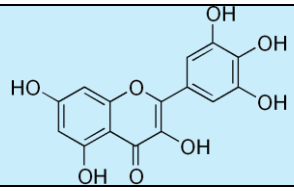
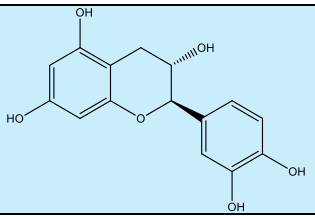
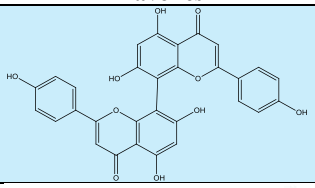
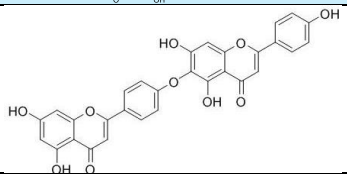
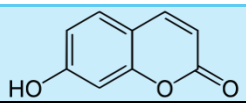
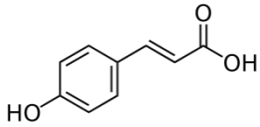
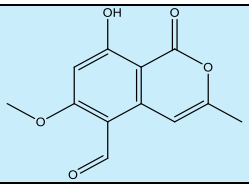
| | | |
|---|---|---|
| **Kampferin** |  | *T. orientalis* *T. occidentalis* |
| **Myricitrin** |  | *T. orientalis* *T. occidentalis* |
| **Hypoletin-7-*O*-*β*-D-xylopyranoside** |  | *T. orientalis* |
| **Mearnsitrin** |  | *T. occidentalis* |
| **Flavonoids** | | |
| **Quercetin** |  | *T. orientalis* |
| **Acacetin** |  | *T. orientalis* |
| **Kampferol** |  | *T. orientalis* |
| **Myricetine** |  | *T. occidentalis* |
| **Flavanes** | | |
| **(-)-Chatechin** |  | *T. occidentalis* |

| | | |
|---|---|---|
| **Biflavones** | | |
| **Cupressuflavone** |  | *T. orientalis* |
| **Hinokiflavone** |  | *T. orientalis* |

## 6.2. Coumarins

Coumarin is a large class of phenolic substances, among which 1300 coumarins were isolated from plants, fungi and bacteria. Coumarins are characterized by their anti-inflammatory, antimicrobial, anticoagulant, antiviral, anticancer, antihypertensive and antitubercular activities [47]. There are few reports for the isolation of coumarins that from *Thuja* plants as listed in **Table 3.**

**Table 3:** Coumarins isolated from *Thuja* species

| Compound | Structure | Species |
|---|---|---|
| **Umbelliferone** |  | *T. occidentalis* |
| ***P*-Coumaric acid** |  | *T. occidentalis* |
| **5-Formyl-8-hydroxy-6-methoxy-3-methyl isocoumarin** |  | *T. koraiensis* |

## 6.3. Essential oils

*Thuja* plants are characterized by the presence of essential oils which are extensively studied for their constituents and biological activities [6]. The most encountered components of such oils are monoterpenes, sesquiterpenes and diterpenes.

Monoterpenes are capable of the flavor and aroma of plant from which they are extracted in addition to their diverse biological



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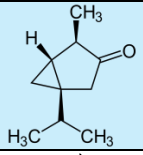
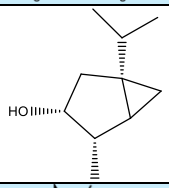
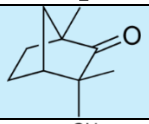
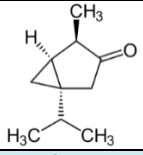
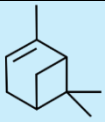
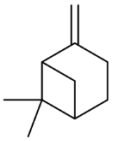
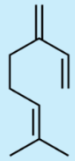
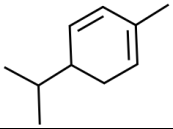
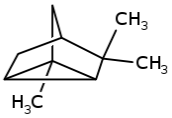
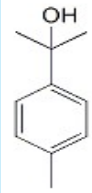
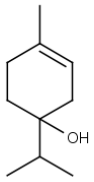
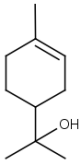
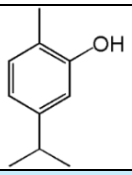
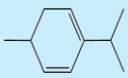
activities, such as: antimicrobial, antioxidant, and spasmolytic activities [48]. The most encountered monoterpenes are $\alpha$ and $\beta$ pinene, sabinene, camphor, dl-Limonene and thujone [6]. There was a debate on thujone content of essential oils of these plants due to its neurotoxicity as it acts as a modulator to GABA –gated chloride channel [49]. In order to avoid the oral toxicity of thujone containing food or herbal drugs, the amount of dietary intake of it should be 1 mg in average which will not result in special concerns [50].

Furthermore, Despite of the presence of many reports of toxicity after oral administration of oils containing thujone, there are no reports of toxicity of thujone after topical application[51]. This sounds good as more applications of essential oils are topical ones. Monoterpenes detected in *Thuja* plants are listed below in **Table 4**.

**Table 4:** Monoterpenes isolated from *Thuja* species

| Compound | Structure | Species |
|---|---|---|
| **Thujone** |  | *T. orientalis* *T. occidentalis, T. plicata* *T. koraiensis* |
| **Neoisothujol** |  | *T. occidentalis* |
| **Fenchone** |  | *T.occidentalis* *T. plicata* *T.sutchuenensis* |
| **Isothujone** |  | *T.occidentalis* |
| **α-Pinene** |  | *T. orientalis* *T.occidentalis, T. plicata T. sutchuenensis* |
| **β-Pinene** |  | *T. orientalis* (syn, *P. orientalis* L. Franco and *B. orientalis* (L.) Endl) *T. standishii* *T. sutchuenensis, T. plicata* |
| **Myrcene** |  | *T. orientalis* *T.occidentalis, T. plicata* *T. sutchuenensis* |
| **α-Phellandrene** |  | *T. orientalis T. occidentalis T. plicata Thuja standishii* |
| **Camphor** |  | *T.occidentalis* *T. koraiensis* *T. plicata* |
| **Cyclofenchene** |  | *T. koraiensis* |
| ***p*-Cymen-8-ol** |  | *T.occidentalis, T. plicata* *T. koraiensis* *T.sutchuenensis* |
| **Terpinen-4-ol** |  | *T.occidentalis* *T. plicata* *T. orientalis* *T.koraiensis T. standishii* *T.sutchuenensis* |
| **α-Terpineol** |  | *T.occidentalis* *T.koraiensis* *T. plicata T. standishii* *T.sutchuenensis* |
| **Carvacrol** |  | *T.occidentalis* *T.occidentalis, T. plicata* *T. orientalis* *T. koraiensis* |
| **δ-Terpinene** |  | *T. orientalis* |



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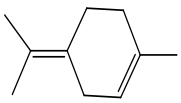
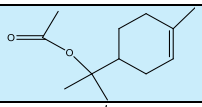
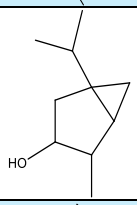
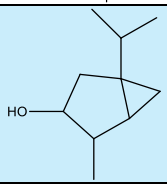
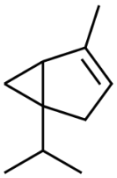
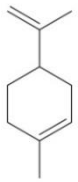
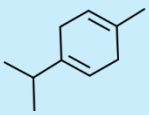
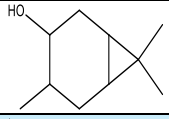
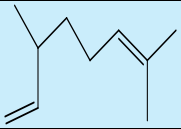
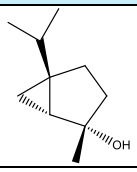
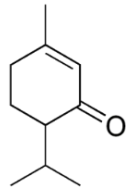
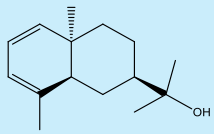
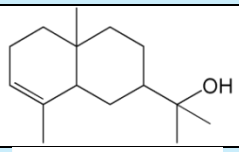
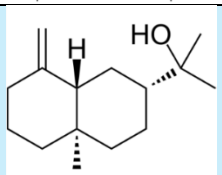
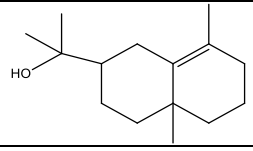
|---|---|---|
| |  | *T. orientalis T. occidentalis, T. plicata T.sutchuenensis* |
| **Terpenyl acetate** |  | *T. orientalis* |
| **Thujanol** |  | *T.koraiensis* |
| ***α*-Thujol** |  | *T.koraiensis, T. plicata T. occidentalis* |
| ***α*-Thujene** |  | *T. orientalis T. occidentalis, T. plicata T.sutchuenensis* |
| ***α*-Fenchene** |  | *T. orientalis T. plicata T. sutchuenensis* |
| **Limonene** |  | *T. orientalis T. occidentalis, T. plicata T.koraiensis* |
| ***γ*-Terpinene** |  | *T. orientalis T. occidentalis, T. plicata T. standishii T. sutchuenensis* |
| **4-Caranol** |  | *T.koraiensis* |
| ***Cis*- Ocimene** |  | *T. orientalis T. occidentalis* |
| ***cis*-Thujane-4-ol** |  | *T. orientalis* |
| **Citronellol** |  | *T.sutchuenensis* |
| **Piperitone** |  | *T.occidentalis T.sutchuenensis* |

Sesquiterpenes are found to have a large range of biological and pharmaceutical activities with effect on central nervous system, antimicrobial, and anti-tumor activities in addition to their the anti-inflammatory effect [52]. The most encountered sesquiterpenes in *Thuja* plants oil are caryophylline, caryophyllene oxide δ-cadinene, γ-eudesmol, α-cedrene, germacrene D &B, α-copaene and α-humulene [6]. Sesquiterpenes detected in *Thuja* plants are listed in **Table 5.**

**Table 5:** Sesquiterpenes isolated from *Thuja* species

| Compound | Structure | Species |
|---|---|---|
| **Occidentalol** |  | *T. occidentalis* |
| ***α*-Eudesmol** |  | *T. occidentalis* |
| ***β*-Eudesmol** |  | *T. occidentalis* |
| **γ-Eudesmol** |  | *T. occidentalis T. orientalis, T. sutchuenensis* |



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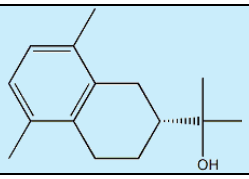
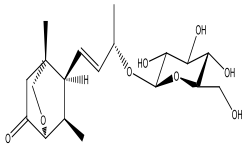
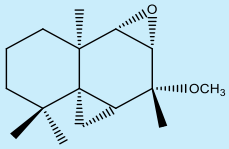
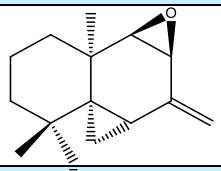
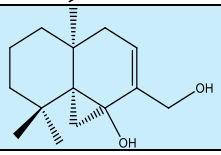
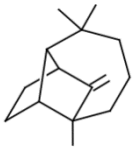
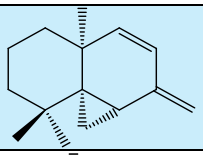
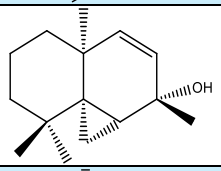
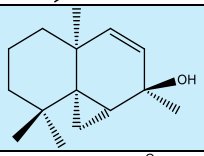
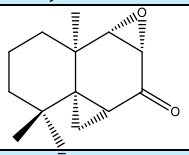
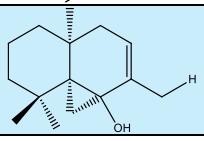
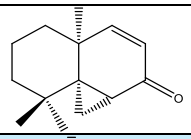
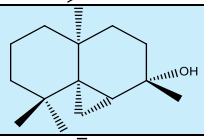
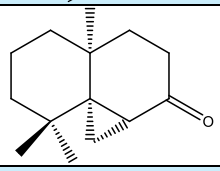
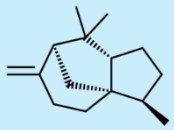
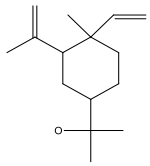
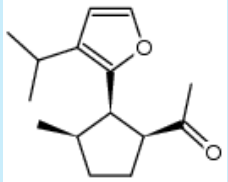
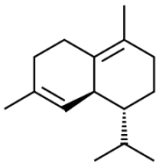
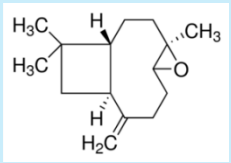
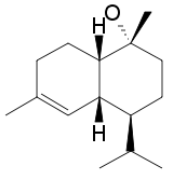
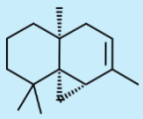
| | | |
|---|---|---|
| **Occidol** |  | *T.occidentalis* |
| **Degalloylmacarangiosid e B** |  | *T. orientalis* |
| **3*α*-Methoxy-4*α*-epoxythujopsane** |  | *T. orientalis* |
| **Δ3,15-4*β*-Epoxythujopsene** |  | |
| **Δ3,4-Thujopsen-2,15-diol** |  | |
| **Longifolene** |  | *T.sutchuenensis , T. orientalis* |
| **Thujopsadiene** |  | *T. orientalis* |
| **3*α*-Hydroxy-4-thujopsene** |  | *T. orientalis* |
| **3*β*-Hydroxy-4-thujopsene** |  | *T. orientalis* |
| **Mayurone oxide** |  | |
| **Thujopsen-12-ol** |  | |

| | | |
|---|---|---|
| **Mayurone** |  | |
| **Thujopsan-2*α*-ol** |  | |
| **Dihydromayurone** |  | |
| ***β*-Cedrene** |  | *T. orientalis T.sutchuenensis* |
| **Elemol** |  | *T. orientalis T. plicata T.sutchuenensis* |
| **Furopelargone B** |  | *T. plicata* |
| **Δ-Cadinene** |  | *T. occidentalis, T. plicata T. orientalis T. plicata T.sutchuenensis* |
| **(-) Caryophyllene oxide** |  | *T. occidentalis, T. plicata T. orientalis T.koraiensis T. standishii T.sutchuenensis* |
| **T-Muurolol** |  | *T. occidentalis, T. plicata* |
| **Thujopsene** |  | *T. orientalis T.sutchuenensis* |



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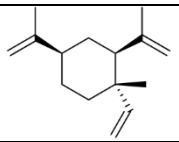
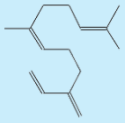
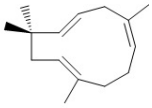
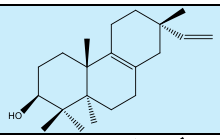
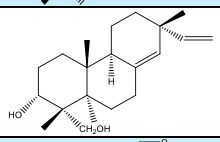
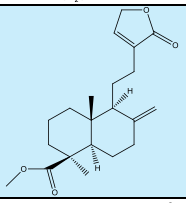
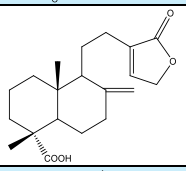
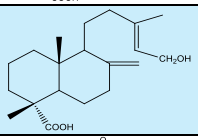
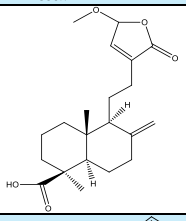
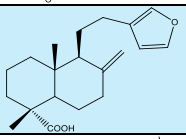
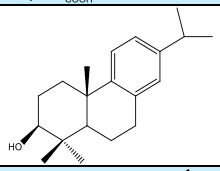
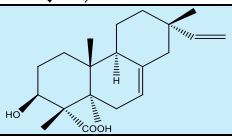
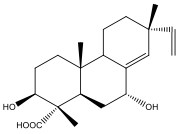
|---|---|---|
| **(-)-*β*-Elemene** |  | *T. orientalis*<br>*T. plicata*<br>*T.sutchuenensis* |
| ***Cis*-*β*-Farnsene** |  | *T. orientalis* |
| ***α*-Caryophyllene** |  | *T.sutchuenensis* |

Literature review showed that the most encountered diterpenes in *Thuja* plants are pimarane and labdane types. The isolated diterpens showed several biological activities, such as: anticancer [53], and anti-inflammatory activities[54]. Moreover, the activity of three new labdane-type diterpenoids along with six known diterpenoids that isolated from the stem bark of *Thuja standishii* was assessed using the previously *mentioned method*. Results showed that 6*α*-hydroxysugiol possessed a strong inhibitory effect on (EBV-EA) induction, while 12*S*-hydroxylabda-8 [17], 13 [16], 14-trien-19-oic acid and 12-methoxyabieta-8,11,13-trien-11-ol showed a moderate inhibitory effect. In addition, 15-oxolabda-8 [17],11*Z*,13*E*-trien-19-oic acid exhibited its antitumor promoting activity via two-stage mouse skin carcinogenesis test using 7,12-dimethylbenz[a]anthracene and TPA [55]. Furthermore, a study was conducted in order to assess the antitumor- promoting activity of six diterpenes including one new natural product which was isolated from the stem of *Thuja standishii*. Results showed that ferruginol, suginol, isocupressic acid and sandaracopimaric acids possessed a strong inhibitory effect [56]. Moreover, cognitive deficits were reduced by V in an AD (Alzehimer's disease) model *via* modulation of the A*β* peptide aggregation pathway [57]. **Table 6** gathered diterpenes that isolated from *Thuja* plants.

**Table 6:** Diterpenes isolated from *Thuja* species

| Compound | Structure | Species |
|---|---|---|
| **8(9), 15-Isopimaradien-3*β*-ol** |  | *T. orientalis* |
| **8(14), 15-Pimaradien-3 *β*, 18-diol** |  | *T. orientalis* |
| **Pinusolide** |  | *T. orientalis* |
| **Demethylpinusolide** |  | *T. orientalis* |
| **Isocupric acid** |  | |
| **15-Methoxypinusolidic acid** |  | *T. orientalis* |
| **Lambertianic acid** |  | |
| **Abietatriene-3*β*-ol** |  | |
| **3*β*-Hydroxysandaraopimaric acid** |  | |
| **(3*β*,7*α*-Dihydroxy-isopimara-8(14),15-dien-19-oic acid)** |  | *T. orientalis* |



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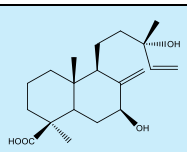
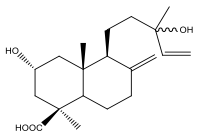
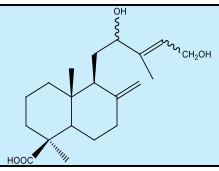
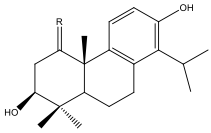
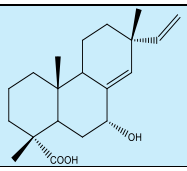
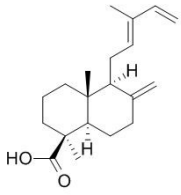
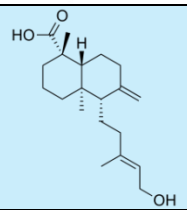
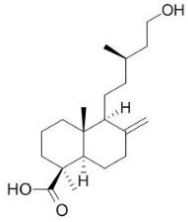
| **7*β*,13*S*-Dihydroxylabda-8(17),14-dien-19-oic acid** |  | *T. orientalis* |
| **Labda-8(17),14-diene-2*α*,13-diol-19-oic acid** |  | *T. orientalis* |
| **12*R*,15-Dihydroxylabda-8(17),13*E*-dien-19-oic Acid** |  | *T. orientalis* |
| **1- R=$H_2$ (3*β*-Hydroxytotarol)**<br>**2- R= O (1-oxo-3*β*-Hydroxytotarol)** |  | *T. orientalis* |
| **7*α*-Hydroxysandaracopimaric acid** |  | |
| **Communic acid** |  | *T. standishii*<br>*T. orientalis* |
| **Isocupressic acid** |  | |
| **Imbricatolic acid** |  | *T. standishii*<br>*T. orientalis* |

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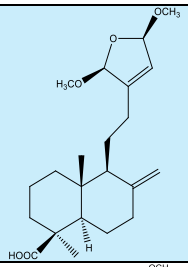
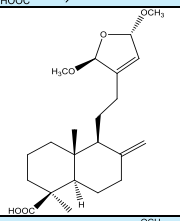
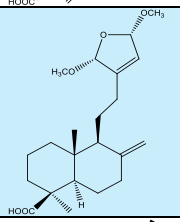
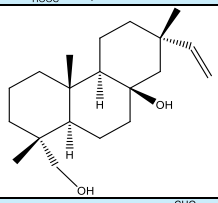
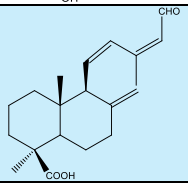
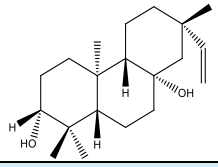
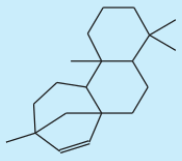
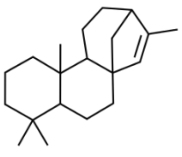
| **Thujoric acid A** |  | *T. orientalis* |
| **Thujoric acid B** |  | *T. orientalis* |
| **Thujoric acid C** |  | *T. orientalis* |
| **8*β*,18-Dihydroxysandaracopimar-15-ene** |  | |
| **15-Oxolabda-8(17),11Z,13Z-trien-19-oic acid** |  | *T. standishii* |
| ***Ent*-Isopimara-15-en-3α,8α-diol** |  | *T. orientalis* |
| **17-Norkaur-15-ene, 13-methyl-, (8*β*,13*β*)-** |  | *T. standishii* |
| **Kaur-15-ene** |  | *T. koraiensis*<br>*T. occidentalis,*<br>*T. plicata* |



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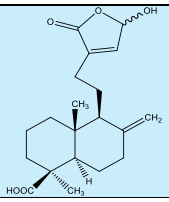
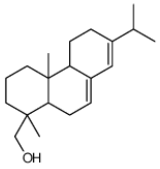
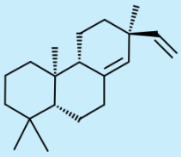
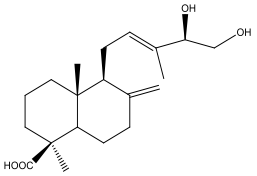
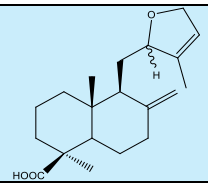
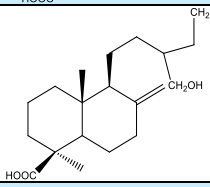
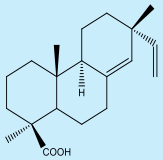
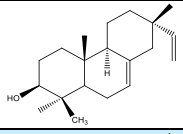
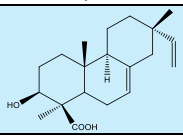
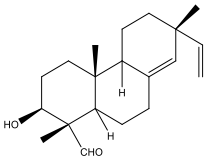
| **15-Oxo-8(17),13-labdadiene-16,19-dioic acid** |  | |
| **Abietol** |  | *T. plicata* |
| **Sandaracopimara-8(14),15-diene** |  | |
| **14(*R*),15-Dihydroxy-8(17),12(*E*)-labdadien-19-oic acid** |  | |
| **16-Methyl-12,15-epoxy-8(17),13-labdadien-19-oic acid** |  | *T. orientalis* |
| **15,16-Dihydroxy-8(17),13(*E*)-labdadien-19-oic acid** |  | |
| **Isopimara-8(14),15-dien19-oic acid** |  | |
| **Isopimara-7,15-dien-3*β*-ol** |  | |
| **Isopimara7,15-dien-3*β*,18-diol** |  | *T. orientalis* |
| **Sandaracopimaradienolal** |  | *T. orientalis* |

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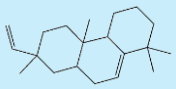
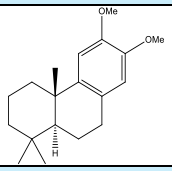
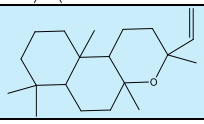
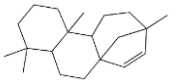
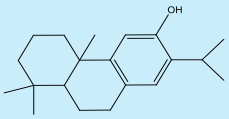
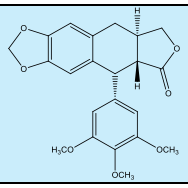
|---|---|---|
| **Rimuene** |  | *T. occidentalis, T. plicata* |
| **12,13-Dimethoxypodocarpa-8,11,13-triene** |  | *T. koraiensis* |
| **Manoyl oxide** |  | *T.sutchuenensis* |
| **Beyerene** |  | *T. occidentalis, T. plicata* |
| **Trans-Ferruginol** |  | *T. standishii T. orientalis T.sutchuenensis* |

### 6.4. Lignans and neolignans

Lignans and neolignans constitute abundant classes of phenylpropanoids. Lignans dimers in which two phenylpropanoid monomers linked by (C8) atoms (C8-C8') linkage and they are further classified into eight subclasses depending on the way in which oxygen is incorporated into the skeleton and the cyclization pattern [58].On the other hand, neolignans are C–8 to C–8′ bond is absent and other linkages are present [59]. They are known for their antiviral, anticancer, anti-inflammatory, antimicrobial, antioxidant, immunosuppressive, hepatoprotective and osteoporosis prevention effects [60].Lignans and neolignans isolated from *Thuja* plants are listed in **Table 7**.

**Table 7:** Lignans and neolignans isolated from *Thuja* species

| Compound | Structure | Species |
|---|---|---|
| **(-)-Deoxypodophyllotoxin** |  | |



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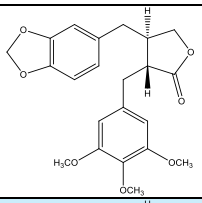
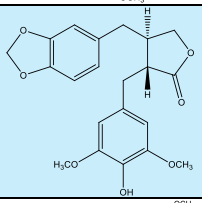
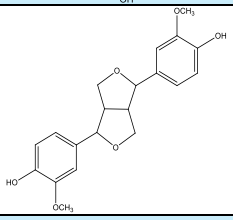
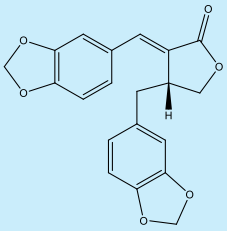
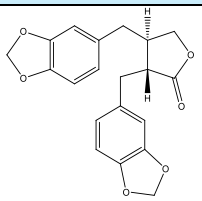
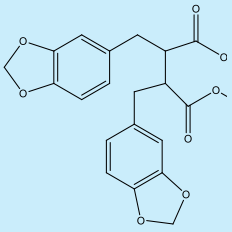
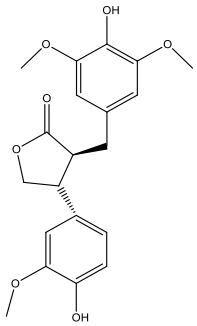
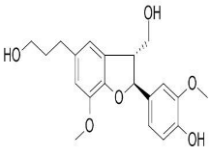
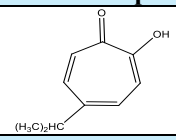
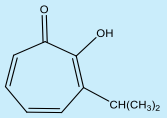
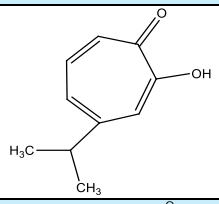
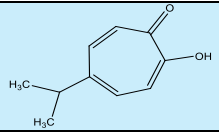
| | | |
|---|---|---|
| **(-)-Deoxypodorhizone** |  | |
| **(8*R*,8 '*R*)-(-)-4-O-Demethylyatein.** |  | *T. occidentalis* |
| **Pinoresinol** |  | *T. occidentalis* |
| **Savinin** |  | *T. orientalis* |
| **Hinokinin** |  | *T. orientalis* |
| **Dehydroheliobuphthalmin** |  | *T. orientalis* |

| | | |
|---|---|---|
| **Thujaplicatin methyl ether** |  | *T. orientalis* |
| **Neolignan** | | |
| **Dihydrodehydrodiconiferyl alcohol** |  | *T. occidentalis* |

### 6.5. Miscellaneous compounds

Other compounds were isolated from *Thuja* plants, such as tropolone derivatives, open chain aliphatic compounds, sterols, tannins, fatty acids, phenolic acids, and esters. These compounds are listed below in **Table 8.**

**Table 8:** Miscellaneous compounds isolated from *Thuja* species

| Compound | Structure | Species |
|---|---|---|
| **10 carbon compounds** | | |
| **7-Methoxy-4-isopropyltropolone** |  | *T.occidentalis* |
| **3-Isopropyltropolone** |  | *T.occidentalis* |
| ***β*-Thujaplicin** |  | *T. plicata* |
| ***γ*-Thujaplicin** |  | *T. plicata* |



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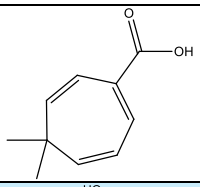
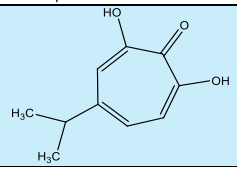
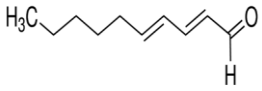
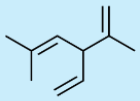
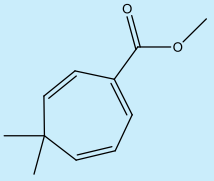
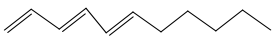
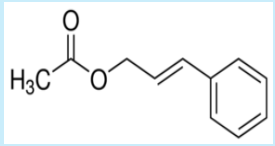
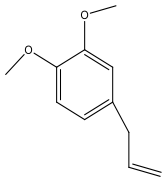
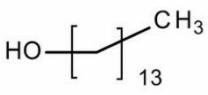
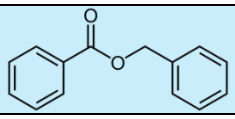
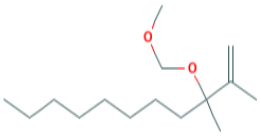
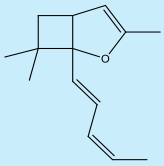
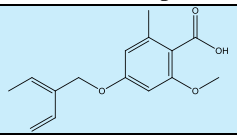
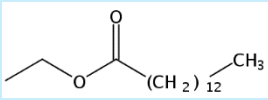
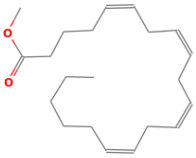
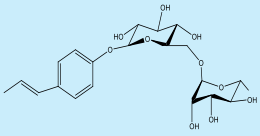
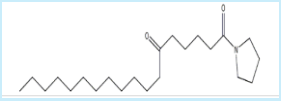
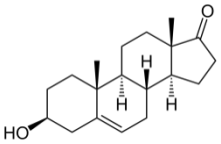
| | | |
|---|---|---|
| **Thujic acid** |  | *T. plicata* |
| ***β*-Thujaplicinol** |  | *T. plicata* |
| ***Trans*-2,4-Decadienol** |  | *T. orientalis* |
| **Santolinatriene** |  | *T. plicata* |
| **11 carbon compounds** | | |
| **Methyl thujuate** |  | *T. plicata* |
| **(*E*,*E*)-1,3,5-Undecatriene** |  | *T. orientalis* |
| **Cinnamyl acetate** |  | *T. occidentalis, T. plicata T. koraiensis* |
| **Methyl eugenol** |  | *T. plicata* |
| **14 carbon compounds** | | |
| **1-Tetradecanol** |  | *T.koraiensis* |
| **Benzyl benzoate** |  | *T. orientalis* |

| | | |
|---|---|---|
| **3-Methoxymethoxy-2,3-dimethylundec-1-ene** |  | *T.koraiensis* |
| **3,7,7-Trimethyl-1-penta-1,3-dienyl-2-oxabicyclo[3.2.0]hept-3-ene** |  | *T.koraiensis* |
| **15 carbon compounds** | | |
| **4-Benzyloxy-6-methoxy-*o*-toluic acid** |  | *T.koraiensis* |
| **16 carbon compounds** | | |
| **Ethyl tetradecanoate** |  | *T. orientalis* |
| **Z-11(13,14-Epoxy)tetradecen-1-ol acetate** |  | *T. koraiensis* |
| **21 carbon compounds** | | |
| **5,8,11,14-Eicosatetraenoic acid methylester** |  | |
| **4-*E*-propenyl-phenol-1-*O*-*β*-D-rutinoside** |  | *T. orientalis* |
| **23 carbon compounds** | | |
| **Pyrrolidine, 1(1,6-dioxooctadecyl)-** |  | *T.koraiensis* |
| **Prasterone** |  | *T. standishii* |



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## 4. Conclusions

This review gathered the botany, uses, biological activities and phytochemistry of *Thuja* plants which are still widely used in the folk medicine in the Far East. The review revealed that *Thuja* plants have diverse biological effects, economic and folk uses. Moreover, the review also surveyed all the different phytoconstituents classes previously reported in different *Thuja* plants. Furthermore, Thuja species can be an important source of lead compounds for the development of new drugs. Finally, it can be concluded that *Thuja* plants are good candidates for intensive research to prove their biological activities by *in vivo* and clinical trials in order to get evidence-based drugs and to discover new drugs from natural source for treatment of several ailments. Furthermore, pharmacodynamic and clinical studies are needed to understand the numerous medicinal profits of the isolated compounds that showed anti-inflammatory, antimicrobial, and anticancer activities when assessed *in vitro* and *in vivo.*

**Declarations**

**Ethics approval and consent to participate:** Not applicable.-

**Consent for publication:** All authors consented to publish the work.

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**Reham S. Darwish**: Conceptualization, Methodology, Data curation, Writing- Original draft preparation, Supervision, Validation, Writing- Reviewing and Editing.

**Eman Shawky**: Conceptualization, Methodology, Data curation, Writing- Original draft preparation, Supervision, Validation, Writing- Reviewing and Editing.

**Hala M. Hammoda**: Methodology, Writing- Original draft preparation Visualization.

**Fathallah M. Harraz**: Methodology, Writing- Original draft preparation Visualization.

**Ethics approval**: Not applicable

**Consent to participate:** All authors consented to participate in the development of the work.

**Abbreviations**

| | |
|---|---|
| **ABTS** | **2, 2'-Azino-Bis-3-Ethylbenzothiazoline-6-Sulfonic Acid** |
| **Alb** | Albumin |
| **ALP** | Alkaline phosphatase |
| **ALT** | Alanine aminotransferase |
| **AST** | Aspartate aminotransferase |
| **CCL4** | Carbon tetra chloride |
| **CFA** | Complete Freund's adjuvant |
| **COX-2** | Cyclooxygenase-2 |
| **DNA** | Deoxy ribonucleic acid |
| **DPPH** | 2,2-Diphenyl-1-picrylhydrazyl |
| **EBV-EA** | Epstein–Barr virus early antigen |
| **G** | Globulin |
| **HBV** | Hepatitis B virus |
| **HIV** | Human immunodeficiency virus |
| **HNE** | Human neutrophil elastase |
| **IBS** | Irritable bowl syndrome |
| **iNos** | Inducible nitric oxide synthase |
| **IP** | Intraperitoneal |
| **LDL** | Low density lipoproteins |
| **LPS** | Lipopolysaccharide |
| **5-LOX** | 5-lipooxygenase |
| **LPO** | Lipid peroxidation |
| **MTT** | 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide |
| **NO** | Nitric oxide |
| **OVA** | Ovalbumin |
| **PAB** | Proxidant/antioxidant balance |
| **PCOS** | polycystic ovary syndrome |
| **PGE2** | Prostaglandin E2 |
| **PLRV** | Potato leaf roll virus |
| **tMCAO** | Transient middle cerebral artery occlusion |
| **TNF-α** | Tumor necrosis factor-alpha |
| **TP** | Reduced serum total protein |
| **TPA** | 12-O-Tetradecanoylphorbol-13-acetate |
| **WMV** | Watermelon mosaic virus |



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