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# An Overview of the Bioactive Constituents, Biological Functions, and Pharmacological Impacts of *Viscum album* L.

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## ABSTRACT

The *Viscum* genus includes a variety of species found in regions such as Europe, Africa, Asia, the Americas, and Australia. Mistletoe extracts and their formulations are widely used in alternative and complementary medicine for treating a wide range of ailments. This review focuses on studies that examine the phytochemical properties of mistletoe, which vary depending on the host tree and highlights research on its therapeutic effects. Mistletoe contains an array of bioactive compounds, including lectins, viscotoxins, phenolic acids, flavonoids, alkaloids, terpenoids, and polysaccharides. These compounds contribute to mistletoe's diverse biological activities, such as anticancer, anti-inflammatory, and cardiovascular benefits, while also helping to alleviate chemotherapy side effects and enhance immune response. This review emphasizes the relationship between the host tree and the bioactive components of mistletoe, especially the lectins, viscotoxins, and phenolic compounds such as flavonoids and phenolic acids. The therapeutic properties of mistletoe are further investigated by examining the subspecies and host trees, and various patents based on mistletoe applications are also discussed. Mistletoe is introduced as a valuable medicinal plant, with high potential for further investigation in the development of targeted therapies.

**Keywords:** Anticancer, *Viscum album*, Flavonoids, Host trees, Phenolic acid, Antioxidant

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## Introduction

Parasitic angiosperms comprise over 4,700 species distributed across 277 genera, with mistletoe representing 87 genera and at least 1,670 species. Mistletoe is classified as a hemiparasite, relying on various tree and shrub hosts, and resembling an extensively developed shrub [1, 2]. Parasitic interactions, whether as a parasite or a host, are vital for maintaining ecosystem balance and promoting biological evolution [3, 4].

Mistletoe (*Viscum album* L.), an evergreen plant, depends on its host for water and nutrients but also produces its carbohydrates through photosynthesis. It is commonly found on both coniferous and deciduous trees [2]. This large hemiparasitic species is found in regions of Europe, Africa, the Americas, Australia, and Asia, exhibiting diverse habits, preferred hosts, and morphologies based on geographical location [5-7].

Pharmacological studies have identified numerous bioactive compounds in mistletoe, including lectins, viscotoxins, lignans, flavonoids, amines, and polysaccharides [8, 9]. Among these, flavonoids and phenolic acids act as potent antioxidants and are involved in the plant's biological effects, particularly in the prevention of diseases like cancer caused by oxidative stress and free radicals in the body [10-13]. Mistletoe has demonstrated therapeutic value in treating various types of cancer, including those affecting the breast [14, 15], pancreas [16], larynx [17], bladder [18], and leukemia [19]. Over time, additional bioactive effects of mistletoe have been

observed, including its impact on neurological disorders, its antiviral and antibacterial properties, anti-inflammatory actions, antiepileptic effects, and immune system stimulation [2, 11, 13, 20].

Due to its bioactive compounds and diverse health benefits, mistletoe has become the subject of numerous studies, leading to the creation of several pharmaceutical preparations, such as Iscador, Isorel, Iscucin, Lektinol, Eurixor, Helixor, Abnoba-Viscum, and recombinant lectin ML-1 [13, 21].

This review focuses on the relationship between the host tree and the bioactive constituents of mistletoe, particularly lectins, viscotoxins, flavonoids, and phenolic acids. It also outlines the potential therapeutic effects of mistletoe according to its subspecies and host tree and discusses the various patents related to mistletoe-based applications.

## Materials and Methods

The review follows the PRISMA 2020 flowchart methodology recommended by Page *et al*. [22], and the steps, along with selection criteria, are illustrated in **Figure 1**. The literature was gathered from PubMed, Scopus, Science Direct, Elsevier, Google Scholar, and Google Patents. Search terms included "*Viscum album*", "*V. coloratum*", "*V. articulatum*", "mistletoe viscotoxin", "mistletoe lectin", "mistletoe effects", "mistletoe patents", "mistletoe compounds", and "mistletoe history". Only studies in English and Romanian were considered. A total of 100 relevant studies were selected and included in this review.

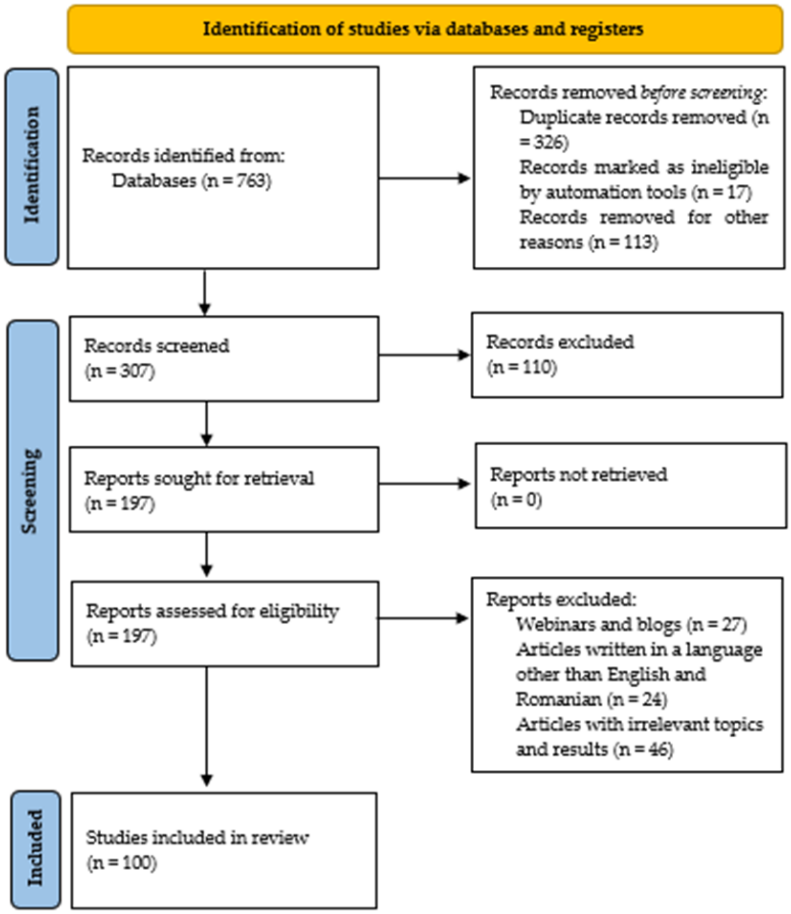


**Figure 1.** PRISMA 2020 flow diagram for the present review

## Results and Discussion

*The historical context of mistletoe*

Over 150 years ago, Charles Darwin took note of the co-evolutionary dynamics between mistletoe and the birds that interact with it, sparking significant scientific interest. In addition, the interactions between herbivorous

insects and plants, which can facilitate transitions between plant species, also gained the attention of researchers. Mistletoe is considered an ancestral host for certain butterfly species [23-25].

The number of host species affected by mistletoe plays a crucial role in determining the parasite's distribution, prevalence, and virulence. However, macroecological studies of this relationship across various regions remain scarce. Over time, human activities and environmental changes, including hybridization, have influenced the dynamics of parasitic species [1, 26, 27].

Mistletoe's remarkable therapeutic effects were later discovered, and it gradually became integrated into traditional medicine, especially species like *V. album* and Loranthus (Taxillus Chinensis (DC.) Danser) [28, 29]. The latter species, native primarily to southern and southwestern China, is known as "Sang Ji Sheng" in traditional Chinese medicine, where its stems and leaves are used to treat conditions like rheumatism, arrhythmia, hypertension, stroke, and angina pectoris [28]. *V. album*, with its longstanding use in German-speaking regions for cancer treatment, has a similar historical significance, spanning nearly a century [29].

Beyond its medicinal properties, mistletoe is also surrounded by numerous legends and beliefs that have been passed down through generations and continue to be remembered today. The plant has been thought to bring good fortune, promote healing, and attract angels. Its mystical reputation dates back to ancient times. The Celts, for instance, believed that mistletoe, created by a bolt of lightning striking a tree, possessed magical qualities. They highly valued mistletoe growing on oak trees, referring to it as the "Oak Tear," and the act of harvesting this plant was a ceremonial event. Only after the winter solstice would the mistletoe be carefully cut with a golden sickle by a priest dressed in white. Mistletoe was also seen as a symbol of femininity (Naturalis Historia, books XVI, XXIV, XXXIII).

The Greeks regarded mistletoe as a symbol of the underworld, associating it with Aeneas' key to the underworld. For the Romans, it was a fertility symbol, often worn as a crown by the goddess Diana. In Scandinavian traditions, mistletoe symbolizes peace, love, harmony, and spiritual purification. It was also believed to ward off evil spirits. In European folklore, mistletoe holds a special place. Around Christmas and New Year's, it was common for people to hang mistletoe branches on doorways and windows to attract good health and fortune. Another legend involves enemies reconciling under the mistletoe, a custom later adopted by lovers, who would exchange a kiss beneath it as a pledge of love, symbolizing happiness and fulfillment. The town of Tenbury Wells in the UK hosts an annual mistletoe festival, where a Mistletoe Queen is crowned, wearing a mistletoe crown [30].

*Botanical description*

*V. album* is a hemiparasitic shrub that grows on the branches of trees. It develops slowly, with its growth increasing yearly, marking its age. This plant can live up to 70 years [31, 32], often growing into a large bush up to one meter in diameter **(Figure 2a)**. The mistletoe attaches firmly to the host tree, sending a well-developed axis into the tree's bark, penetrating the woody tissue. This structure extends into the host tree, forming a root-like system (haustorium) that absorbs water, sugars, amino acids, and minerals, while also synthesizing its own primary and secondary metabolites [33].

The stem of mistletoe is cylindrical, thick, and dichotomously branched, ranging from 30-60 cm in width, growing thicker near the nodes, and can be easily torn. It is yellow-green. Its leaves are evergreen, arranged in opposite pairs, without stalks, and possess entire edges. The leaves have a ribbon-like appearance, thick and narrow, and display a yellow to intense green color. They also show 4-5 veins on the underside **(Figure 2b)**. The size of the leaves varies based on the host tree and harvest time. Leaves gathered in April, especially those from mistletoe on acacia trees, are larger. These leaves emit a specific scent and have a bitter-sour taste.

The optimal harvesting period for mistletoe is from November to April. Its flowers are small (2-3 mm in diameter), yellow-greenish, and dioecious, blooming in March-April **(Figure 2c)**. The fruits of mistletoe are spherical, with a translucent, glassy appearance, approximately 8 mm in diameter. They are green when young and turn white and translucent from September to October **(Figure 2d)**, but are toxic from November to March **(Figure 2f)**. Typically, the fruits, containing 1-2 seeds surrounded by a sticky, jelly-like substance, are harvested in clusters between September and December **(Figure 2e, 2g)**.

Botanists mistakenly identified *V. album* as oak mistletoe (*L. europaeus*) up until the 18th century. *V. album* belongs to the Viscaceae family, while *L. europaeus* belongs to the Loranthaceae family. Both species are part of the Santalales order [7, 34].

*L. europaeus* has young twigs that are brownish, lance-shaped leaves, and short, entire edges. It sheds its leaves in winter, unlike *V. album*, which retains its green leaves throughout the year. *L. europaeus* blooms between May

and June, with small yellow-greenish leaves, whereas *V. album* produces small clusters of yellowish fruits, ripening in October, which are dispersed by birds [35].

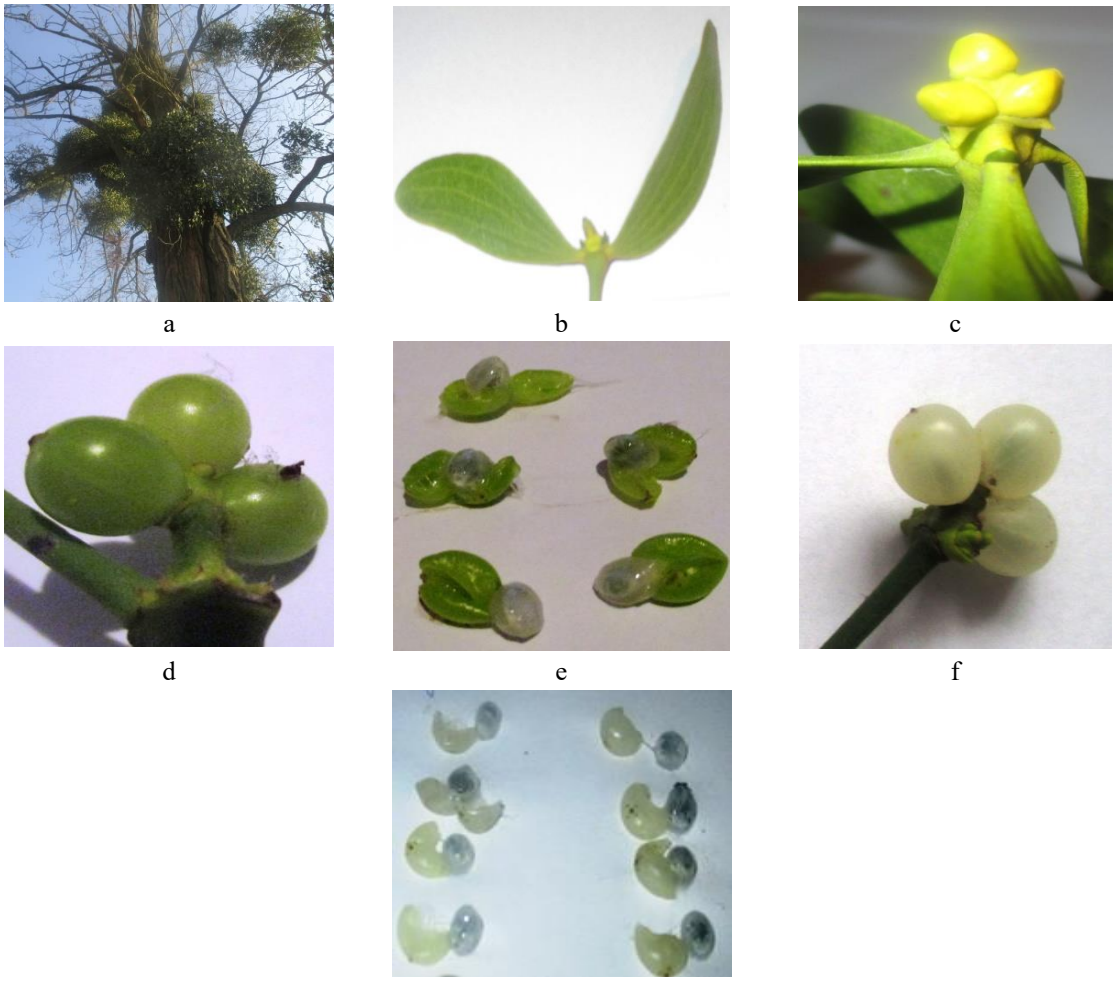

**Figure 2.** Morphology of *V. album*. a) Mistletoe (*V. album* on acacia), b) leaves of mistletoe, c) Flower of mistletoe, d) Unripe fruits of mistletoe, e) Unripe fruits with seeds, f) White fruits of mistletoe, g) White fruits with seeds

*Taxonomic classification*

The Viscaceae family includes seven genera: *Viscum*, *Phoradendron*, *Notothixos*, *Korthalsella*, *Ginalloa*, *Dendrophthora*, and *Arceuthobium*. Traditionally, *V. album*, commonly known as mistletoe, was classified under the Viscum genus within the Viscaceae family. However, recent genetic studies and the updated APG III (Angiosperm phylogeny group) system suggest that mistletoe is more appropriately placed within the Santalaceae family. The Viscum genus consists of approximately 90 species, with about two-thirds found in Africa and one-third in both Eurasia and Africa [36].

The Phoradendron genus, which includes the North American oak mistletoe (*Phoradendron serotinum*), is primarily found in North and South America, extending to Argentina. Loranthus europaeus, a species of mistletoe from the Loranthaceae family, is widespread in the Americas. The *Notothixos* genus is native to eastern Australia and its surrounding islands. *Korthalsella* species are primarily found in East Asia, Malaysia, Australia, and New Zealand. The *Ginalloa* genus contains a small number of species, located mostly in Southeast Asia. The *Dendrophthora* genus, like Phoradendron, is found in Central America. The *Arceuthobium* genus consists of around 24 species, distributed across the USA and Mexico [37].

*Host trees and geographical distribution*

The European mistletoe is classified into various subspecies, which can be distinguished based on their host trees, as these subspecies are often morphologically quite similar. Differences in leaf shape and size, fruit color, and the

specific host tree help in identifying these mistletoe species. *V. album* parasitizes over 400 host species [38]. **Table 1** provides a summary of existing literature on mistletoe species and subspecies, detailing their host trees across different continents, leaf size, and fruit color.

**Table 1.** Mistletoe species from different continents, their host trees, leaf size, and fruit color

| Mistletoe species | Spread | Host tree | Leaves | Fruits | References |
|---|---|---|---|---|---|
| | | **Europe** | | | |
| *V. album* ssp. *abietis* | Central Europe | Fir (*Abies alba*) | Up to 8 cm | Whites | [7] |
| *V. album* ssp. *album* | Europe, Southwest Asia | Apple(*Malus*), Linden (*Tilia*), Willow (*Salix vitellina*), Poplar (*Populus nigra*), Oak (*Quercus*) Hawthorn (*Crataegus monogyna*), Apricot (*Prunus armeniaca*), Acacia (*Robinia pseudoacacia)* It never appears on Beech. | Up to 5 cm | Whites | [7] |
| *V. album* ssp. *austriacum* | Central Europe, rarely in Greece | Coniferous (*Larix, Pinus, Picea*). | 4-6 cm | Yellow | [7] |
| *V. album* ssp. *Creticum* | Eastern Crete | Pine (*Pinus*) | Small | Whites | [5] |
| | | **Asia** | | | |
| *V. album* ssp. *meridianum* | Southeast Asia | Hornbeam (*Carpinus monbeigiana*), Ash (*Fraxinus*), Maple (*Acer*), Walnut(*Juglans regia*), Plum(*Prunus pseudocirasus*) Mountain ash (*Sorbus megalopa)* | 3-5 cm | Yellow | [39] |
| *V. album* ssp. *coloratum* | China | Oak (*Quercus sp*). | 2-4 cm | Red | [40-42] |
| | | **Africa** | | | |
| The red mistletoe (*V. cruciate*). | North Africa (Morocco, Libya) ends in South Africa, Rarely in South-western Spain, southern Portugal | Olive (*Olea europaea)* | Small | Red | [43] |
| *L. ferrrugineus* | Africa | Oak (*Quercus* sp.), Acacia (*Robinia pseudoacacia*) Euphorbia | 4-8 cm | Yellow | [44] |
| *L. micranthus* | Nigeria | Oak (*Quercus*), | 4-6 cm | Yellow | [45] |
| | | **Australia** | | | |
| *Amyema maidenii* ssp. *maidenii* | Australia | *Eucalyptus* | Flat | Yellow | [46] |
| *A. gibberula* ssp. *gibberula* | | | Long and cylindrical | Whites | [46] |
| *A. bifurcata* ssp. *bifurcata* | | | Flat | Red | [47] |
| *Lysiana exocarpi* ssp. *exocarpi* | | *Acacia* | 3-15 cm | Red or black | [48] |
| *L. murrayi* | | | 2.5–6 cm | Pink or red | [46] |
| *L. spathulata* | | | 3-7 cm | Red | [47] |
| *L. subfalcata* | | | 2-12 cm | Yellowish | [46] |
| | | **America** | | | |

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|---|---|---|---|---|---|
| The American Mistletoe (*Phoradendron californicum*) and the dwarf mistletoe (*Arceuthobium minutissimum* ) | North, America, California, | Oak (*Quercus* sp.), | 4-8 cm | Red | [49] |
| | South America, Argentina | Pine (*Pinus*) | 1-2 cm | Whites | |

Mistletoe thrives in diverse environments, including woodlands, hillsides, and mountainous regions, where it attaches to various host trees. It is commonly found on deciduous species such as birch, ash, maple, poplar, lime, and willow, as well as on coniferous trees like fir and pine. Additionally, it parasitizes fruit-bearing trees, including apples, pears, plums, and cherries. Species within the *Viscum* genus are distributed across temperate regions of Europe and Asia, as well as tropical and subtropical zones in Africa, Madagascar, Australia, and North and South America.

*Bioactive compounds in mistletoe*

V. album L. has long been the subject of scientific inquiry due to the bioactive nature of its constituents. Numerous metabolites have been extracted from European mistletoe, some of which are not synthesized within the plant itself but instead originate from the host tree, such as specific alkaloids [50].

A study conducted by Jäger *et al*. [33] identified key biomarkers—including arginine, pipecolic acid, lysine, dimethoxycoumarin, and sinapyl alcohol—associated with *V. album* ssp. *album* growing on three different host species: *Malus domestica*, *Quercus robur*, and *Ulmus carpinifolia* [33].

Similarly, Zhang *et al*. [51] analyzed the metabolic profile of *V. coloratum* collected from three distinct host species—*Ulmus pumila* L., *Salix babylonica*, and *Populus ussuriensis* Kom.—in two different climatic regions of China (temperate continental and warm temperate humid monsoon climates). Their findings revealed that the synthesis and accumulation of three primary flavanone-class metabolites varied depending on both the host tree and environmental conditions [51].

*Polyphenols: structure and classification*

Flavonoids, a subgroup of polyphenolic compounds, are secondary metabolites of plant origin with antioxidant properties. In mistletoe leaves, these compounds occur in either free form or as esters and glycosides. Across the plant kingdom, over 4,000 flavonoid variants have been identified [52].

Polyphenols play a crucial role in plant metabolic processes, with approximately 8,000 plant-derived polyphenolic compounds documented for their antioxidant and antitumor effects [53-58]. These organic, water-soluble compounds possess at least one aromatic ring with one or more hydroxyl groups, which contributes to their strong antioxidative capacity [52, 59-61].

Among the polyphenols found in mistletoe, phenolic acids are particularly significant, including hydroxybenzoic acids (such as gallic acid and protocatechuic acid) and hydroxycinnamic acids (such as caffeic acid, ferulic acid, and synaptic acid). Additionally, mistletoe contains various flavonoids, including flavanones (naringenin, eriodyctiol), flavones (apigenin), and flavonols (3-O-methylquercetin, myricetin, kaempferol). **Figure 3** provides an overview of the key polyphenols identified in different *V. album* subspecies and their respective host trees.

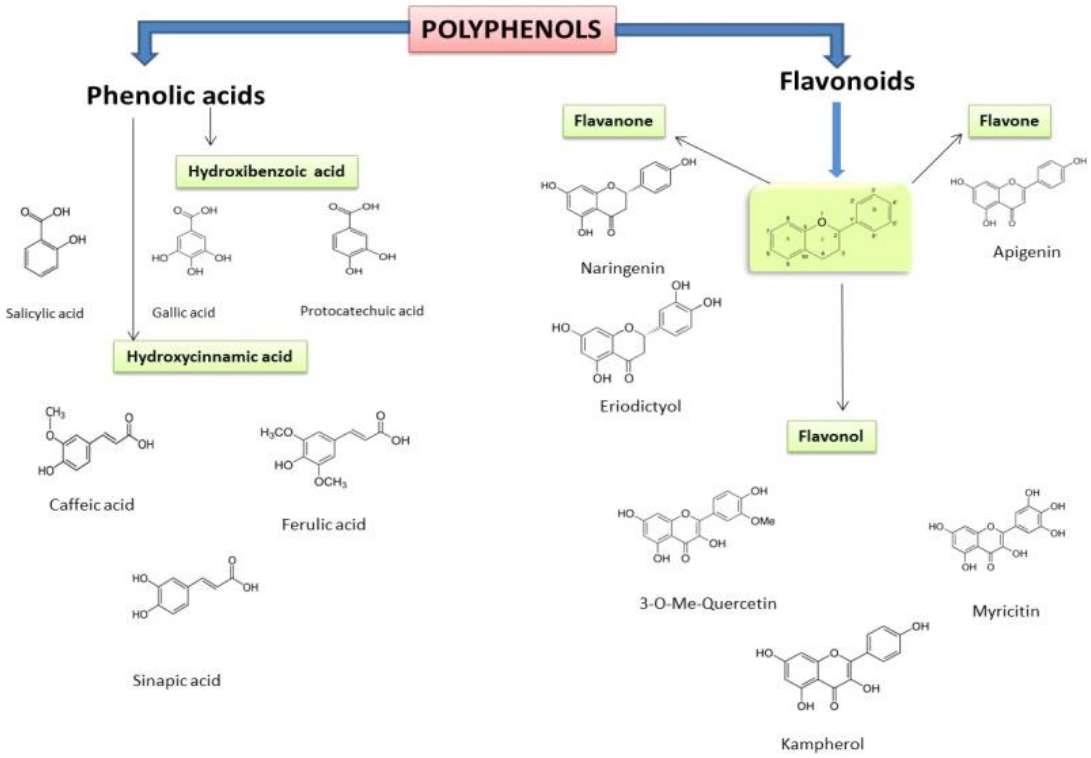


**Figure 3.** The classification and chemical structure of the main polyphenols identified in *V. album*

The concentration and profile of flavonoids in mistletoe can differ substantially based on factors such as the host tree, the stage of vegetation, and the timing of harvest [33, 41, 51, 62, 63]. **Table 2** presents the most significant flavonoids identified to date in mistletoe leaves and stems.

**Table 2.** Polyphenols identified in different subspecies mistletoe leaves or stems depending on the host tree

| Species | Host trees | The part used | Flavonoids | Phenolic acids | References |
|---|---|---|---|---|---|
| *V. album* ssp. *album* | Maple (*Acer platanoides* L.) | Leaves | **Flavone:** Apigenin<br>**Flavonol:** 3-O-Metil Quercetin<br>**Flavanones**: Naringenin | **Hydroxibenzoic acid**:<br>Gallic acid, Gentisic acid, Protocatechuic acid, p-hydrobenzoic, Salicylic acid,<br>**Cinnamic acid**:<br>Caffeic acid,Ferulic acid, p-cumaric acid,<br>Rosmarinic acid,<br>Sinapic acid | [64] |
| | | | | **Hydroxycinnamic acid:** Rosmarinic acid | [65] |
| *V. album* ssp. *album* | Jugastru (*Acer campestris*) | Leaves | **Flavonol:** Kampherol<br>Quercetin | **Hydroxibenzoic acid**:<br>Salicylic acid, p-Hydrobenzoic acid,<br>**Hydroxycinnamic acid:**<br>Caffeic acid,<br>Chlorogenic acid.<br>Ferulic acid,<br>Sinapic acid,<br>trans-Cinnamic acid. | [64] |

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| | | | | **Hydroxibenzoic acid**:<br>p-Hydrobenzoic acid<br>Salicylic acid,<br>**Hydroxycinnamic acid:**<br>Caffeic acid,<br>Chlorogenic acid.<br>Ferulic acid,<br>Sinapic acid,<br>trans-Cinnamic acid, | [65] |
| | | Stems | **Flavonol:** Kampherol | **Hydroxycinnamic acid:**<br>Rosmarinic acid,<br>trans-Cinnamic acid | [65] |
| *V. album* ssp. *album* | Silver coat (*Acer saccharinum* L.) | Leaves | **Flavanol:** Myricetin<br>**Flavonol:** 3-O-Metil Quercetin<br>Rhamnazin | | [12] |
| | | | | **Hydroxibenzoic acid**:<br>Gallic acid,<br>Gentisic acid,<br>p-Hydrobenzoic acid, Salicylic acid,<br>Vanillic acid<br>**Hydroxycinnamic acid:**<br>Caffeic acid,<br>Ferulic acid,<br>p-Coumaric acid,<br>Sinapic acid,<br>Rosmarinic acid, | [64] |
| *V. album* ssp. *album* | Hawthorn (*Crataegus monogyna*) | Leaves | **Flavanones**: Eriodictyol<br>**Flavonol**: 3-O-Metil Quercetin | **Hydroxibenzoic acid**: Protocatechuic acid,<br>Salicylic acid<br>Syringic acid,<br>**Hydroxycinnamic acid:**<br>Caffeic acid,<br>Ferulic acid<br>p-Coumaric acid, Sinapic acid, | [12] |
| *V. album* ssp. *album* | Ash (*Fraxinus excelsior* L.) | Leaves | **Flavonol**: Kampherol<br>Quercetin<br>3-O-Metil Quercetin<br>**Flavanones**: Eriodictyol | **Hydroxibenzoic acid**:<br>Protocatechuic acid,<br>p-Hydrobenzoic acid,<br>Salicylic acid,<br>Syringic acid<br>**Hydroxycinnamic acid:**<br>Caffeic acid,<br>Chlorogenic acid<br>Ferulic acid,<br>p-Coumaric acid<br>Sinapic acid,<br>trans-Cinnamic acid, | [65] |
| | | Stems | **Flavonol**: Kampherol | **Hydroxibenzoic acid**:<br>Syringic acid Protocatechuic acid<br>**Hydroxycinnamic acid:**<br>Caffeic acid,<br>Chlorogenic acid,<br>Ferulic acid,<br>Rosmarinic acid,<br>Sinapic acid,<br>trans-Cinnamic acid, | [65] |

| | | | | | |
|---|---|---|---|---|---|
| *V. album* ssp. *album* | Ash (*Fraxinus pensylvanica* Marsh*)* | Leaves | **Flavanones**: Eriodictyol Naringenin **Flavonol**: 3-O-Metil Quercetin Sakuratin Rhamnazin | **Hydroxibenzoic acid**: Protocatechuic acid, Salicylic acid, Syringic acid, **Hydroxycinnamic acid:** Caffeic acid, Ferulic acid, Sinapic acid | [64] |
| | | | **Flavanones**: Eriodictyol Naringenin **Flavonol**: Quercetin 3-O-Metil Quercetin Sakuratin Rhamnazin | | [12] |
| *V. album* ssp. *album* | Apple (*Malus Domestica* Borkh) | Leaves | **Flavonol**: Quercetin 3-O-Metil Quercetin Myricetin, Sakuratin Isorhamnetin Rhamnetin Rhamnazin **Flavanones**: Naringenin Eriodictyol | | [64] |
| | | | **Flavonol**: Quercetin | | [65] |
| | | | **Flavonol**: Quercetin 3-O-Metil Quercetin Isorhamnetin Sakuratin Rhamnazin **Flavanones**: Naringenin | | [12] |
| | | | | **Hydroxibenzoic acid**: Gallic acid Vanillic acid, Gentisic acid, Protocatechuic acid, Veratric acid **Hydroxycinnamic acid:** p-Coumaric acid | [64] |
| | | | | **Hydroxibenzoic acid**: p-hydroxybenzoic acid, Protocatechuic acid, Salicylic acid, **Hydroxycinnamic acid:** Caffeic acid, Ferulic acid, Sinapic acid, Rosmarinic acid, | [65] |
| *V. album* ssp. *album* | Apple (*Malus Domestica* Borkh) | Stems | | **Hydroxibenzoic acid**: Syringic acid, **Hydroxycinnamic acid:** Caffeic acid, Ferulicacid, Rosmarinic acid Sinapic acid, | [65] |

| | | | | | |
|---|---|---|---|---|---|
| *V. album* ssp. *album* | Poplar (*Populus nigra* L.*)* | Leaves | **Flavonol**: Quercetin<br>3-O-Metil Quercetin<br>Isorhamnetin<br>Sakuratin,<br>Rhamnazin<br>**Flavanones**: Naringenin<br>**Flavone:** Apigenin | | [65] |
| | | | | **Hydroxibenzoic acid**:<br>Gallic acid,<br>Gentisic acid,<br>Protocatechuic acid,<br>**Hydroxycinnamic acid:**<br>p–Coumaric acid | [64] |
| | | | **Flavonol**: Quercetin | **Hydroxibenzoic acid**:<br>Salicylic acid,<br>Protocatechuic acid,<br>p-hydrobenzoic acid,<br>**Hydroxycinnamic acid:**<br>Ferulic acid,<br>Rosmarinic acid,<br>Sinapic acid, | [65] |
| | | | **Flavanones**: Naringenin<br>Eriodictyol<br>Sakuranetin<br>**Flavonol**: Quercetin<br>3-O-Metil Quercetin<br>Isorhamnetin<br>Rhamnazin | **Hydroxibenzoic acid**:<br>p-hydrobenzoic acid, Salicylic acid,<br>Syringic acid<br>Vanillic acid<br>**Hydroxycinnamic acid:**<br>Caffeic acid,<br>Ferulic acid, | [12] |
| *V. album* ssp. *album* | Poplar (*Populus nigra* L.*)* | Stems | | **Hydroxibenzoic acid**:<br>Protocatechuic acid, Salicylic acid<br>**Hydroxycinnamic acid:**<br>Caffeic acid,<br>Ferulic acid, | [65] |
| *V. album* ssp. *album* | Acacia (*Robinia pseudoacacia*) | Leaves | **Flavonol**: Quercetin<br>Kaempferol | **Hydroxibenzoic acid**:<br>Gallic acid,<br>**Hydroxycinnamic acid:**<br>Ferulic acid,<br>Sinapic acid, | [65] |
| | | Stems | **Flavonol**: Kampherol | **Hydroxibenzoic acid**:<br>Protocatechuic acid, | [65] |
| *V. album* ssp. *album* | Mountain ash *(Sorbus aucuparia* L.) | Leaves | **Flavonol**: Quercetin<br>3-O-Metil Quercetin<br>Isorhamnetin<br>Myricetin,<br>Sakuratin<br>Rhamnazin<br>**Flavanones**: Naringenin | | [12] |

| | | | | | |
|---|---|---|---|---|---|
| | | | | **Hydroxibenzoic acid**:<br>Gallic acid,<br>Gentisic acid<br>Protocatechuic acid,<br>p –hydroxybenzoic acid<br>Salicylic acid,<br>Syringic acid<br>Vanillic acid,<br>Veratric acid,<br>**Hydroxycinnamic acid:**<br>Caffeic acid,<br>Ferulic acid,<br>p-Coumaric acid<br>Sinapic acid, | [64] |
| | | | **Flavanones**: Naringenin<br>Eriodictyol<br>**Flavonol**: Quercetin<br>3-O-Metil Quercetin<br>Isorhamnetin<br>Sakuratin<br>Rhamnazin | | [12] |
| *V. album* ssp. *album* | Linden (*Tilia cordata* Mill) | Leaves | **Flavanones**: Naringenin<br>Eriodictyol<br>**Flavonol**: 3-O-Metil<br>Quercetin<br>Isorhamnetin<br>Rhamnazin<br>**Flavones**: Luteolin | **Hydroxibenzoic acid**:<br>Gallic acid, Protocatechuic acid,<br>p-hydrobenzoic acid, Salicylic acid<br>Syringic acid,<br>Vanillic acid<br>**Hydroxycinnamic acid:**<br>Caffeic acid,<br>Ferulic acid,<br>p-Coumaric acid,<br>Sinapic acid. | [12] |
| *V. album* ssp. *abietis* | Fir (*Abietis alba* Mill) | Leaves | **Flavanones**: Naringenin<br>**Flavonol**: 3-O-Metil<br>Quercetin<br>Rhamnazin<br>Rhamnetin<br>**Flavone:** Apigenin | **Hydroxibenzoic acid**:<br>Salicylic acid,<br>Protocatechuic acid,<br>4-hydrobenzoic acid, Vanillic acid,<br>**Hydroxycinnamic acid:**<br>Caffeic acid,<br>Ferulic acid,<br>p-Coumaric acid,<br>Sinapic acid. | [66] |
| *V. album* ssp. *austriacum* | Pine (*Pinus sylvestris* L.) | Leaves | **Flavanones**: Naringenin<br>Eriodictyol<br>Sakuranetin<br>**Flavonol:** Quercetin<br>3-O-Metil Quercetin<br>Isorhamnetin<br>Myricetin,<br>Rhamnazin<br>Rhamnetin,<br>Kampherol | | [12] |
| | | Leaves<br>fruits<br>seeds | | **Hydroxibenzoic acid**:<br>Protocatechuic acid,<br>Salicylic acid,<br>4-hydroxybenzoic acid, Vanillic acid,<br>**Hydroxycinnamic acid:**<br>Caffeic acid,<br>Ferulic acid, | [67] |

| | | | | |
|---|---|---|---|---|
| | | | p-Coumaric acid, Sinapic acid | |
| *V. album* ssp. *austriacum* | Guava (*Psidium guajava*) | Leaves | **Flavanones**: Naringenin | [68] |
| *V. album* ssp. *coloratum* | Oak (*Quercus crispula)* | Leaves stems | **Flavanones:** Eriodictyol | [19] |
| | Elm (*Ulmus pumila* L.) *Willow* (*Salix babylonica* L.) Poplar (*Populus ussuriensis* Kom) | Leaves | **Flavanones:** Eriodictyol | [51] |

*V. album* is a medicinal plant known for its diverse range of phytochemicals. Among its bioactive compounds, quercetin stands out due to its strong antioxidant properties and significant antitumor activity. This flavonol has been identified in multiple subspecies, including *V. album* ssp. *album*, *V. album* ssp. *abietis*, *V. album* ssp. *austriacum*, and *V. album* ssp. *coloratum* [12, 63]. The flavanones Naringenin and Eriodictyol are present in both *V. album* ssp. *album* and *V. album* ssp. *austriacum* [12, 51, 65]. Additionally, caffeic acid, a hydroxycinnamic acid, has been found in various *V. album* subspecies [12, 67].

*Lectins and viscotoxins*

V. album contains a range of bioactive molecules, from small compounds like phenolic acids and flavonoids to larger proteins such as lectins and viscotoxins [69].

Lectins are proteins or glycoproteins that can selectively reversibly bind to carbohydrates without modifying their structure. They are classified based on their sugar-binding specificity—monospecific lectins interact with a single sugar (e.g., glucose or galactose), while polyspecific lectins can bind multiple sugars [24, 70]. Three distinct lectins, designated ML-1, ML-2, and ML-3 (ML for Mistellectin), are found in mistletoe, differing in molecular weight and carbohydrate affinity [71-73].

ML-1 consists of two polypeptide chains connected by a disulfide bridge [74]. The A chain comprises three domains with molecular weights of 29 kDa, 27 kDa, and 25 kDa, respectively, and exhibits RNA N-glycosidase activity [75]. The B chain, made up of two domains with molecular weights of 32 kDa and 25 kDa, specifically binds to D-galactose [24, 76, 77]. The B chain's carbohydrate-binding ability is associated with lectins' cytotoxic action, particularly their role in tumor cell targeting. When lectins interact with receptors on cancer cell surfaces, they induce apoptosis, disrupt the cell cycle, and inhibit angiogenesis, leading to tumor suppression [78]. Both chains of ML-1 contribute to its cytotoxic properties [24]. ML-2 binds to D-galactose/N-acetyl-D-galactosamine, while ML-3 is specific to N-acetyl-D-galactosamine [72, 79]. Host tree species influence the composition of lectins in mistletoe, with ML-1 being prevalent in *V. album* growing on oak (*Quercus* spp.) and poplar (*Populus nigra*), while ML-3 is dominant in mistletoe found on conifers like fir (*Abies alba*) and pine (*Pinus sylvestris*) [71].

Viscotoxins are polypeptides with a high cysteine content, consisting of approximately 46 amino acids and three to four disulfide bonds, with molecular weights around 5 kDa [80]. Six structurally distinct viscotoxin isomers—A1, A2, A3, B, B2, C1, and 1-PS—have been identified in *V. album* [72]. These peptides exhibit cytotoxic effects on tumor cells and also play a role in immune modulation [15]. The concentration and composition of lectins and viscotoxins in mistletoe are influenced by the host tree species.

In *V. album* ssp. *album*, viscotoxins A2 and A3 are the predominant types, with 1-PS absent. *V. album* ssp. *austriacum*, on the other hand, contains mostly viscotoxin 1-PS, while A2 and A3 appear in smaller amounts. *V. album* ssp. *abietis* is characterized by the presence of all viscotoxins, with A3 being the most abundant and A2 not detected [81].

*Biological activities and medicinal potential*

Mistletoe has been shown to exhibit a wide range of biological activities, including anticancer effects, apoptosis induction, antiviral and antibacterial properties, and immune system modulation [2, 11, 20, 82, 83].

Both in vitro and in vivo studies have demonstrated the pharmacological effects of V. album. **Table 3** provides an overview of the medicinal activities associated with various mistletoe subspecies (*V. album* ssp., *Viscum coloratum*, and *Viscum articulatum*) about their respective host trees.

**Table 3.** The pharmacological activity of *V. album* ssp., *Viscum coloratum*, and *Viscum articulatum*

| Species/Host tree | Biological activity | Bioactive compounds | Sample type | Type of experiment | References |
|---|---|---|---|---|---|
| *Viscum album/* Apple (*Malus domestica*) | Anticancer | Lectins | Aqueous Extract + triterpene extract | The human osteosarcoma cell lines 143B and Saos-2 | [84] |
| *V. album* ssp. *coloratum/* Poplar (*Populus nigra*) | | Lectins | Aqueous extract | *In vitro* and *vivo*-on the growth of melanoma cells in mice. | [85] |
| *V. album* ssp. *coloratum/*ns* | | | | | |
| *Viscum album/* Apple (*Malus domestica*), Oak (*Quercus* ssp) Poplar (*Populus nigra*) Acacia (*Robinia pseudo-acacia)* | | Viscotoxins | Aqueous extract | Randomized clinical trial in patients with locally advanced or metastatic pancreatic cancer | [86] |
| | | | | Patient with differentiated squamous cell carcinoma | [87] |
| *V. album* L. / Citrus | Antihypertension | | Aqueous extract | Male rats-salt-induced hypertension | [88] |
| *V. album* L. /ns* | | Flavonoids | Ethanolic extract | Wistar rats of both sexes | [89] |
| *V. album* /ns* | | | Ethanolic extract | Hypertensive patient | [90] |
| *V. articulatum/ Cordia macleodi* | | Acid oleanolic | Methanolic extract | Male Wistar rats- dexamethasone-induced hypertension | [91] |
| *V. album/ Kola acuminate* tree | Antidiabetic | | Aqueous extract | Alloxanized male Wistar rats | [92] |
| | | | Aqueous extract | STZ-diabetic male Wistar rats | [93] |
| *V. album* | Antivirals | | Aqueous extract | Human parainfluenza virus type 2 (HPIV-2) growth in Vero cells | [83] |
| *V. album* ssp. *abietis* | Antibacterial | | n-hexane extract | In vitro (*Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, and *Proteus vulgaris)* | [94] |
| *V. album*/ns* | | | Extracts (1% HCl, ethanol, acetone, and 5% acetic acid) | In vitro *(Escherichia coli*, *Pseudomonas aeruginosa*, *Staphyloccocus aureus*, and *Klebsiella aerogenes)* | [95] |
| *V. album/* cocoa and cola trees | | | Methanolic extract | In vitro *(Aspergillus niger*, *Fusarium exosporium*, *Penicillium oxalium*, and *Microsporum canis)* | [96] |
| *V. album* L. ssp. *album/Armeniaca vulgaris* Lam. *(apricot); V. album* ssp. *abietis /Abies bornmülleriana* Mattf. *(fir); V. album* ssp. *austriacum/ Pinus nigra* (pine) | | | Ethanolic extract | In vitro (*Mycobacterium tuberculosis* H37Ra) | [97] |

| | | | | | |
|---|---|---|---|---|---|
| *V. album L.* ssp. *album/Armeniaca vulgaris* Lam. *(apricot); V. album* ssp. *abietis /Abies bornmülleriana* Mattf. *(fir), ; V. album* ssp. *austriacum/ Pinus nigra (pine)* | Antioxidant | Flavonoids | Ethanolic and aqueous extracts | STZ-induced diabetic rats/ (GSH and MDA in liver, kidney, and heart tissues) | [98] |
| *V. album/ Acer campestre; Fraxinus excelsio; Populus nigra; Malus domestica; Robinia pseudoacacia* | | | Aqueous extract | In vitro (DPPH, ORAC, and TEAC assay) | [65] |
| *V. coloratum/*ns* | | | Ethanolic extract | In vitro (Hydroxyl Radical Scavenging Assay; Superoxide Anion Radical Scavenging Assay) | [99] |
| *V. album* L./ Citrus | Antiepileptic | | Aqueous extract | Swiss albino mice and Wistar albino rats (MES-induced seizure; INH-induced convulsions) | [100] |

*ns- not specified; MDA- malondialdehyde; MES- Maximum electroshock; INH-Isoniazid;

*Utilization of mistletoe extract in medicine, cosmetics, and functional products*

Patents issued from 2011 to 2021 related to mistletoe extract (*V. album*) and its applications in medical treatments, cosmetic formulations, and functional products are outlined in **Table 4**.

**Table 4.** List of patents published from on *V. album* (2011-2021)

| Patent no. | Publication date | Title | Purpose |
|---|---|---|---|
| KR20110136539A | 2011-12-21 | Korean mistletoe extracts have antiobesity and hepatic steatosis protection activity | - Reduces obesity by preventing fat accumulation in the epididymal region and liver. |
| KR20140115730A | 2014-10-31 | Shampoo composition for preventing hair loss and promoting hair growth comprising extracts of *V. album* and *Chamaecyparis obtusa* | -Helps combat hair loss. - Demonstrates enhanced antioxidant properties. |
| CN104707097A | 2015-06-17 | Pharmaceutical composition *Viscum* and astragali radix powder and use thereof in the preparation of medicines for blocking precancerous lesions of the liver and treating liver cancer or viral hepatitis | - Lowers the incidence of GGT foci in early-stage precancerous lesions. - Exhibits hydroxyl radical scavenging activity, preventing the initiation and progression of liver precancerous lesions. |
| KR20160017903A | 2016-02-17 | *V. album* extract containing a sweet jelly preparation method and sweet jelly prepared by the method | - Strengthens the immune system. - Suggested for use in immunotherapy and cancer prevention. |
| KR20170053544A | 2017-05-16 | Cosmetic composition for moisturizing and anti-aging containing extracts of *Viscum album*, *Chamaecyparis obtusa*, *Quercus Robur,* and *Camellia japonica* Linne | - Acts as a skin astringent. - Minimizes cytotoxic effects triggered by environmental stressors. - Regulates inflammatory mediator expression. |
| CN106692909A | 2017-05-24 | *Pyrus pyrifolia* tree *Viscum coloratum* grease with lung-clearing and phlegm-eliminating effects | - Aids in lung detoxification and phlegm clearance. |

| | | | |
|---|---|---|---|
| CN108295100A | 2018-07-20 | Application of the *V. album* extract in preparing drugs for rheumatoid arthritis | - Inhibits inflammatory mediator synthesis by targeting NF-κB signaling pathways.<br>-Reduces inflammation in the synovial membrane.<br>- Protects against joint and bone degradation. |
| KR102007096B1 | 2019-08-02 | Composition for preventing or treating hearing loss comprising *Viscum ovalifolium* extracts | - Helps prevent hearing impairment. |
| KR20200109068A | 2020-09-22 | A soap comprising *V. album* fermentation product and method for preparing the same | - Rapidly penetrates the skin.<br>- Soothes skin inflammation.<br>- Provides an exfoliating effect, eliminating harmful substances from the skin's surface.<br>- Delays skin aging due to the antioxidant components in V. album. |
| BR102020003563A2 | 2021-09-08 | Topical pharmaceutical composition with antitumor activity containing *V. album* | - Exhibits antitumor properties. |

GGT gamma-glutamyltranspeptidase, GPT glutamic—pyruvic transaminase, NF-κB Nuclear factor-κB

## Conclusion

Mistletoe demonstrates significant therapeutic potential for various health conditions. Its unique phytochemical makeup and corresponding biological effects are influenced by the host tree from which it grows. Among its key bioactive compounds, lectins and viscotoxins play a crucial role in its anticancer properties. Additionally, mistletoe contains an array of beneficial secondary metabolites, including flavonoids and phenolic acids, which are widely distributed in plants. There is strong evidence suggesting that the consumption of these compounds can contribute to a reduction in the incidence of cancer, cardiovascular diseases, and diabetes. Further research into the interactions between mistletoe polyphenols and lectins is essential to uncover new therapeutic applications of mistletoe-based treatments.

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