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ON OVERVIEW OF BIOACTIVE COMPOUNDS, BIOLOGICAL AND PHARMACOLOGICAL EFFECTS OF MISTLETOE (*VISCUM ALBUM* L)

Eva Kleszken[1#], Adrian Vasile Timar[2], Adriana Ramona Memete[1#], Florina Miere (Groza)[3], Simona Ioana Vicas[2]*

1. ***Doctoral School of Biomedical Science, University of Oradea, Oradea, Romania.***
2. ***Department of Food Engineering, University of Oradea, Oradea, Romania.***
3. ***Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania.***

#These Authors Contributed equally to this work

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ABSTRACT

The genus Viscum includes many species that are mainly distributed in Europe, Africa, Asia, America, and Australia. Viscum extracts or their various preparations are widely used as complementary and alternative medicines in the treatment of various ailments. In the present review, articles related to the phytochemical composition of mistletoe were selected, depending on the host tree on which it grows, as well as articles in which its beneficial effects were highlighted. Viscum contains different active ingredients, including lectins, viscotoxins along with phenolic acids, flavonoids, alkaloids, terpenoids, and polysaccharides. Based on its composition, mistletoe extract is associated with multiple bioactivities, including anticancer, anti-inflammatory, and cardiovascular disease, attenuating the side effects of chemotherapy and enhancing immunity. The purpose of this review was to highlight the link between the host tree and the bioactive components of mistletoe such as lectin and viscotoxin, with a focus on phenolic compounds such as flavonoids and phenolic acids. The potential therapeutic effects of mistletoe are summarized by subspecies and host trees. Numerous mistletoe-based patents with various applications have been developed and presented in this review. Mistletoe is a medicinal plant with great biological potential that is worth exploring for various targeted treatments.

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Introduction

Parasitic angiosperms are over 4,700 species of 277 genera, of which 87 genera and at least 1,670 species belong to the mistletoe which is considered hemiparasites that grow on the host branches of various species of shrubs and trees looking like a highly developed shrub [1, 2]. Living organisms are involved in parasitic relationships, either as parasites or as hosts, these interactions having an essential role in the proper functioning of the biosphere and the process of biological evolution [3, 4].
Mistletoe (*Viscum album* L.) is an evergreen plant that depends on the host tree for some nutrients and water, while it produces carbohydrates in a process of photosynthesis, normally found growing on a variety of trees, both deciduous and coniferous trees [2]. Mistletoe (*V. album*), is a large hemiparasitic species found in northern, central, and southern Europe, Africa, America, Australia, and Asia, accompanied by a wide variety of habits, host preferences, morphologies, and development patterns depending on the geographical distribution [5-7].
Several chemical and pharmacological studies have identified various types of compounds in mistletoe, such as lectins, viscotoxins, lignans, amines, flavonoids, and polysaccharides [8, 9]. Among them, flavonoids and phenolic acids are natural antioxidants involved in the biological activity of the plant and used in the prevention of diseases such as cancer, caused by oxidative stress induced by free radicals in the body [10-13]. Cancer therapy is one of the most important uses of mistletoe, proving to have beneficial effects on various types of cancer such as breast [14, 15], pancreatic [16], laryngeal [17] bladder [18], or leukemia [19]. Over time, other bioactive activities of mistletoe have been reported, such as those related to neurological disorders, antiviral, antibacterial, anti-inflammatory, antiepileptic, or immunostimulatory activities [2, 11, 13, 20].

Corresponding Author: Simona Ioana Vicas; Department of Food Engineering, University of Oradea, Oradea, Romania. E-mail: svicas@uoradea.ro.

Due to its bioactive compounds and its beneficial effects on the human body, mistletoe has become more and more studied, developing various pharmaceutical formulations (Iscador, Isorel, Iscucin, Lektinol, Eurixor, Helixor, Abnoba-Viscum and recombinant lectin ML -1) [13, 21].

This review aimed to highlight the link between the host tree and the bioactive components of mistletoe such as lectin and viscotoxin, with a focus on phenolic compounds such as flavonoids and phenolic acids. The potential therapeutic effects of mistletoe are summarized by subspecies and host tree. Numerous mistletoe-based patents with various applications have been developed and presented in this review.

Materials and Methods

This review was performed using the PRISMA 2020 flow chart based on the suggestion of Page *et al*., 2021 [22]. The steps and selection criteria, followed by the number of studies used for our review, are shown in **Figure 1**. Databases such as PubMed, Scopus, Science Direct, Elsevier, Google Scholar, Google Patents have been accessed to search the literature. The keywords of the medical subject titles included in the search were: ″*Viscum album*″, ″*V. coloratum*″, ″*V. articulatum*″, ″mistletoe viscotoxin″, ″mistletoe lectin″, ″mistletoe effects″, ″mistletoe patents″, ″mistletoe compounds″, ″mistletoe history″, etc. All the information systematized in the tables was obtained from research articles. Studies published in languages other than English and Romanian were excluded. A total of 100 studies were selected and included in this review.

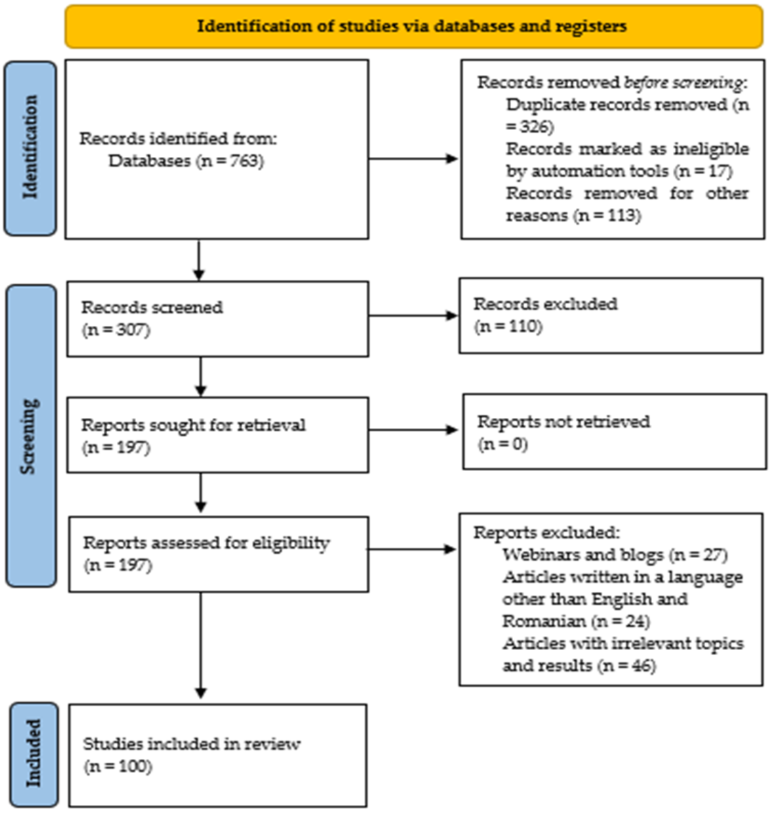

Figure 1. PRISMA 2020 flow diagram for the present review

The Historical Approach of Mistletoe

Given the co-evolutionary history between plants and the organisms that use them, over 150 years ago, the co-adaptation between mistletoe and birds caught the attention of Charles Darwin, stimulating considerable scientific research. Equally important for other researchers was the understanding of the interactions between herbivorous insects and plants, which can make the transition between plant taxa. The mistletoe is also considered the ancestral host of butterflies [23-25].

The number of host species infected with mistletoe is critical in that it influences the overall distribution of the parasite, its prevalence, and virulence. Therefore, macroecological analyzes of this feature related to the history of mistletoe life are missing for many regions, and with the evolution of mankind, geographical and environmental changes have influenced the parasitic species, through hybridization processes [1, 26, 27].

Mistletoe was later discovered for its miraculous effects, and traditional medicine spread it over time to many parts of the world, in particular, *V. album* L. and *Loranthus* (*Taxillus Chinensis* (DC.) Danser) [28, 29]. The latter belongs to the family *Loranthaceae*, distributed mainly in southern and southwestern China, is known as "Sang Ji Sheng", and its leaves and stems have a long history in traditional Chinese medicine, is used to treat rheumatism, arrhythmia, angina pectoris, hypertension, stroke [28]. *V. album* L. also has a long traditional history of about 100 years, used in German-speaking countries in cancer treatment therapy [29].

In addition to the fact that mistletoe was used for medicinal purposes, there are also several legends gathered from different regions of the world, related to this plant, legends that our ancestors respected and mentioned and which are still remembered today.

Because of its beliefs to bring good luck, to heal illnesses, and to attract angels, mistletoe is known since old times. It is said to bring health and prosperity. It had a very important part in the Celtic rituals. They believed that mistletoe was created by a bolt of lightning that hit a tree giving him magical powers. The Celts believed that a very precious mistletoe was grown by the oak, also known as the „Oak Tear", and poaching this kind of mistletoe was always a moment of ceremonial cutting. Thus the mistletoe was cut only after the winter solstice with the Golden Sickle, by a white dressed priest. Mistletoe was also considered the symbol of femininity (*Naturalis Historia*, books XVI, XXIV, XXXIII).

The Greeks considered mistletoe from the underworld, believing that a branch of mistletoe was the key Aeneas that opened the underworld. The Romans put on Goddess Diana's head a crown of mistletoe, as a symbol of fertility. In the Scandinavian legends, mistletoe was something very special symbolizing peace, love, harmony, spiritual cleansing, and throwing away bad spirits.

In European mythology, mistletoe has a unique place. Around Christmas and New Year's Eve, people put mistletoe twigs on doors and windows to bring luck and health. Other legends talk about a peculiar custom that if two enemies were met under a tree that grew mistletoe, they come to terms on behalf of the mistletoe. Later this custom was taken by the lovers, who kissing under the mistletoe felt like a love pledge, bringing happiness and fulfillment. In the town Tenbury Wells, from the UK, a mistletoe festival is held every year and a mistletoe Queen is chosen, bearing a crown of mistletoe [30].

Botanical Characterization

V. album is a hemiparasite shrub species that grows on branches and twigs of trees. It is a plant with slow development, usually being a nod to the blooming season. Every year mistletoe develops more and more branches, so its growth tells us its age. Mistletoe can live up to 70 years [31, 32] It looks like a very big bush, having a diameter of up to one meter **(Figure 2a)**. The mistletoe is stuck on the host tree. It looks like a vertical, well-developed ax that enters the bark of the host tree, pervading its woody tissue. This network continues to grow, creating a root system (haustorium) that absorbs water, sugars, amino acids, and minerals from host trees, being able to biosynthesize their own primary and secondary metabolites [33]. Its stem is cylindrical, thick, dichotomic ramification, wide off 30 - 60 cm, thicker towards the nods, where it can be torn easily, having a yellow-greenish color. Leaves are green all year round, have no stalk, full edges, being seen like a ribbon, thick, skinny, bearing no wintergreen shrubs, having a yellow to intense green color, and are set in opposite pairs. On its lower part, one can notice 4 - 5 veins **(Figure 2b)**. The size of the mistletoe leaves varies according to the host tree and the harvesting time.

The leaves harvested in April are larger, especially in the case of mistletoe leaves hosted by acacia. Leaves have a specific smell and a soft bitter sour taste. The optimal period to harvest is November to April, as the flowers are small (2-3 mm in diameter), yellow-greenish color, dioice, can be seen on top of young twigs. It blooms in March- April **(Figure 2c)**. The fruits are spherical, having a glassy look, with a diameter of approximately 8 mm, green at the base. Between September - October, **(Figure 2d)** the fruits are white translucent, while in November- March they are toxic (**Figure 2f**). As a rule, the fruits are gathered thrisome during September-December **(Figure 2e)**, containing 1-2 seeds covered by a jelly, sticky liquid **(Figure 2g)**.

Up to the 18th-century botanists confused white mistletoe (*V. album*) with oak mistletoe (*L. europaeus*). The *V. album* belongs to the Viscaceae family, while *L. europaeus* belongs to the Loranthaceae family. The link between them is of taxonomic order and both belong to the Santalales order [7, 34].

The *L. europaeus* has younger twigs, brownish color, lance-like leaves, short stark and whole edge. It loses its leaves during wintertime, while white mistletoe keeps its leaves the entire year-round, being always green. The last leaves are small, all yellow-greenish, like a spike shape, blooming around May - June. The fruits of *V. album* are small, yellowish, in the form of a small cluster shape. Its fruit is ripe in October, usually has a seed, that is spread by birds [35].

a

b

c

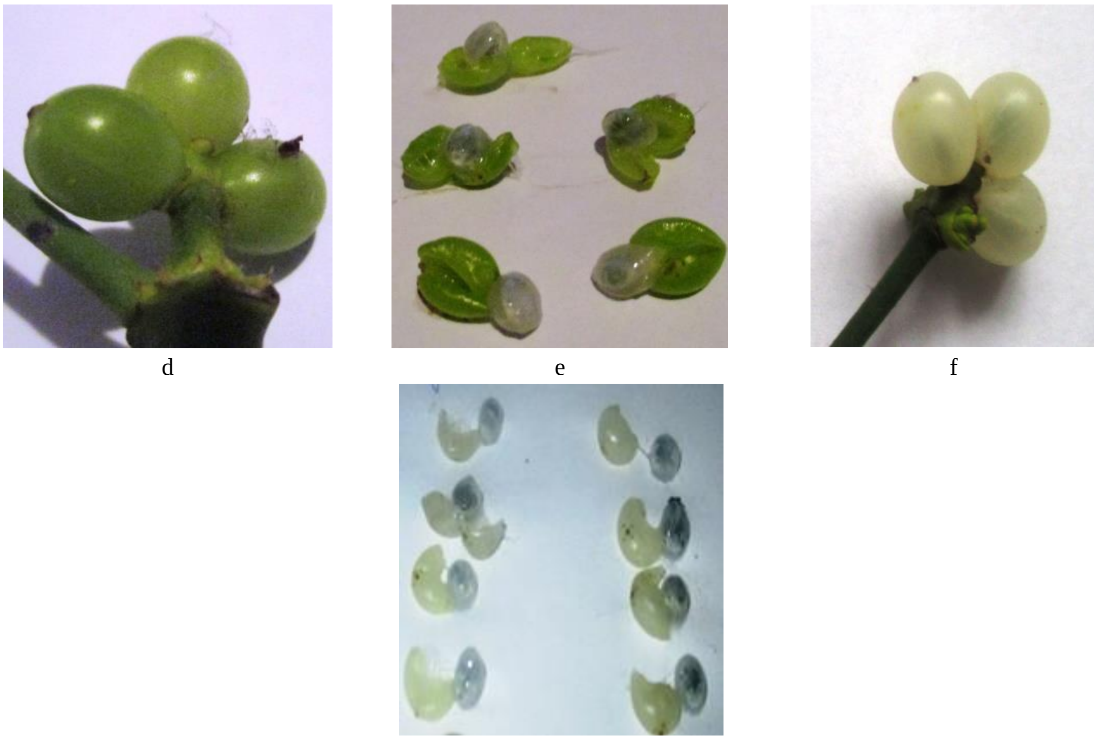

Figure 2. Morphology of *V. album*. a) Mistletoe (V. albumon acacia), b) leaves of mistletoe, c) Flower of mistletoe, d) Unripe fruits of mistletoe, e) Unripe fruits with seeds, f) White fruits of mistletoe, g) White fruits with seeds

Taxonomy

The Viscaceae family has seven genres: *Viscum*, *Phoradendron*, *Notothixos*, *Korthalsella*, *Ginalloa*, *Dendrophthora,* and *Arceuthobium*. Regarding the scientific rating the mistletoe (*V. album* L) belongs to the *Viscum* genus, part of the Viscaceae family, but genetic research, new approach in APG (Angiosperm Phylogeny Group) III system, show that mistletoe belongs to the Santalaceae family. The genus *Viscum* comprises about 90 species, of which two-thirds are native to Africa and one-third to Eurasia and Africa [36].

The *Phoradedron* mistletoe is set in a part of Northern America (the North American Oak mistletoe, *Phoradendron serotinum*) and South America, Argentina. *Loranthus europaeus* belongs to the family Loranthaceae, which is widespread in America. Genera *Notothixus* mistletoe is found in the East of Australia and the Island. The *Korthalsella* kind is seen in East Asia, Malaysia, Australia, New Zealand. The genus *Ginalloa* includes only a few species that can be found in the South East of Asia. The mistletoe belonging to the genus *Dendrophthora* has a distribution similar to that of the genus *Phoradendron*, with an area in Central America. Genera *Arceuthobium* has approximately 24 species, being found in the USA and Mexico [37].

Host Trees and Geographical Area

The European mistletoe has several accepted subspecies that can be easily differentiated according to the host tree, as they are morphologically very similar. Mistletoe species differ in leaves' shape and size, their fruits color, and host tree. *V. album* species parasitize over 400 host trees [38]. **Table 1** summarizes literature data on mistletoe species/subspecies, their host trees on 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, South - vest 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) end 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 – 6cm	pink or red	[46]
L. spathulata			3-7 cm	red	[47]
L. subfalcata			2-12 cm	yellowish	[46]
		America			
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 can be seen in forests, on hills, and in the mountains, on various host trees, such as birch, ash, maple, poplar, lime, willow, or on conifers: fir, pine. The mistletoe also parasitizes fruit trees such as apples, pears, plums, cherries. The genus *Viscum* included species seen in the temperate areas of Europe, in Asia, in the tropical and subtropical parts of Africa, in Madagascar, in Australia, and the north and south of America

Mistletoe Bioactive Compounds

The mistletoe species (*V. album* L) has presented and still has a high interest in researching the bioactivity of its compounds. Many types of metabolites have been isolated from European mistletoe, some of which are not synthesized by mistletoe, but are obtained from the host tree, for example, some alkaloids [50].

Jäger *et al*., 2021 identified the specific biomarkers (arginine, pipecolic acid or lysine, dimethoxycoumarin, and sinapyl alcohol) of *V. album* ssp. *album* grew on three different host trees (*M. Domestica, Q. Robur*, and *U. carpinifolia*) [33].

The metabolite profile of *V. coloratum* harvested from three different host plants (*Ulmus pumila* L., *Salix babylonica,* and *Populus ussuriensis* Kom.) in two habitats (temperate continental climate and warm temperate humid monsoon climate, China) was investigated by Zhang *et al*., 2021 [51]. Three main metabolites, from the flavanone class, were identified, their synthesis and accumulation in mistletoe were dependent both on the host plant and environment [51].

Polyphenols - Chemical Structure and Classification

The flavonoids are a class of polyphenol compounds, secondary metabolites of vegetal origin, with antioxidant properties, which are found in the free state or seen as esters or glycosides in mistletoe leaves. More than 4.000 types of flavonoids have been identified in the plant kingdom [52].

Polyphenols occupy an important place in the life of plants by intervening in their metabolism. There are known about 8.000 plant-derived polyphenol compounds with antioxidant and antitumor properties [53-58]. Polyphenols are organic, water-soluble compounds that contain in their molecule one or more aromatic rings with one or more hydroxyl groups. Due to their chemical structural characteristics, polyphenols are compounds with high antioxidant power [52, 59-61]. The main polyphenols identified in mistletoe are from phenolic acids class, both hydroxybenzoic acid (gallic acid, protocatechuic acid) and hydroxycinnamic acid (caffeic, ferulic acid, synaptic acid) and flavonoids including flavanone (Naringenin, Eriodictiol), flavone (Apigenin), flavonol (3-O-Met Quercetin, Myricetin, Kamferol). The main polyphenols identified in the different subspecies of *V. album* and its host trees are presented in **Figure 3**.

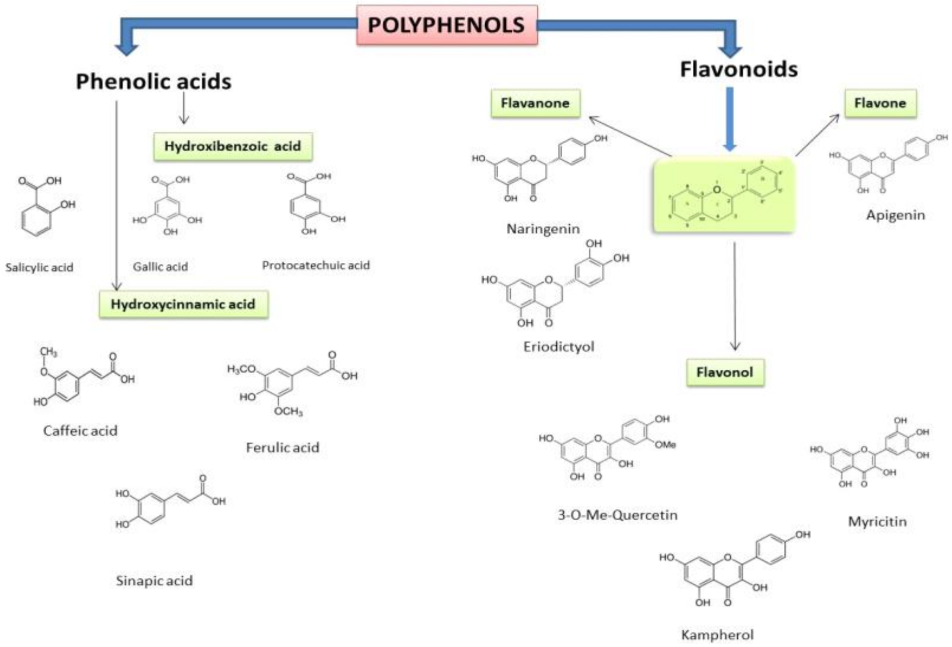

Figure 3. The classification and chemical structure of the main polyphenols identified in *V. album*

The amount and composition of mistletoe flavonoids can vary significantly depending on the host tree, vegetation period, and harvest period [33, 41, 51, 62, 63].

The most important flavonoids identified so far in mistletoe leaves or stems are shown in **Table 2**.

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 **Flavonol:** 3-O-Metil Quercetin **Flavanones**: Naringenin	**Hydroxibenzoic acid**: Gallic acid, Gentisic acid, Protocatechuic acid, p-hydrobenzoic, Salicylic acid, **Cinnamic acid**: Caffeic acid,Ferulic acid, p-cumaric acid, Rosmarinic acid, Sinapic acid	[64]
				Hydroxycinnamic acid: Rosmarinic acid	[65]
V. album ssp *album*	Jugastru (*Acer campestris)*	leaves	**Flavonol:** Kampherol Quercetin	**Hydroxibenzoic acid**: Salicylic acid, p-Hydrobenzoic acid, **Hydroxycinnamic acid:** Caffeic acid, Chlorogenic acid. Ferulic acid, Sinapic acid, trans-Cinnamic acid.	[64]
				Hydroxibenzoic acid: p-Hydrobenzoic acid Salicylic acid,	[65]

				Hydroxycinnamic acid: Caffeic acid, Chlorogenic acid. Ferulic acid, Sinapic acid, trans-Cinnamic acid,	
		stems	**Flavonol:** Kampherol	**Hydroxycinnamic acid:** Rosmarinic acid, trans-Cinnamic acid	[65]
V. album ssp *album*	Silver coat(*Acer saccharinum L)*	leaves	**Flavanol:** Myricetin **Flavonol:** 3-O-Metil Quercetin Rhamnazin		[12]
				Hydroxibenzoic acid: Gallic acid, Gentisic acid, p-Hydrobenzoic acid, Salicylic acid, Vanilic acid **Hydroxycinnamic acid:** Caffeic acid, Ferulic acid, p-Coumaric acid, Sinapic acid, Rosmarinic acid,	[64]
V. album ssp *album*	Hawthorn (*Crataegus monogyna*)	leaves	**Flavanones**: Eriodictyol **Flavonol**: 3-O-Metil Quercetin	**Hydroxibenzoic acid**: Protocatechuic acid, Salicylic acid Syringic acid, **Hydroxycinnamic acid:** Caffeic acid, Ferulic acid p-Coumaric acid, Sinapic acid,	[12]
V. album ssp *album*	Ash (*Fraxinus excelsior* L*)*	leaves	**Flavonol**: Kampherol Quercetin 3-O-Metil Quercetin **Flavanones**: Eriodictyol	**Hydroxibenzoic acid**: Protocatechuic acid, p-Hydrobenzoic acid, Salicylic acid, Syringic acid **Hydroxycinnamic acid:** Caffeic acid, Chlorogenic acid Ferulic acid, p-Coumaric acid Sinapic acid, trans-Cinnamic acid,	[65]
		stems	**Flavonol**: Kampherol	**Hydroxibenzoic acid**: Syringic acid Protocatechuic acid **Hydroxycinnamic acid:** Caffeic acid, Chlorogenic acid, Ferulic acid, Rosmarinic acid, Sinapic acid, 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 Vanilic 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 3-O-Metil Quercetin Isorhamnetin Sakuratin, Rhamnazin **Flavanones**: Naringenin **Flavone:** Apigenin		[65]
				Hydroxibenzoic acid: Gallic acid, Gentisic acid, Protocatechuic acid, **Hydroxycinnamic acid:** p–Coumaric acid	[64]
			Flavonol: Quercetin	**Hydroxibenzoic acid**: Salicylic acid, Protocatechuic acid, p-hydrobenzoic acid, **Hydroxycinnamic acid:** Ferulic acid,	[65]

				Rosmarinic acid, Sinapic acid,	
			Flavanones: Naringenin Eriodictyol Sakuranetin **Flavonol**: Quercetin 3-O-Metil Quercetin Isorhamnetin Rhamnazin	**Hydroxibenzoic acid**: p-hydrobenzoic acid, Salicylic acid, Syringic acid Vanillic acid **Hydroxycinnamic acid:** Caffeic acid, Ferulic acid,	[12]
V. album ssp *album*	Poplar (*Populus nigra* L)	stems		**Hydroxibenzoic acid**: Protocatechuic acid, Salicylic acid **Hydroxycinnamic acid:** Caffeic acid, Ferulic acid,	[65]
V. album ssp *album*	Acacia (*Robinia pseudoacacia*)	leaves	**Flavonol**: Quercetin Kaempferol	**Hydroxibenzoic acid**: Gallic acid, **Hydroxycinnamic acid:** Ferulic acid, Sinapic acid,	[65]
		stems	**Flavonol**: Kampherol	**Hydroxibenzoic acid**: Protocatechuic acid,	[65]
V. album ssp *album*	Mountain ash *(Sorbus aucuparia* L*)*	leaves	**Flavonol**: Quercetin 3-O-Metil Quercetin Isorhamnetin Myricetin, Sakuratin Rhamnazin **Flavanones**: Naringenin		[12]
				Hydroxibenzoic acid: Gallic acid, Gentisic acid Protocatechuic acid, p –hydroxybenzoic acid Salicylic acid, Syringic acid Vanillic acid, Veratric acid, **Hydroxycinnamic acid:** Caffeic acid, Ferulic acid, p-Coumaric acid Sinapic acid,	[64]
			Flavanones: Naringenin Eriodictyol **Flavonol**: Quercetin 3-O-Metil Quercetin Isorhamnetin Sakuratin Rhamnazin		[12]
V. album ssp *album*	Linden (*Tilia cordata* Mill)	leaves	**Flavanones**: Naringenin Eriodictyol **Flavonol**: 3-O-Metil Quercetin Isorhamnetin Rhamnazin **Flavones**:Luteolin	**Hydroxibenzoic acid**: Gallic acid, Protocatechuic acid, p-hydrobenzoic acid, Salicylic acid Syringic acid, Vanillic acid **Hydroxycinnamic acid:** Caffeic acid, Ferulic acid, p-Coumaric acid, Sinapic acid.	[12]

V. album ssp *abietis*	Fir (*Abietis alba* Mill)	leaves	**Flavanones**: Naringenin **Flavonol**: 3-O-Metil Quercetin Rhamnazin Rhamnetin **Flavone:** Apigenin	**Hydroxibenzoic acid**: Salicylic acid, Protocatechuic acid, 4-hydrobenzoic acid, Vanilic acid, **Hydroxycinnamic acid:** Caffeic acid, Ferulic acid, p-Coumaric acid, Sinapic acid.	[66]
V. album ssp *austriacum*	Pine (*Pinus sylvestris* L)	leaves	**Flavanones**: Naringenin Eriodictyol Sakuranetin **Flavonol:** Quercetin 3-O-Metil Quercetin Isorhamnetin Myricetin, Rhamnazin Rhamnetin, Kampherol		[12]
		leaves fruits seeds		**Hydroxibenzoic acid**: Protocatechuic acid, Salicylic acid, 4-hydroxybenzoic acid, Vanilic acid, **Hydroxycinnamic acid:** Caffeic acid, Ferulic acid, p-Coumaric acid, Sinapic acid	[67]
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 that contains a wide variety of phytochemicals. Quercetin, with high antioxidant activity and a strong antitumor effect, is one of the flavonols present in mistletoe being identified in *V. album* ssp. the *album*, *V. album* ssp. *abietis*, *V. album* ssp. *austriacum* and *V. album* ssp. *coloratum* [12, 63]. Among the flavanones, Naringenin and Eriodictyol are found both in *V. album* ssp. *album* and *V. album* ssp. *austriacum* [12, 51, 65]. Caffeic acid, a hydroxycinnamic acid, has been identified in various subspecies of *V. album* [12, 67].

Lectins and Viscotoxins

V. album is a medicinal plant that contains a wide variety of chemical compounds, from small molecules such as phenolic acids, flavonoids, to high molecular weight molecules proteins: lectins and viscotoxins [69].

Lectins are a class of proteins or glycoproteins, that can reversibly bind specific carbohydrates without altering their structure. Based on the specificity of carbohydrate-binding, lectins can be: monospecific - binds to one carbohydrate, (glucose, galactose) and polyspecific - binds to several sugars [24, 70]. In terms of chemical structure, mistletoe contains three lectins that differ in their molecular weight, about 60000Da and depending on the binding of carbohydrates [71, 72]. These lectins are coded as follows: ML 1, ML 2 and ML 3; (ML – Mistellectin) [73]. Lectin ML 1, is a glycoprotein that has two polypeptide chains linked together by a disulfide bond [74]. The chain A of lectin ML 1 is composed of three distinct individual domains, having a molecular weight of 29 kDa, 27 kDa, and 25 kDa, possessing RNA N-glycosidase activity [75]. The lectin B chain consists of two domains with the same configuration, with a molecular weight of 32 KDa and 25 KDa, respectively [24]. It has a specific carbohydrate-binding system, it binds specifically to D-galactose [76, 77]. The specificity of lectin B chain binding to carbohydrates plays a key role in explaining the selective cytotoxicity of lectins to tumor cells when interacting with various receptors. The specific interaction of lectins with receptors on the surface of cancer cells causes agglutination, apoptosis, and the stopping of the cell cycle and thus inhibition of angiogenesis and cell proliferation [78]. Thus, both lectin chains have cytotoxic action [24]. Lectin ML-2 binds specifically to D-galactose / N-acetyl-D-galactosamine [79]. Lectin ML-3 has a specificity for N-acetyl-D-galactosamine [72]. *V. an album* that grows on the following species: oak (*Quercus* ssp), poplar (*Populus nigra*) contains mostly lectin ML-1. *V. album* on conifers: fir (*Abies alba*), pine (*Pinus sylvestris*) contain mainly lectin ML-3 [71].

Viscotoxins are small polypeptides, rich in cysteine, and consist of about 46 amino acids, containing 3-4 disulfide bridges. They have a molecular weight of about 5KDa [80]. Depending on the amino acid sequence, the *V. album* contains 6 isomeric compounds: A1, A2, A3, B, B2, C1, 1-PS [72]. Viscotoxin has cytotoxic activity against different types of tumor cells and has immunomodulatory effects [15]. The composition and content of lectin and viscotoxin vary depending on the host tree.

In the *V. album* ssp *album* viscotoxin A2, A3 predominates, and 1-PS is missing while the *V. album* ssp *austriacum* is dominated by viscotoxin 1-PS, and viscotoxins A2, A3 have been detected in small amounts. *V. album* ssp *abietis* contains all viscotoxins, A3 predominates and viscotoxin A2 was not detected. [81]

Biological Properties and Pharmaceutical Action

Many biological effects of mistletoe, such as anticancer, apoptosis-inducing, antiviral, antibacterial, and immunomodulatory activities have been reported [2, 11, 20, 82, 83].

A series of *in vitro* and *in vivo* studies confirm a broad spectrum of the therapeutic action of mistletoe (*V. album*). **Table 3** summarizes the pharmacological activities of mistletoe (*V. album* ssp / *Viscum coloratum* / *Viscum articulatum*) depending on the host tree.

Table 3. The pharmacological activity of *V. album* ssp/ Viscum coloratum/ 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;

Therapeutic, Cosmetic, and Functional Applications of Mistletoe Extract

Table 4 shows the patents published with mistletoe extracts (*V. album*) with therapeutic, cosmetic, and functional applications in the period 2011-2021.

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 having antiobesity and hepatic steatosis protection activity	-suppresses obesity by inhibiting fat around epididymis and fatty liver
KR20140115730A	2014-10-31	Shampoo composition for preventing hair losing and promoting hair growth comprising extracts of *V. album* and *Chamaecyparis obtusa*	-prevents hair loss -possesses an improved antioxidant capacity
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	-reduce the GGT foci incidence of parts of precancerous lesions -hydroxyl free radical scavenging effect blocking the occurrence and development of precancerous lesions of the liver
KR20160017903A	2016-02-17	*V. album* extract containing a sweet jelly preparation method and sweet jelly prepared by the method	-enhances immunity -proposed for 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	-skin astringent -reduction of cytotoxicity caused by external stress -control of the expression of inflammatory mediating factors.
CN106692909A	2017-05-24	*Pyrus pyrifolia* tree *Viscum coloratum* grease with lung-clearing and phlegm-eliminating effects	-effects on cleaning the lungs and eliminating phlegm
CN108295100A	2018-07-20	Application of the *V. album* extract in preparing drugs for rheumatoid arthritis	-inhibit the synthesis of inflammatory mediator downstream by targeting NF- κ B* signal accesses, -inhibit the inflammatory reaction of the synovial membrane, -mitigate the destruction of articular cartilage and bone.
KR102007096B1	2019-08-02	Composition for preventing or treating hearing loss comprising *Viscum ovalifolium* extracts	-suppress hearing loss

KR20200109068A	2020-09-22	A soap comprising *V. album* fermentation product and method for preparing the same	-easily absorbed into the skin, -alleviate skin inflammation. -exfoliating effect, it can remove harmful agents from the surface of the skin, -prevent the aging of the skin, due to the antioxidant components of the V . album
BR102020003563A2	2021-09-08	Topical pharmaceutical composition with antitumor activity containing *V. album*	-antitumor activity

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

Conclusion and Future Prospects

Mistletoe is a plant with a high potential for the treatment of various diseases. Its phytochemical composition and at the same time its biological effects depend on the host tree. The key components responsible for anticancer activity are lectin and viscotoxin. In addition, mistletoe also contains a sufficient amount of secondary metabolites from the class of flavonoids and phenolic acids, compounds with important beneficial effects. These compounds are widely distributed in plants and there is sufficient evidence to show that their consumption is closely linked to a decrease in the incidence of cancer, diabetes, and cardiovascular disease. Studies on the synergistic effects between mistletoe polyphenols and lectins should be further developed to identify new targeted therapeutic applications of mistletoe preparations.

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