

Viscum album: A comprehensive review of Taxonomic Insight, Botanical Overview, and Pharmacological Prospects

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Abstract

Mistletoe, scientifically known as *Viscum album*, is a plant that has been used for medicinal purposes by different cultures for centuries. Its natural components have been found to offer a plethora of health benefits such as enhancing the immune system, providing anti-inflammatory effects, and promoting cardiovascular health. Additionally, recent research has highlighted the immunomodulatory properties of mistletoe, which could prove to be a promising treatment option for individuals with immune-related conditions.

Studies have revealed that extracts obtained from mistletoe possess immunomodulatory properties, which could prove to be extremely beneficial for individuals grappling with immune-related disorders. Moreover, mistletoe is known to exhibit potent antioxidant and anti-inflammatory activities, which indicate its therapeutic potential in mitigating oxidative stress and inflammatory conditions. Furthermore, the vasodilatory effects of mistletoe could potentially confer antihypertensive benefits, paving the way for its potential use in treating cardiovascular ailments. Besides, the ability of mistletoe to influence cellular proliferation and apoptosis presents a promising avenue for complementary cancer therapy. The underlying mechanisms of action of key phytoconstituents, such as lectins, viscotoxins, and flavonoids, are believed to contribute to these beneficial effects.

Throughout history, various societies have utilized mistletoe, scientifically referred to as the *Viscum album*, for its medicinal attributes. Its organic components have been discovered to provide numerous health advantages, such as boosting the immune system, reducing inflammation, and supporting cardiovascular wellness. Recent research has also revealed the immunomodulatory properties of mistletoe, indicating that it could be a potential treatment alternative for people with immune-related ailments.



1. Introduction

The most prevalent species of its genus (c. 450 species), *Viscum album* L. (Santalaceae, previously Viscaceae or Loranthaceae), is mostly found in Europe and Asia and is known as European mistletoe or just mistletoe [Christenhusz M.J.M., et al., (2017)]. Despite having a general look and shape that is extremely similar to many other shrubs found in temperate flora, *Viscum* plants are an outstanding example of variety in dicotyledonous angiosperms [Büssing A., et al., 2000]. It is a woody shrub with evergreen leaves that has extensive dichotomous branching on stems that are 30 to 100 cm long. Yellowish-green leaves in the shape of leather straps cover the whole plant. This species is dioecious and has unnoticeable yellowish-green blooms. The fruits are often opalescent globose berries with one (or, very rarely, numerous) seeds embedded in an extremely sticky, glutinous pulp. [Zube D. et al., (2004)].

The plant is found to contain various chemical constituents such as lectins [Stirpe et al., 1992; Peumans et al., 1996], viscotoxins [Samuelsson, 1974; Orru et al., 1997], flavonoids (Lorch, 1993; Wollenweber et al., 2000), polysaccharides, biogen amines [Hoffmann, 1990], alkaloids, terpenoids [Deliorman et al., 2001 a, b], saponins, tannins, phytosterols, vitamins, hydrocarbons, and long-chain fatty acids, etc. [Radenkovic et al., 2006]. *Viscum album* L. has been reported to possess antitumors and immunomodulatory [Jurin et al., 1993], anticancer

[Burger et al., 2001], hypotensive [Ofem et al., 2007], anti-inflammatory [Hegde et al., 2011], hypoglycaemic and antioxidant [Orhan et al., 2005], neurophysiological [Radenkovic et al., 2006], cytotoxic [Cebovic' et al., 2008], antimycobacterial [Deliorman et al., 2001a, b] etc. activities.

Viscum album L. Wight & Arn belongs to the Santalaceae family. It is a hemi-parasitic shrub, meaning that rather than the soil, its roots are buried in the trunks and branches of other trees [A. Anselm, et al., 2009]. The plant grows on oak tree stems in Pakistani highlands on tree trunks. According to Skidmore-Roth et al. (2010), the plant is used in alternative cancer therapies to treat diabetes, stomach issues, insomnia, chronic cramps, stroke, anxiety, heart palpitations, hypertension, atherosclerosis, breathing difficulties, hot flushes during menopause, and diabetes [Skidmore-Roth et al., 2010]. Mistletoe, young twigs, and leaves were employed by herbalists in Europe, particularly in Germany, to treat circulatory and pulmonary system issues [E. Ernst, et al., 2006].

According to M. Jurin et al. (1993), the phytochemicals glycosides, alkaloids, viscotoxins, phenylpropanoids, tannins, lignin, and sugars have all been found in *V. album* when it was collected from several host plants. The pharmacological effects of *Viscum* species depend on the host trees [U. F. Umoh, et al., (2011)]. Its utility in the control of diabetes was proven by several pharmacological and ethnobotanical research. Despite this, there is no proof to back up the claims that *V. album* contains phytochemicals or functions as an antidiabetic agent. Therefore, the purpose of this study was to look into the phytochemicals and antidiabetic potential of *V. album* based on its traditional uses.



2. *Viscus album*

A species of mistletoe in the Santalaceae family called *Viscum album* is sometimes referred to as common mistletoe, European mistletoe, or just mistletoe (Old English mistle) [Zuber, Doris (2004)]. Western and southern Asia, as well as Europe, are its original continents [O'Neill, A. R.; Rana, S. K. (2019)].

Viscum album is a hemiparasite on a variety of tree species, where it obtains nutrients and water. It plays a big part in the myths, stories, and traditions of Europe. It is frequently used in Christmas decorations and symbolism nowadays. (*V. album* is an imported plant that is very sometimes seen in North America; *Phoradendron leucarpum*, a closely related native species, typically fills its cultural duties).

3. Description

It is an evergreen hemi parasitic shrub that grows on other trees' stems. It has

Stem: 30-100 cm (12-39 in) long stems with dichotomous branching.

Leaves: leaves are opposite-paired, strap-shaped, whole, leathery, and 2 to 8 centimetres (0.79 to 3.15 in) long by 0.8 to 2.5 centimetres (0.31 to 0.98 in) wide. They are also yellowish-green tints. This plant is insect-pollinated and dioecious.

Flowers: are tiny, yellowish-green, and range in diameter from 0.079 to 0.118 inches.

Fruit: a white or yellow berry with one (or, very seldom, several)

Seeds: seeds embedded in the thick, glutinous fruit pulp.

Broad-leaved trees, especially apple, lime (linden), hawthorn, and poplar, are known to have it in their crowns [Broadmeadow. (2006)]. The production of usable energy for cells depends on the respiratory complex I protein, which is solely absent from the electron transport chain of the European mistletoe [science.org, 2022]. According to Fonseca-Pereira et al. (2018), it is thought to survive by stealing adenosine triphosphate and other energy-dense chemicals from its host, rearranging its other respiratory complexes, and reducing its metabolic rate and energy needs.

4. Taxonomical Classification

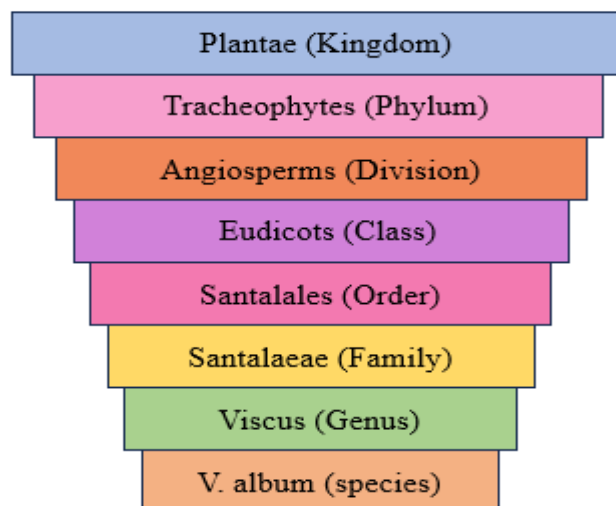


Fig 2: Taxonomical Classification of *Viscum album*

5. Pharmacological potential of *V. album*

Ancient cultures believed the European mistletoe to be a powerfully influencing magical plant. It was a treatment for a number of illnesses in medieval times. Hildegard von Bingen (1098–1179), for instance, utilized it to cure her spleen and liver. *V. album* extracts have been used to treat cancer patients since the 1920s [Busing 2004]. Mistletoe extracts and preparations have received approval from the German Commission E for use as a

palliative therapy for malignant tumours as well as a curative in degenerative and inflammatory joints [Commission E Monographs 1984].

5.1. Anticancer therapy

The majority of current research on *V. album* focuses on its anticancer properties. Mistletoe treatment has been found to increase survival time, enhance quality of life, and cause cancer remission in several clinical investigations. Different plans, dosages, and administration methods are utilized in cancer therapy depending on the stage of the illness and the patient's response [Jurin *et al.*, 1993]. Scientists and medical professionals have proved the advantages of mistletoe extracts in various clinical trials, and isolated components have been shown to be beneficial in the treatment of cancer. Lectins play a significant part in this procedure because they directly activate cytotoxic action on cancer cells and induce death in these cells.

Lectins activate ML III and the apoptotic pathway, which results in a reduction in nuclear p53 and Bcl-2 proteins and an increase in telomeric connections [Busing *et al.*, 1998]. Interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF) transcription and secretion were activated by these substances at non-toxic quantities. This provides a potential way to stop cancer cell proliferation [Ribe'reau-Gayon *et al.*, 1996].

For the first time, various subspecies of *V. album* mother tinctures inhibited the glycolytic enzymes HK, PFK-1, and PK in breast cancer cells. The cytotoxicity shown in MDA-MB-231 cells was associated with the host tree and seasonal factors. Compared to winter preparations, summer MT encouraged more cellular damage. Additionally, *V. album* subsp. *Album* and *V. album* subsp. *Abietis* were shown to have the most potential antitumoral action [Melo, M. N. D. O., *et al.*, (2022)].

5.2 Anti-inflammatory activity

The *V. album* extracts exhibit their action as a phyto complex, wherein they work with extracellular signal-regulated enzymes in addition to microproteins like viscotoxins and viscolectins. They also contain numerous other constituents that can participate in the main property, antioxidant, anti-inflammatory, and anti-stress activity, which supports the overall actions in restoring or maintaining homeostasis. The metabolome's components, especially the identification of novel active elements that differ greatly from microproteins, should get special attention. Recent publications demonstrating the effectiveness of European mistletoe extracts as a complementary and adjuvant cancer treatment encourage their use in other fields, but these applications must be supported by additional research on the characteristics of this unique plant. [Nicoletti, M. (2023)].

5.3 Antihypertensive activity

Recent studies have validated the traditional use of mistletoe extracts in the treatment of hypertension. Studies on animals have shown that administering an ethanol extract considerably lowers blood pressure. Muscarinic receptors were the principal pathway via which *Viscum* extract exerted its effects [Radenkovic *et al.*, 2009]. Blood pressure was also significantly reduced by the aqueous extract, and this effect was more pronounced in hypertensive than in normotensive rats. The study methodology used allows for the assumption that the extract's activity results mostly from the nervous system's positive response and its impact on peripheral blood vessels [Ofem *et al.*, 2007]. In a dose-dependent way, phenolic chemicals, including phenylpropanoids and flavonoids,

are extracted from *V. album* ssp. the album produced vascular relaxation, which can also help decrease blood pressure.

5.4 Antidiabetic properties

Studies conducted in vitro and in vivo have supported the traditional use of mistletoe as an anti-diabetic agent. In clonal B-cells, aqueous extracts had a dose-dependent insulin-releasing action. Additionally, it has been shown that active ingredients may withstand heat [Grey & Flatt 1999]. After receiving mistletoe water extract, alloxan-hyperglycaemic rabbits and rats showed a considerable reduction in serum glucose level and a rise in serum insulin level [Ohiri et al. 2003; Shahaboddin et al., 2011]. According to [Shahaboddin et al., (2011)], the extract improved the serum's antioxidant activity, which is crucial for preventing diabetes complications. In a rat model of diabetes brought on by streptozotocin, a similar result was attained. After 3 weeks of treatment with methanolic extract, normal rat hyperglycemia levels were significantly reduced, and α -amylase activity was found to be two times greater. The study also showed that liver enzymes and lipid profiles were normalized and that there may be a protective effect against diabetes-related kidney impairment [Adaramoye et al., 2012]. According to research by [Choudhary et al., (2010)], some phenolic compounds can prevent the development of advanced glycation end products, which are the root of many diabetic issues.

5.5 Sedative, antiepileptic, and antipsychotic effects of *Viscum album* L.

Additionally, there is mounting proof that a number of herbal remedies, including Ginkgo biloba (Ginkgo trees), Hypericum perforatum (St. John's wort), Piper methysticum (Kava strub), and Valeriana officinalis (Valerian), may be effective in the treatment of mental diseases [Noel et al., 2008]. The purpose of the current investigation was to assess the effects of acute administration of aqueous leaf extract of the plant in several models of experimental epilepsy and behavior. The antiepileptic and neuropharmacological actions of the plant have not been properly investigated. The actophotometer's locomotor activity was decreased and the pentobarbital-induced sleep period was extended when *Viscum album* L.'s aqueous leaf extract was used. As a result, it seems that decreased locomotor activity aids GABAergic transmission. Additionally, the extract lessened convulsions brought on by MES, INH, and PTZ, which suggests that it may be possible to block Na⁺ channels, open Cl⁻ channels, or improve the GABAergic system. The extract potentiated the HAL-induced cataleptic score and reduced the stereotyped behavior caused by apomorphine, which shows the extract has antidopaminergic action [Gupta, G., et al., 2012].

5.6 Pathogenic and antibacterial properties of *V. album*

The particular investigation included in vivo rats that had been exposed to *S. aureus*, *B. cereus*, and *E. coli* together with *P. aeruginosa*. Seven days after using the extract of the *Viscum album*, investigations in haematology, microbiology, and histopathology demonstrated its therapeutic impact. In this study, it was determined if a set of clinically isolated bacteria were directly inhibited by aqueous extracts of *Viscum album* and *Apium graveolens*, or if adhesion and biofilm development were inhibited instead. Both *Apium graveolens* and *Viscum album* extracts significantly inhibited the majority of the tested Gram-positive and Gram-negative bacterial isolates, with inhibitory ranges of 20-35 and 18-28 mm, respectively. *Viscum album* also significantly

and strongly inhibited adhesion and biofilm formation, while *Apium graveolens* showed less inhibition [Oubaid, E. N., *et al.*, (2022)].

6. Toxicity of *V. album* plant

In concentrated form, European mistletoe may be lethal, and consuming the berries can make people very unwell [Poison Control]. *Viscum album* has produced the poisonous lectin viscumin, according to [Olsnes S. *et al.*, (2009)]. RIP, also known as viscumin, is a cytotoxic protein that binds to the galactose residues of cell surface glycoproteins and can be internalized by endocytosis [Stirpe F, *et al.*, 2009]. By deactivating the 60 S ribosomal subunit, viscumin severely reduces protein synthesis. This protein's structure resembles that of other RIPs, most notably ricin and abrin [Olsnes S. *et al.*, 2009; Stirpe F. *et al.*, 2009]. Some birds, like the mistle thrush, which got its name from its preferred meal, are immune to the toxin and like the berries.

Conclusion

In conclusion, the extensive body of research on the *Viscum album* underscores its diverse and substantial pharmacological activities, making it a valuable subject of scientific interest. The plant has exhibited a range of effects that hold potential for various medical applications. *Viscum album* immunomodulatory properties have been demonstrated through its ability to modulate immune responses, suggesting its possible utility in autoimmune disorders and immune-related conditions. Moreover, its anti-inflammatory and antioxidant activities contribute to its potential in managing oxidative stress-related diseases and inflammatory ailments. The plant's impact on the cardiovascular system, including vasodilation and potential antihypertensive effects, opens avenues for addressing cardiovascular disorders. Additionally, its influence on cellular proliferation and apoptosis offers intriguing possibilities for cancer therapy, potentially serving as an adjuvant treatment alongside conventional method. Despite these promising findings, further research is essential to identify and isolate the specific bioactive compounds responsible for these effects. Clinical trials are necessary to validate its efficacy, safety, and optimal dosage in diverse medical contexts. As researchers delve deeper into the mechanisms underlying the *Viscum album* pharmacological activities, it may emerge as a source of novel therapeutic agents. Its integration into modern medicine could lead to the development of innovative treatments, enriching the options available for patients and healthcare providers. In this pursuit, *Viscum album* holds the potential to contribute significantly to the advancement of pharmacological science and the improvement of human health.

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