Eco. Env. & Cons. 30 (Nov. Suppl. Issue) : 2024; pp. (S386-S395)
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ISSN 0971–765X

DOI No. http://doi.org/10.53550/EEC.2024.v30i07s.067

A Comprehensive Review on Phytochemical Profile, Traditional Uses, Pharmacology and Host-parasite Dynamics of *Viscum album* L.

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(Received 14 June, 2024; Accepted 29 August, 2024)

ABSTRACT

Viscum album L. is an extremely specified perennial flowering plant that have evolved to live as parasites on their hosts' aerial parts. This comprehensive review examines the biochemical constituents, traditional uses, and pharmacological properties of *Viscum album* L. (mistletoe), a hemi-parasitic plant of the Santalaceae family. The study synthesizes current research on the plant's diverse phytochemical composition including lectins, viscotoxins, flavonoids, and polysaccharides. Traditional applications across various cultures are explored highlighting mistletoe's historical significance in herbal medicine. The review presents an analysis of pharmacological aspects, focusing on its anti-inflammatory, antioxidant, Immunomodulatory, and anticancer properties of *Viscum album* L. Particular attention is given to its potential in cancer therapy, cardiovascular health, and as an adjuvant in conventional treatments due to presence of various bioactive components. While the plant shows promise in several therapeutic areas the paper emphasizes the need for further research to elucidate specific mechanisms of action, optimize extraction and formulation processes, and conduct rigorous clinical trials.Despite the fact that mistletoe has detrimental effect on the host trees, this review concludes that *Viscum album* L. represents a significant area of pharmacological interest warranting continued exploration to realize its potential in modern medicine.Enhancing knowledge of the *Viscum album* L. host relationship can help manage infested forest plantations more effectively for the production of resources, biodiversity preservation, and protection of endangered species.

Keywords*: Bioactive compounds, Host-parasite interaction, Traditional medicine, Pharmacology*

Introduction

Parasitic angiosperms are plants that obtain nutrients and water from other plants, called hosts. The hemiparasitic angiospermic plant *Viscum album* L., often known as mistletoe, is belonging to the family Santalaceae. *Viscum album* L. are hemiparasites, indicates that although they are capable of producing their own food through photosynthesis, but they still need the water and nutrients from their host plants. They are often found growing on the branches of trees and shrubs(Amico *et al*., 2019; Szurpnicka *et al*., 2019). The plant is distributed in various regions, including northern, central, and southern Europe,

America, Australia, Africa, and Asia (Fig. 1). The specific habits, host preferences, morphologies, and developmental patterns of mistletoe can varysignificantly depending on its geographical location. This diversity reflects adaptations to different environmental conditions and host plants(Bohling *et al*., 2002; Costa *et al*., 2020). Chemical and pharmacological investigations have revealed a diverse array of compounds within *Viscum album* L. These include lectins, viscotoxins, lignans, amines, flavonoids, andpolysaccharides (Peñaloza *et al*., 2020). Among these, flavonoids and phenolic acids, renowned for their antioxidant properties, are particularly noteworthy. These substances are essential to the biological function of the plant and have been studied for their potential in preventing diseases like cancer, which is often linked to oxidative stress caused by free radicals (Bonamin *et al*., 2017; Kwon *et al*., 2021). One of the most prominent applications of *Viscum album* L. is in cancer therapy. Research has demonstrated its potential benefits in treating various cancers, including breast, pancreatic, laryngeal, bladder, and leukemia. Beyond cancer, mistletoe has also been explored for its potential in addressing neurological disorders, antiviral, antibacterial, anti-inflammatory, antiepileptic, and immune stimulatory activities.

Methodology

Several web search tools were used to conduct a thorough literature search such as PubMed, Science Direct, Scopus, Google, Google Scholar, Research Gate, and Elsevier. The general keywords "*Viscum album* L.", "pharmacological activity", "traditional uses", "pharmaceutical importance", "anticancer properties", and "host-parasite interaction"were used for that article search. For the purpose of completing an objective systematic review, all information obtained from electronic data via an online literature search was assembled and organized into distinct parts based on its accessibility.

Botanical description of the plant

Viscum album L. in Sp. Pl.: 1023 (1753).
Perennial, evergreen, hemiparasitic shrub, up to 1m. Stem terete, green, glabrous, up to 100 cm. Leaves simple, opposite, yellowish green, oblanceolate, base attenuate, margin entire, apex rounded, glossy green, 2-8 × 0.8-2.5 cm. Inflorescence, terminal or axillary, spike with 3-5 flowers. Small, yellowish-green, dioecious flowers. Fruit berry, white to yellow fruits, globose ca. 6 mm, contains one, or occasionally several, seeds embedded in a thick, sticky pulp.

Host-parasite interaction

A hemiparasite of tree branches, *Viscum album* L. absorbs nutrients and water from its host (Thomas *et al*., 2023). Seeds of *Viscum album* L. is dispersed through birds, certain birds (such as the fieldfare, waxwing, and mistle thrush) consume the berries and then scatter the seed after it passes through their digestive tract and in case of the blackcap (*Sylvia atricapilla*), consume only the berry's outer layer before leaving the seed on the host tree's branch (Or directly on the mistletoe) (Zuber, 2004). Due to the presence of glutinous viscin in the seed pulp the seed firmly adhere to the host branch (Horbelt *et al*., 2019). The mistletoe grows a so-called haustorium

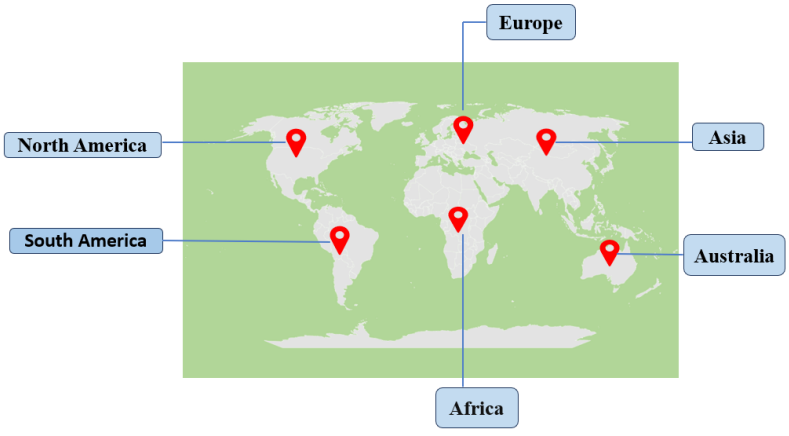

Fig. 1. Distribution of *Viscum album* **L.**

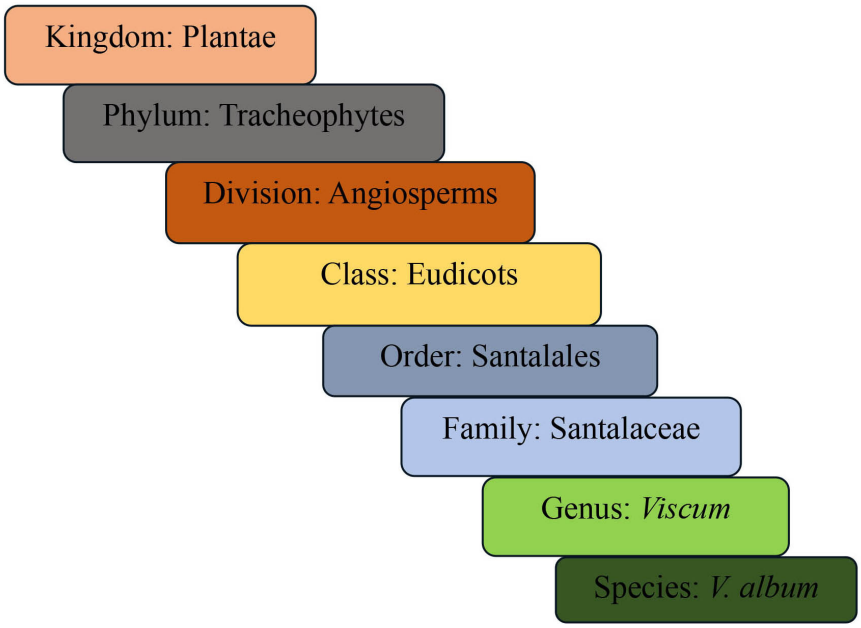

Fig. 2. Taxonomic classification of *Viscum album* L.

during the course of the following several months. The organ particular to the parasite makes the connection with the host,permitting the transfer of genetic information, mineral salts, and water(Teixeira-Costa, 2021). A meristem emerges from the haustorium to form the invading organ, which pierces the host's live tissues and comes into contact with the host xylem (Mylo *et al*., 2022),and after reaching cambium haustorial meristem is formed, active penetration ceases and soon develops sinkers in the form of wedges (Mylo *et al*., 2022). A vascular bridge is established between two plants, xylem-xylem or xylem-phloem (Krasylenko *et al*., 2020). Through this connection, the parasite can obtain nutrients and water, which may lead to mineral and water shortages in the host. Additionally, the haustorium permits the transport of substances like mRNA, viruses, and proteins(Liu *et al*., 2020).

The haustorialestablishment is a continuous process and is divided into four basic stages (Heide-Jørgensen, 2008), which are as follows-

Stage 1: Following germination, the formation of a haustorium straight from the radicle marks the beginning of haustorial initiation in the spring (Mylo *et al*., 2022).

Stage 2: This stage is the adhesive stage of haustorium. In order to prevent the parasite and host from being forced apart and to counteract the mechanical features of penetration, a holdfast is developed during this sticky stage. The holdfast, which is made up of lipids released by epidermal glandular cells, functions as a kind of glue for the seedlings to adhere to the branch after drying and solidifying (Mylo *et al*., 2022).

Stage 3: It is the intrusive stage. The invasive organ, which enters the host's live tissues and comes into touch with the host xylem, is developed and produced by a meristem. Active penetration ceases when the invading organ reaches the host cambium. This causes the haustorial meristem to establish. Rather, the haustorial meristem forms wedge-shaped sinkers and yearly rings by producing tissue concurrently with the host cambium. A number of cortical strands emerge and pass through the host branch in addition to the sinker (Mylo *et al*., 2022).

Stage 4: It is the conductive phase, where a xylem bridge differentiates(Heide-Jørgensen, 2008).

Phytochemicals present in *Viscum album* L.

Chemical analysis of *Viscum album* L. has revealed a diverse range of bioactive compounds. These include lectins (Peumans *et al*., 1996), viscotoxins, (Orrù *et al*., 1997), flavonoids (Wollenweber *et al*., 2000), polysaccharides, biogenic amines, alkaloids, terpenoids (Deliorman *et al*., 2001), saponins, tannins, phytosterols, vitamins, hydrocarbons, and long- chain fatty acids. The lectins of Mistletoe(ML I, ML II, ML III) are classified as type II ribosome-

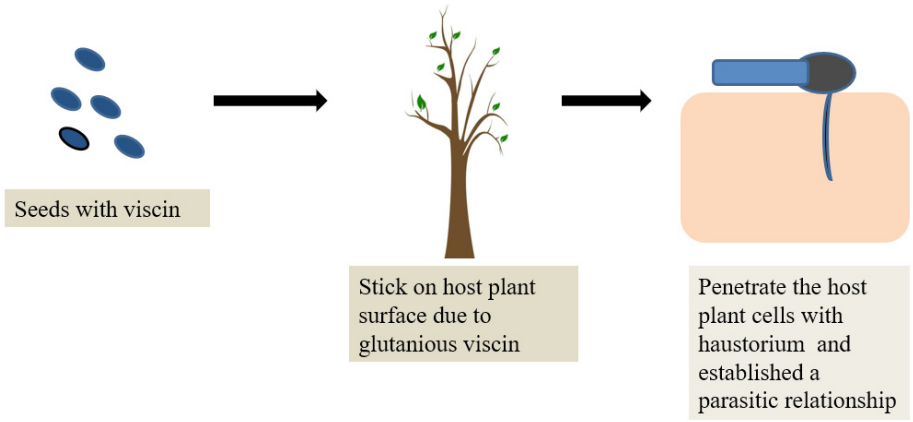

Fig. 3, Establishment of parasitic relationship with host cells (*Viscum album* L.)

inactivating proteins, consisting of two peptide chains, an A-chain B-chain (Nazaruk and Orlikowski, 2016). Viscotoxins are consisting of 46 amino acids, small polypeptides, cysteineriched compounds containing 3-4 disulfide bridges .*Viscumalbum*L. consisting of 6 isoformeric compounds, A1, A2, A3, B, B2, C1, 1-PS(Wacker *et al*., 2004). Depending on the host plant, viscotoxins have different contents and compositions.

The viscotoxin isoforms VTA1 (85nm), VTA2(18nm), and VTA3 (8nm) exhibit varying degrees of bioactivity related to NK lysis, all of which are lethal to the targets at broad doses. A variety of phenylpropanoids were extracted from the leaves and stems, including lignans - syringaresinol 40,400-di-O-glucoside (eleutheroside E), syringenin 4-O-b-D-glucoside (syringin), coniferyl alcohol- and syringenin 4-O-b-D-apiosyl (1!2)-b-D-glucoside, and syringaresinol-O-glucoside(Panossian *et al.*, 1998; Wagner *et al*., 1986).

The primary polyphenols found in mistletoe belong to the phenolic acids class and flavonoids. The phenolic acid contains both hydroxybenzoic acid (gallic acid, protocatechuic acid) and hydroxycinnamic acid (caffeic, ferulic acid, synaptic acid) and flavonoids includingflavanone (Naringenin, Eriodictiol), flavone (Apigenin), and flavonol (3-O-Met Quercetin, Myricetin, Kamferol) (Kleszken *et al*., 2022). Chalcones and flavanones are two classes of flavonoids isolated from methanol extract of *Viscum album*L.

According to BUSSING (2000), the alkaloids found in the *Viscum album*L., such as tyramine, phenylethylamine, choline, and acetylcholine are described as "alkaloids- like" and are not thought to be normal alkaloids. *Viscum album*L.is a plant abundant in triterpenes, betulinic acid (Fukunaga *et al*., 1987), oleanolic acid, ursanolinic acid (Wagner *et al.*, 1986). Beta-sitosterol and stigmasterolphytosteroid are also present in *Viscumalbum* L.extracts.

Traditional uses

Traditional uses of *Viscumalbum* L. date back many centuries, especially in European civilizations. Here's an overview:

Pharmacological aspects of *Viscum album* L.

Since ancient times,*Viscum album* L. has been widely used for its many medicinal properties, which include its analgesic, anti-inflammatory, antidiabetic, and anticancer activities. In Central Europe, particularly in Switzerland and Germany, hydro-alcoholic extracts of *Viscum album*L. arewidely used inanthroposophic medicine,a comprehensive framework that incorporates the use of phytomedicinal substances (Nicoletti, 2023). The anti-inflammatory properties of mistletoeare noteworthy, with extracts reported to selectively inhibit cytokine-induced expression of cyclooxygenase-2 (COX-2) (Hegde *et al*., 2011), reduce the synthesis of cytokine-induced PGE2 production by selectively inhibiting COX2 and destabilize COX-2 mRNA (Elluru *et al*., 2015). Additionally, these extracts have the ability to cause pre-activated neutrophils to undergo apoptosis without inducing an inflammatory response (Lavastre *et al*., 2004). *Viscum album* L.is also well-known for its antioxidant effects which are ascribed to flavonoids and other polyphenols, which help inhibit lipid peroxidation along with antiproliferative and antioxidant activities in vitro,

Table 1. Traditional uses of different parts of *Viscum album* L.

c	Traditional uses	References
1.	**Traditional medicine:** Mistletoe has been widely used in ethno-medicine for centuries to treat various conditions. According to Büssing (2000), it has been traditionally used for: • Epilepsy • Hypertension • Headaches • Menopausal symptoms • Arthritis	(Bussing, 2000)
	2. Cancer treatment: One of the most notable traditional uses of *Viscum album* L. has been in cancer treatment. This practice was popularized by Rudolf Steiner in the early 20th century.	(Ernst, 2006)
	3. Cardiovascular health: Mistletoe has been used traditionally to support heart health and regulate blood pressure.	(Poruthukaren *et al.*, 2014)
	4. Immune system support: Traditional use includes boosting the immune system, particularly during winter months.	(Kienle&Kiene, 2003)
	5. Digestive aid: In some traditional practices, mistletoe tea has been used to aid digestion and relieve stomach cramps	(Wichtl, 2004)
	6. Nervous system disorders: Traditionally used for treating nervous system disorders, including anxiety and insomnia.	(Büssing and Schietzel, 1999)
	7. Arthritis and rheumatism: Mistletoe has been traditionally used to alleviate pain and inflammation associated with arthritis and rheumatism.	(Cogo *et al.*, 2023)
	8. Fertility and reproductive health: In some traditional practices, mistletoe has been used to enhance fertility and support reproductive health.	(Kienle *et al.*, 2009)
	9. Respiratory conditions: Mistletoe has been used in ethno-medicine for various respiratory conditions, such as asthma, and abronchitis.	(Nazaruk & Orlikowski, 2016)
	10. Liver and gallbladder support: In some traditional systems, mistletoe has been used to support liver function and treat gallbladder issues.	
	11. Detoxification: Mistletoe has been traditionally used as a detoxifying agent in some herbal practices.	(Horneber *et al.*, 2008)
	12. Stress relief and mood regulation: Some traditional uses include the application of mistletoe for stress relief and mood improvement.	(Kienle and Kiene, 2010)

and it also has scavenging activity (Holandino *et al.*, 2020; Nicoletti, 2023; Pieme *et al.*, 2012).

Furthermore, it has been discovered that the ethanolic extract inhibits ADP- induced platelet aggregation and raises low plasma antioxidant activity (Panossian *et al.*, 1998; Sárpataki *et al.*, 2014).In oncology, mistletoehas been researched for its immunomodulatory and anticancer properties. Introduced by Rudolf Steiner in 1920 mistletoe extracts have been used for cancer treatment. Since then they have demonstrated promise in increasing the effectiveness of chemotherapy, lowering metastases, and enhancing patients' well-being.

The cytotoxic and response modifying properties of *Viscum album* L. are thought to combine to produce the active components of phytotherapeutics, which strengthen the host's resistance to cancer (Zarkovic *et al.*, 2001). The lectins found in the plant particularly the viscotoxins and lectin-I are essential for immune system modulation. Research havedemonstrated that Isorel, an aqueous extract obtained from the whole fresh mistletoe plant under controlled circumstances with batch consistency confirmed by bioassay might be valuable as an adjuvant cancer treatment in experimental settings, perhaps boosting the effectiveness of cyclophosphamide chemotherapy (Zarkovic *et al.*, 2001).

Additionally, isorel has been shown to enhance immune response on immunosuppressed lymphocytes in cancer patients as evidenced by the fact that it increased the responsiveness of Lymphocytes from tumor-bearing mice to mitogens especially LPS

and ConA in vitro (Zarkovic *et al.*, 2001).

According to experimental research animals receiving isorel had less occurrence of lung metastases (approximately three times) compared to control animals (Zarkovic *et al.*, 2001). Moreover, physicians noticed that patients receiving *Viscum album* L.extracts experienced an improved QoL (quality of life) and reduced severe the adverse consequences of chemotherapy during both conventional and palliative oncological treatments (Sunjic *et al.*, 2015). This included ovarian, breast, and lung cancers. Clinical reports from 1919 show that the use of mistletoeformulations were found to be effective in the treatment of neuroblastoma and other various cancer bearing patients (Zarkovic *et al.*, 2001).In traditional medicine *Viscum album* L. has also been utilized to treat cardiovascular conditions (Khan *et al.*, 2016). Studies has demonstrated that the use of mistletoe has been successful in ameliorating left ventricular dysfunction and that both aqueous and methanolic extracts of the plant can lessen the degree of infarction when compared to untreated hearts (control). It is thought that the underlying mechanism is the activation of NO pathway (Nitric oxide) (Suveren *et al.*, 2017). Improved histological alterations, decreased left ventricular hypertrophy as well as improved biochemical indicators such as NO levels have all been reported after *Viscum album*L.treatment (Karagoz, 2016).

Bioactive compounds of *Viscum album* L. as inhibitor of genes related to cancer

The primary classes of compounds involved in the biological activity of *Viscum album* L. are cytotoxic thionins (viscotoxins) and lectins that induce apoptosis and ribosome inactivation (Ochocka and Piotrowski, 2002). The flavonoid and phenolic acid constituents of mistletoe contain bioactive substances that may be used as therapeutic agents for inhibiting tumor protein-63 (TP63) expression in pancreatic ductal adenocarcinoma (PDA) squamous-subtype tumors(Dairo *et al.*, 2023). Furthermore, the pharmacokinetic research demonstrated that the mistletoe lead compounds have promising drug-likeness features, indicating a potential therapeutic intervention for pancreatic cancer. For the first time, Szurpnicka, *et al*. (2022) demonstrated that *Viscum album* L. shows an effect on activity of the monoamine oxidase enzyme along with dopamine, serotonin, and serotonin receptor 5-HTR1A levels in vivo. Among the mistletoelectins (ML) present in *Viscum album* L. ML I is being widely studied in medical research for a variety of purposes, including anti-cancer activity (Ahmad *et al.*, 2018; Szurpnicka *et al.*, 2022). Lectin ML I is a glycoprotein with two polypeptide chains, lectin A, and lectin B, and the carbohydrate-binding specificity of lectin B chain helps to explain lectin's preferential cytotoxicity to tumor cells when interacting with different receptors (Kleszken *et al.*, 2022). Tumor á-factor,

Table 2. Effects caused due to high dosage of plant toxins.

Sl. No.	TOXICITY	REFERENCES
1.	**General toxicity**: *Viscum album* L. contains several toxic compounds, including viscotoxins and lectins, which can cause various adverse effects if ingested in large quantities	(Olsnes *et al.*, 1982)
2.	**Gastrointestinal symptoms**: Ingestion of mistletoe berries or leaves can cause severe gastrointestinal distress, including nausea, vomiting, and diarrhoea.	(Evens and Stellpflug, 2012)
3.	**Cardiovascular effects:** In high doses, *Viscumalbum* L. can affect heart rate and blood pressure, potentially leading to cardiovascular complications	(Deliorman *et al.*, 2001)
4.	**Neurological symptoms:** Severe poisoning can lead to neurological symptoms such as seizures and even coma in extreme cases	(Pietrzak *et al.*, 2014)
5.	**Allergic reactions:** *Viscum album* L. may cause allergic reactions in certain people, ranging from mild skin irritation to more severe anaphylactic responses	(Stein and Berg, 1997)
6.	**Pregnancy risks**: *Viscum album* L. is contraindicated during pregnancy due to potential risks to the foetus	(Ernst *et al.*, 2003)
7.	**Drug interactions**: Mistletoe may interact with a number of drugs, especially those that influence the immune system or cardiovascular system	(Weissenstein *et al.*, 2014)
8.	**Hepatotoxicity:** Some studies have reported potential liver toxicity associated with long-term use of mistletoe preparations	(Huber *et al.*, 2005)

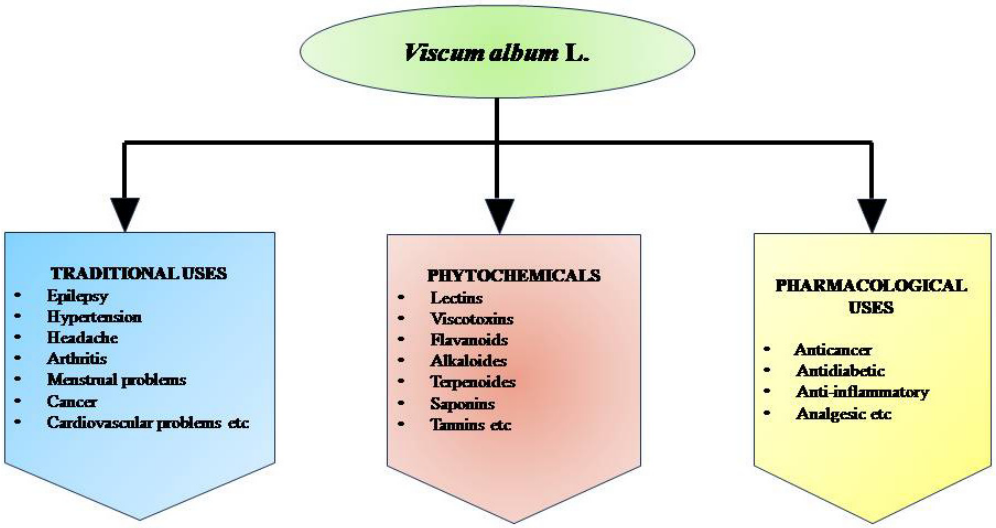

Fig. 4. Outline representing *Viscum album*L. uses and its phytochemical components.

interleukin (IL)-1, and IL-6 were among the major cytokines released by human mononuclear cells exposed to ML I, as highlighted by Ochocka, *et al*. (2002). Semiglasov, *et al.* (2004) demonstrated that using GLQ-8 and Spitzer's uniscale to measure quality of life (QoL), PS76A2, a mistletoe extract preparation standardized to mistletoe lectin, improved the QoL of breast cancer patients after adjuvant CMF chemotherapy (Semiglasov *et al*., 2004).

Conclusion and future perspective

This comprehensive review elucidates the multifaceted aspects of *Viscum album* L., commonly known as mistletoe, encompassing its biochemical constituents, traditional uses and pharmacological properties. This investigation reveals that mistletoe is a rich source of bioactive compounds such asviscotoxin, lectins,and various polysaccharides which may enhance its wide range of medicinal applications. The plant's traditional uses spanning across different cultures and medicinal practices, underscore its historical significance and enduring relevance in herbal medicine. Pharmacologically, *Viscum album* L. demonstrates a broad spectrum of bioactivities including anti-cancer, immunomodulatory, and cardiovascular effects. The lectins and viscotoxins present in the plant exhibit promising anti-tumor properties with numerous studies emphasizing their potential for cancer treatment.Furthermore, the plant is essential for controlling immunological responses, and influencing cardiovascular health. Though there are evidences supporting the medicinal value of the *Viscum album* L., it is also crucial to acknowledge the need for further research. In order to confirm the effectiveness and safety of *Viscum album* L. in medicinal applications, future research should concentrate on clarifying the specific mechanisms of action of its bioactive constituents, streamlining the extraction and formulation procedures, and carrying out carefully planned clinical trials. *Viscum album* L. stands out as a plant of significant pharmacological interest with a rich tradition of use and a promising future in medicine. Its biochemical diversity and potential therapeutic benefits warrant continued research and exploration to fully harness its medicinal properties and integrate them into modern therapeutic practices.

Acknowledgement

The authors sincerely express heartfelt gratitude to the Department of Botany, Dakshin Kamrup College, Mirza, Assam, India for their utmost support and guidance.

Conflict of Interest

There is no conflict of interest regarding the subject.

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