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Viscum Album - Literature Review

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Abstract: ***Viscum album L., popularly known as "Mistletoe", is considered a semi-parasitic plant that grows on several host trees. It has a wide variety of biologically active compounds that can be used to treat various diseases, being its most significant indication for the adjuvant treatment of cancer patients. However, little data is found in the literature on the in vitro and in vivo effects of Viscum album(VA), although formulations for commercial use are available, with extremely low doses of its active compounds. Previous studies used anthroposophical VA and provided information on the mechanisms of action of this extract in tumor and immune system cells. Therefore, the objective of this study was to perform a literature review on the VA plant regarding its botanical behavior and action in cancer patients.***

Keywords: Mistletoe, literature review, cancer patients

1. Introduction

The use of *Viscum album* (VA) as a medicine dates back to the ancient Celtic people, being incorporated into popular medicine after the Middle Ages and included among the homeopathic medical matters in the 19th century. In the 20th century, VA was frequently approached by Rudolf Steiner (1861-1925) and ItaWegmann (1876-1943) around 1917, within the scope of the emergence of the Anthroposophical Medicine, when it was related to the treatment of tumor diseases. These scholars considered that the active therapeutic ingredient would have to be extracted in two seasons (summer and winter) to obtain the therapeutic action more efficiently (LEGNANI, 2008), taking into account the defense system of the plant and the synthesis of various substances throughout the seasons (VALLE, 2008). The first publication on this topic is dated 1933 (KAELIN, 1933).

Over time, different forms of VA extract preparations were performed, such as aqueous, hydroalcoholic, ethanolic extract, among others (DELEBINSKI *et al.*, 2015; ÜNGER, 1987). The observed pharmaceutical effects are generally more detectable with the use of whole extracts rather than the use of purified lectins and viscotoxins alone (LICHOTA; GWOZDZINSKI, 2018). Its therapeutic action was demonstrated as being an immunomodulator, apoptosis inducer, and having a cytotoxic activity (SZURPNICKA*et al.*, 2020).

Classical studies show that viscotoxins can increase the amount of circulating naturalkiller (NK) cells and consequently improve the anti-tumor immune response (TABIASCO *et al.*, 2002). Similarly, viscotoxin has an effective immunomodulatory effect on human and animal granulocytes (SÁRPATAKI *et al.*, 2014; GIUDICI *et al.*, 2003) besides acting on cellular apoptosis (KAUCZOR *et al.*, 2012). The viscotoxin cytotoxic action is comparable to that of conventional chemotherapy agents (WEISSENSTEIN *et al.*, 2014; VAN WELY *et al.*, 1999; KUTTAN *et al.*, 1990).

Within this context, the use of homeopathic medicines prepared from plant extracts is highlighted, which have been experimentally studied in Brazil and other countries (BONAMIN *et al.*, 2015; ENDLER *et al.*, 2010). However, no data on the effects of the prepared VA commercial formulations, which present very low doses of their active ingredients, is found in the literature (CARVALHO, 2015). The published experimental studies record punctual information on the mechanisms of action of this medicine in tumor or immune system cells. However, the cytotoxic, apoptotic, and immunologic aspects of VA are not demonstrated in the papers.

2. Literature Review

Viscum album

Botanical characteristics

Viscum album, also called Mistletoe, Muerdago, Visco, or white Visco (Figure 1-A, E), belongs to the*Loranthaceae*and *Viscaceae* families, which are related to the Santalales order.The *Viscaceae*family has seven genera: *Arceuthobium*, *Dendrophthora*, *Ginalloa*, *Korthalsella*, *Notothixos*, *Phoradendron*, *Viscum*, and various other genera worldwide (URECH; BAUMGARTNER, 2015; BUSSING, 2000; BARLOW, 1983). The European *Viscum* (*Viscum album* L.) is an evergreen, perennial, and hemiparasitic plant (URECH; BAUMGARTNER, 2015; ELLURU *et al.*, 2009; KIENLE *et al.*, 2007; BUSSING, 2000; BARLOW, 1983). This plant is widely distributed throughout Europe. Male and female plants live as hemiparasites of woody trees, from which they obtain water and inorganic compounds dissolved directly from the xylem. Insects pollinate the discrete flowers (Figure 1 – C). The mature pseudofruits (Figure 1 – D) are dispersed by various birds, being the most important way of dispersing their seeds (URECH; BAUMGARTNER, 2015; BARLOW, 1983), as shown in figure 1.

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Figure 1: (A and E) Adult plant of a *Viscum album* species; (B) haustory, (C) Flowering; (D) Fruits. Source: A and B images Zone (2020). Images C and D Mistletoe (2020). Image E, author's collection

The *VA* plant can colonize a large number of host trees, such as fir (*Abies*), almond (*Prunus dulcis*), hawthorn (*Crataegus*), ash (*Fraxinus*), elm (*Ulmus*), willow (*Salix alba*), pine (*Pinus*), apple tree (*Malus mali*), poplar (*Populus*), or oak (*Quercus*), the last three being the main growth sites of VA(URECH; BAUMGARTNER, 2015; NICKRENT, 2002; BUSSING, 2000).

The mistletoe is a small shrub with linear and lanceolar leathery leaves that persist for several seasons. Its yellowish-green flowers and develop translucent and whitish berries in late autumn and early winter. VA does not grow on land but is spread to tree trunks by birds whose excreta contain seeds. Unlike other plants, VA has a vegetation period of 12 months, never touches the land, and blooms during the winter (URECH; BAUMGARTNER, 2015; NICKRENT, 2002; BUSSING, 2000).

Viscum album is attached to a host branchusing a primary haustory (Figure 1 - B), described as a modified radicle. During germination and once in contact with the host/surface, the radicle tip becomes expanded and flattened to form an adhesive disc (RUBIALES; HEIDE-JØRGENSEN 2011). When contact with the host is established, the outermost cell layer (epidermis) develops a growth point (meristem) (URECH; BAUMGARTNER, 2015; NICKRENT, 2002; BUSSING, 2000). Each leaf supports a bud, which produces the growth increase for the next year. The number of subsequent internodes reveals the approximate age of the plant. It takes 2-4 years to germination occurs, endophyte establishes, and leaf starts its development. The leaves are perennial (NICKRENT, 2002; BUSSING, 2000).

Bioactive Compounds

It is challenging to identify all active phytochemicals compounds present in the *Viscum album* plant. A broad spectrum of different compounds has been described, such as proteins, polysaccharides, oligosaccharides, steroids, triterpenes, flavonoids, alkaloids, lipophilic molecules (SZURPNICKA et al., 2019; URECH; BAUMGARTNER, 2015; AMER et al., BUS0709 et al., BUS0709 et al., BUS0709 2000), syringin (PANOSSIAN et al., 1998), viscumneoside XII, viscumneoside XIII, viscumneoside XIV (DAI et al., 2019), and conjugated acetylene compounds (CAO et al., 2019). It is widely reported that the plant's main effects are derived from lectins and low molecular weight proteins, such as viscotoxins, which were described around 1950 (BUSSING, 2000; URECH; BAUMGARTNER, 2015). Viscotoxins (VTs) are thionines and are classified in alpha and beta. They are rich in cysteine, proteins with a low molecular weight of approximately 5kD (TABIASCO *et al.*, 2002; BUSSING, 2000; SCHALLER *et al.*, 1996), and are resistant to protease (TABIASCO *et al.*, 2002). However, seven more forms were identified, such as VT A1, A2, A3, B, (TABIASCO *et al.*, 2002; BOGOMOLOVAS *et al.*, 2009; SCHALLER *et al.*, 1996) B2, C1, and OS, each with a chain of 46 amino acids with homologous sequences. Thirty-two of 46 positions have identical amino acids, and all forms have three disulfide bridges (Cys3/Cys40, Cys3/Cys32, and Cys16/Cys26), providing a compact structure. Thischaracteristic probably explains the high stability regarding denaturation (URECH; BAUMGARTNER, 2015).

Analysis of the 3D structure of the VTs produced information about a specific phosphate-binding site. This bond and the amphipathic structure of the VT must interfere with the cell membrane and destroy its integrity, generating cytotoxic effects (ORRÙ *et al.*, 1997).First, stimulating necrosis and a minor induction of apoptosis (BÜSSING, 2000). Interestingly, despite their identical structure, VTs present a different biological behavior in the three VAspecies (SHALLER *et al.*, 1996). TheVTs micromolar

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concentrations are cytotoxic to the targets; the bioactivity concerning NK lysis is within the nanomolar range and differs among the viscotoxin isoforms: VTA1 (85 nm), VTA2 (18 nm), and VTA3 (8 nm).

According to Senthilkumar and Rajasekaran (2017), VTs can be considered promising antimicrobial compounds that belong to the antimicrobial peptides (AMP) family. These authors tested the different VTs for their antimicrobial potential and concluded that VTA3 has a better efficacy since several physicochemical characteristics demonstrated its antimicrobial peptide stability among the available VTs. Knowledge of how this peptide establishes its conformation represents the first step in determining the mechanisms adjacent to its antimicrobial activity and in the planning of rational treatments. It is suggested that the rigid nature and stability of a VT peptide framework make it usefulin planning for new medicines. A study demonstrated the VTA3 stable structure provided by various physicochemical parameters and the S-S bonds that made this VT a model for potential peptide therapies (SENTHILKUMAR & RAJASEKARAN, 2017).

As stated by Tabiasco *et al.* (2002), VTs have an immunomodulatory capacity. Therefore, the authors demonstrated that when VTs are administered in non-toxic concentrations, they may increase the death of tumor cells, mediated by NK cells. In its turn, they spare non-target cells from NK lysis, showing a specific selectivity, which is still unknown. Additionally, Tabiasco et al. (2002) indicate that, within such non-toxic concentrations, VTs do not activate NK cells but act in cellular conjugates to increase the resulting lysis. The authors also reported that VTs micromolar concentrations might be cytotoxic to targets, and their bioactivity concerning NK lysis is within the nanomolar range and differs among the VT isoforms A1, A2, A3.

Lectins are carbohydrate-binding proteins with various activities, such as anti-tumor and immunomodulatory effects (KOVACS *et al.*, 2000; LYU; PARK, 2007), such as increased phagocytic activities and the release of cytokines by granulocytes and monocytes (KOVACS *et al.*, 2000). These substances are proposed as potentials, in biological and therapeutic research, due to their interactions with glycans bound to receptors on cell surfaces, responsible for primary cell signaling and biological responses (SOUZA *et al.*, 2013). In particular, lectins can induce the activation of several immune cells through the binding of Toll-like receptors (TLRs). They can also induce the secretion of cytokines (IL-10 and IL-12) through the activation of macrophages and dendritic cells by connection to TLR2 (PANUNTO-CASTELO *et al.* 2001; COLTRI *et al.*, 2008).

Three different types of ML lectins were identified in VA: MLI (115kDa) - galactose, MLII (60kDa) - galactose-and N-acetyl-D-galactosamine, and MLIII (60kDa) - N-acetyl-D-galactosamine (JUNG *et al.*, 1990; AHMED *et al.*, 2018; BUSSING, 2000; URECH; BAUMGARTNER, 2015). These lectins belong to the type 2 ribosome inactivation protein consisting of a protein with B subunit and a toxophoric chain A, an N-glycosidase RNA. ML blocks protein synthesis by hydrolysis of 28S rRNA in the ribosome of eukaryotic cells, inducing apoptosis. The amino acid sequence of tertiary and quaternary structures of the MLI and the A chain of the MLIII is not yet fully understood (AHMED *et al.*, 2018).

The biological action exerted by lectins is considered to be somewhat limited due to their high toxicity. Park *et al.* (2000) reported that VA lectin could induce nitric oxide production and secretion of TNF-α in macrophages. However, although ML has several biological and immunological activities, its use is limited in cancer therapy or as an adjuvant due to its toxicity to normal cells.

Viscum album polysaccharides are found among fruits and green parts of the plant (leaves and stems). High methylation of galacturonan, pectin with a molecular weight of 42kD, and arabinogalactan, with a molecular weight of 110kD, were isolated from stems and leaves (JORDAN, WAGNER, 1986). Fruits are especially rich in polysaccharides and contain rhamnogalacturonan, arabinogalactans (above 1, 340kD), and small amounts of xyloglucans (EDLUND *et al.*, 2000). The high molecular weight of arabinogalactan selectively stimulates the proliferation of CD4+ T helper lymphocytes (STEIN & BERGER1999) and stimulates NK cells (MÜLLER; ANDERER, 1990). A recent study by Chai and Zhao (2017) describes the anti-tumor activity of VA-derived polysaccharides. Such activity supposedly occurred through the apoptosis induction by the interference in the G1 phase of the cell cycle and was observed in hepatocarcinoma cells.

Viscum album is a plant rich in triterpenes, betulinic acid (FUKUNAGA *et al.*, 1987), oleanolic acid, ursanolinic acid (WAGNER *et al.*, 1984), and lupeol acetate (URECH *et al.*, 2006; ORHAN *et al.*, 2006). Stigmasterol phytosteroid and beta-sitosterol are also present in the VA extracts (URECH *et al.*, 2006). Lipophilic extracts contain saturated oils, such as palmitic, arachidonic, lignoceric, and cerotic acids, and unsaturated oils, such as linoleic and linolenic acids (URECH *et al.*, 2006; ORHAN *et al.*, 2006).

Stammer *et al.* (2017) mentioned that oleanolic acid and its derivatives inhibit *in vitro* cell proliferation and induce cell apoptosis. Moreover, *in vivo* experiments demonstrated the cytotoxic effect of oleanolic acid on gallbladder carcinoma cells (LI *et al.*, 2015), hepatocellular carcinoma (YANG ET AL., 2012), and pancreatic carcinoma (WEI *et al* ., 2012). Due to their low solubility, triterpene acids do not occur in significant amounts in the VA commercially produced extracts (JAGER *et al.*, 2007). However, the use of cyclodextrins potentiated the solubilization of triterpene acids, overcoming the loss in standardized aqueous extracts. Previous studies have shown the effectiveness of a combined mistletoe extract produced by adding solubilized triterpene and fatty acids (TT) to aqueous VA extracts, creating a whole plant extract added with triterpenes (viscumTT). This whole plant extract effectively induced apoptosis in acute and lymphoblastic myeloid leukemia (DELEBINSK et al., 2015), Ewing's sarcoma (TWARDZIOK et al., 2017), and osteosarcoma (KLEINSIMON et al., 2017), and also inhibited tumor growth in *in vivo* murine melanoma cells (STRUH et al., 2012).

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Flavonoids (HÄNSEL et al., 1994; FUKUNAGA et al., 1987; BECKER; EXNER, 1980), phenylpropanoids (FUKUNAGA et al., 1987; WAGNER et al., 1984), and alkaloids (KHWAJA et al., 1986; KHWAJA et al., 1980) represent the group of the most abundant substances in the plant kingdom and are present in the VA. Several pieces of evidence of their pharmacological roles in various pathologies are responsible for the growing interest of the scientific community (LORCH, 1993). The first description of flavonoids present in VA dates 1955. After that date, some subtypes were discovered, such as aglycahomoeriodyctiol, sakuranetin, rhamnazin, and isorhamnetin (BECKER; EXNER, 1980; FUKUNAGA *et al.*, 1987; HÄNSEL *et al.*, 1994). However, there are no data available in the literature for most of these subtypes. Becker and Exner (1980) studied the flavonoid patterns of the VA subspecies being quercetin and a series of methyl ether of quercetin, which can be accumulated in the plant (WOLLENWEBER *et al.*, 2000). Other authors have also reported some flavanones and chalcones as constituents of this plant (WOLLENWEBER *et al.*, 2000).

According to Panossian*et al.* (1998), four phenylpropanoids were isolated from the VA extract, such as coniferin, syringin, and syringenin. The structures were established based on spectral and chemical data. They also describe these substances' biological activities, such as the ability to inhibit ADP-induced platelet aggregation, inhibit leukotriene B4 release from TPA, and from human granulocytes stimulated with calcium ionophore A-23187, as well as an anti-tumor activity associated with protein kinase C (PKC) inhibition. The alkaloids present in the VA extracts are not considered typical alkaloids and are reported as "alkaloids-like" including tyramine, phenylethylamine, choline, and acetylcholine (BUSSING, 2000). Other components of VA include carbohydrates such as homogalacturonan, pectin, arabinogalactan, and rhamnogalacturonan. In addition, the contents of the plant (monosaccharides and polyols) were evaluated after acid hydrolysis. The results varied depending on the host tree (quercusor pine). The compounds inositol and galactose were dominant in the pines, with 58% and 44% dry weight (JORDAN, WAGNER, 1986).

Cao *et al.* (2019) identified two new conjugated acetylene compounds, dibutyl (2Z, 6Z)-octa-2, 6-dien-4-yne dioate and dibutyl (2E, 6E)- octa-2, 6-dien-4-yne dioate. The mechanism of action of these two substances was evaluated by the antioxidant activity of the compounds and used the xanthine oxidase inhibitory activity test, obtaining satisfactory results.

Furthermore, Dai *et al.*(2019) reported three new flavonoid glycosides, called viscumneoside XII, viscumneoside XIII, and viscumneoside XIV, which were isolated from the aerial part of the *V. album* plant. Their structures were identified by spectroscopic data analysis. Also, the cytotoxicity assay showed these flavonoids had significant inhibitory activities against C6, A549, and MDA-MB-231 (the inhibition rate reached about 50%, 70%, and 74%, respectively, with IC50 $\leq$ 60.00 $\mu mol \cdot L^{-1}$), while the inhibition of TF-1 and Hela was not significant, with approximately 10% inhibition. A549, TF-1, Hela, MDA-MD-231, and C6 cell lines were obtained from the Shanghai cell bank. All tests were performed in duplicate with positive control with doxorubicin hydrochloride.

Viscum album and its action in cancer patients

Since ancient times, VA has been used in Europe to treat various diseases by conventional and complementary medicines (LONGHI *et al.*, 2020; LOEF; WALACH, 2020). Since 1917 VA preparations have been administered in therapy against cancer and are considered the most used treatment by complementary medicine for cancer patients (FELENDA *et al.*, 2019).

Therapy with VA is indicated for the treatment of cancer patients in a curative and/or palliative way with increasing frequency (KAESTNER *et al.*, 2019; MENKE *et al.*, 2019). It is considered the most frequently prescribed medication among German doctors (ROSTOCK, 2020; MATTHES *et al.*, 2020), including among pediatricians (MENKE *et al.*, 2020). In Europe, more than 88% of cancer patients opt for complementary therapies, and 77% of them use therapy with VA (MATTHES *et al.*, 2020).

The administration of VA extracts have already been described in the treatment of medulloblastoma (MENKE *et al.*, 2020), cholangiocarcinoma (VALLE *et al.*, 2019), transmissible venereal tumor (VALLE *et al.*, 2019), melanoma (STRÜH *et al.*, 2012; WERTHMANN et al., 2017; MELO et al., 2018; VALLE et al., 2020), cervical carcinoma in situ (REYNEL et al., 2018), carcinoma pancreatic (SCHAD et al., 2013; WERTHMANN et al., 2018), renal carcinoma (WEI et al., 2013; WERTHMANN et al., 2019), squamous cell carcinoma (KLINGBEIL et al., 2013), bladder carcinoma (URECH et al., 2006), hepatocellular carcinoma (YANG et al., 2012; WANG; ZHANG, 2013; KUMAR et al., 2016; YANG et al., 2019), ewing's sarcoma (TWARDZIOK et al., 2017), myeloma (KOVACK et al., 2012; VALLE et al., 2018), aoveolar rhabdomyosarcoma (STAMMER et al., 2017), glioma and glioblastoma (SCHÖTTERL et al., 2019), neuroblastoma (DELEBINSKI et al., 2011; KAESTNER et al., 2019), gastric carcinoma (KIM et al., 2012), among others.

Viscum album has bidirectional activity in the treatment against cancer, showing a direct relationship in terms of improving the patients' quality of life (KAESTNER *et al.*, 2019; LOEF; WALACH, 2020) by reducing fatigue, exhaustion, nausea, vomiting, depression, anxiety, pain, and side effects caused by conventional therapies, thereby improving the patient's sleep and appetite (KAESTNER *et al.*, 2019). It also demonstrates anti-tumor activity by selective cytotoxicity (VALLE *et al.*, 2020), induction of apoptosis (HAN *et al.*, 2015), and inhibition of angiogenesis (ELLURU *et al.*, 2009) by mechanisms of action not well elucidated until this moment.

Oei *et al.* (2019) describes that the anti-cancer activity demonstrated by VA is linked to its immunomodulatory activity, such as increased maturation and activation of dendritic cells (STEINBORN *et al.*, 2017), increase in leukocytes, eosinophils, granulocytes (HUBER *et al.*, 2011) and lymphocytes, increased cytokine secretion (ELLURU *et al.*, 2009), and increased natural killer cell activity (KIM *et*

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al., 2012).

Melo *et al.* (2018) demonstrated and identified that some secondary metabolites, such as the phenolic compounds present in VA extracts, presented anti-cancer activity against B16F10 and K562 tumor cell lines, showing selective tumor effect, cytotoxicity with apoptosis induction, and effect on the cell cycle. Moreover, the authors propose that the identified compounds are the possible contributors to the antiproliferative and apoptotic effects of VA, suggesting an interesting potential for cancer pharmacotherapy.

According to Oei *et al.* (2020), the impact of oncological therapies in the reports of patients with breast cancer without the occurrence of metastasis is very significant and stressful in the long term. Chemotherapy and immunotherapy are included as points that increase fatigue, decrease thermal balance, and affect physical functioning. In its turn, their research showed that the co-administration of VA to conventional treatments had better effects in reducing fatigue, insomnia, and the physical activity itself, as well as in thermoregulation. Therefore, they concluded that complementary therapies with VA administration could be indicated to relieve and decrease the burden of clinical signs during conventional treatments for breast cancer.

Kaestner *et al.* (2019) described a decrease of neuroblastoma tumors in patients submitted only to chemotherapy treatment. However, a reduction in their quality of life was also observed. They also observed that, despite being subjective, the quality of life of patients undergoing chemotherapy treatment associated with VA therapy could be preserved for a long time, even after the disease's recurrence or progression.

3. Conclusion

Viscum album has been used for centuries for different purposes. It includes various preparation forms, such as extracts, teas, and creams by the traditional medicine with its simple herbal preparations, or by the anthroposophic medicine or homeopathy with more complex forms of preparation. Its variety of bioactive compounds is notorious, and its complex range of pharmacological activities that have not been deeply studied yet. This plant is gaining more relevance each day in *in vitro* and *in vivo* studies mainly due to its cytotoxic and immunomodulatory activities. It is a medicine with bidirectional activity when administered to cancer patients since it stimulates the vital forces of the organism, improving immunity, and has a selective cytotoxic activity for tumor cells. Therefore, due to its satisfactory clinical area results, *Viscum album* is receiving much attention from the scientific community. This review sought to gather as much information about the *Viscum album* plant regarding its botanical characteristics, bioactive compounds, and activity in cancer patients. Although known for a long time, few scientific evidences of the plant effects in the molecular field are known. Therefore, this is a new field for further studies by the scientific community concerning the isolation and identification of bioactive compounds, pharmacologic activities, interactions, and synergy among compounds and possible mechanisms of action. It is a new field for science that should be explored, given all its clinical evidence and proven clinical activity.

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