

REVIEW OF MISTLETOES — A RESOURCE IN DIABETES

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Abstract: The mistletoe is a group of plants that is made up of more than 1300 species, which grow in a diverse number of environments; worldwide; with exception of Antarctica; and areas of extremely dry or cold weather from which they are not able to grow. All of them share a common form to grow. This form is known as obligate hemiparasitism that works with an organ called the haustorium; from which they can absorb water and mineral salts from their hosts. For this reason, it is known that these types of plants are rich in polyphenolic compounds with several biological activities. This group is made up by five families within the Santales. The *Loranthaceae* and *Viscaceae* families are well studied and distributed throughout the world, Europe, the Americas, Africa, Asia, and Australia. These families comprise the majority (> 98%) of mistletoe species. Mistletoe has been used as a medical treatment for various diseases in traditional medicine. They have been used to treat diseases like cancer, immunomodulatory diseases, cardiac diseases, hepatoprotective diseases, neuropharmacological diseases, besides of having found antibacterial and antifungal activities within them. The objective of this review is to focus on the research on the antidiabetic, antioxidant, and anti-inflammatory properties of different species of mistletoe since diabetes is a growing global health problem. Further and deeper research will be needed to determine solvent type and which chemical compounds are responsible for biological activities. As a result, mistletoe could become a source of new therapies that support diabetes treatments.

Keywords: Mistletoe, antidiabetic, antioxidant, alpha-amylase, alpha-glucosidase.

INTRODUCTION

The obligate hemiparasite plants of the order *Santalales*, receive the common name of mistletoe. Mistletoes belong to a group of plants called parasites, which to complete their life cycle they require a host tree. Mistletoes that are aerial parasites attach to the branches of the host through a specialized vascular connection called haustory (modified root), with which they subtract water and nutrients from the host even though they are capable of photosynthesis (hemiparasites) Szurpnicka et al. (2020).

Mistletoes play an important role in mythology, legends, and some European customs. In 1990's *Viscum (V.) album* was released in Northern California. It is currently used as a decoration and as a symbol of the Christmas season. This mistletoe is one of the best known and studied due to its anticancer, immunomodulatory, antibacterial, antioxidant and among other activities (Kleszken et al., 2022). Mistletoe *V. album*, is a semi-parasitic plant of several species of trees belonging to the family of santalaceas. It is native to Europe and Western and Southern Asia (Szurpnicka et al., 2020).

In the present review, the composition, antidiabetic activity, antioxidant and inflammation activity of different species of mistletoe are shown. The responses have been very diverse due to the regions, types of extract, climate and host tree from which mistletoes are obtained. In the case of diabetes mellitus pathophysiological complications such as microvascular and macrovascular are associated with oxidative and inflammatory stress processes, one of the reasons that more research is needed in this field of study.

METABOLITES IDENTIFIED IN MISTLETOES

The importance of knowing the composition of a plant is because secondary metabolites and their interactions with other molecules within another organism give a specific biological activity. The composition of plants complies with the activity of defense and preservation of plants (Kumal et al., 2021). In addition, it has been verified that compounds such as catechins, flavonoids, tannins, alkaloids, polysaccharides, carbohydrates, peptidoglycans, guanidines, steroids, glycopeptides and terpenoids, have bioactivity against hyperglycemia. In the case of mistletoes, it has been detected that the main constituents are those extracted from the host tree, among these constituents are phenolic compounds, flavonoids, tannins, glycosides, proteins, and carbohydrates (Table 1) (Li et al., 2018). Other components with good activity are lectins and viscotoxins (Pietrzak & Nowak, 2021; Tsekouras et al., 2020; Urech et al., 2006). The variety of components that can be extracted in water, due to their solubility are polyphenols, phenolic acids, flavonoids, terpenoids and alkaloids, so their biological activity can be restricted by the type of extraction. Reports have been published where viscothionine (46-amino acid peptide), promotes insulin secretion from pancreatic β cells (Park et al., 2019).

In the extraction of compounds, it is important to consider the polarity of molecules and the use of solvents with different polarity. In the *P. Capitata* study the phenological evaluation, the effect of the extraction solvent, the host plant, on phytochemical compounds, antioxidants, and antidiabetic activities were performed. The HPLC profile revealed the dynamics of phenolic compounds and helped to establish the best solvent and harvest status (Feudjio et al., 2020). For *V. album* extracts, ethanol and methanol are best suited for

extracting compounds that have a wide range of polarities, water is the most suitable solvent for extracting very polar compounds. In the ethanolic and methanolic extracts, the most abundant compounds are phenols and flavonoids (Majeed et al., 2021).

In Nigeria, cocoa trees were found; bread tree; tail nut tree; and almond trees infested with mistletoe *L. begwensis* *L.* contain a wide variety of phenolic compounds. However, a significant amount of hydroquinone (19,909 mg/100 g), and protocatechic acid (1,359 mg/100 g) were found only in the almond tree (Oboh et al., 2018). According to the stage of growth, it was found that during flowering and fruiting, in the extract of *P. capitata* of *Persea americana* and *P. sidium guajava* the total content of phenols, flavonoids, flavonols and tannins was significantly higher ($p < 0.05$) than *P. capitata* of *Podocarpus mannii* (Feudjio et al., 2020). In Nepal, the mistletoe species *S. elata* and *S. parasitica* in addition to their high content of phenols and flavonoids, the species *S. parasitic* has the highest antioxidant activity. Therefore, it is suggested that mistletoes that are used as fodder can be consumed by humans. Currently, the species of these mistletoes are used for therapeutic purposes *H. ligustrina* (for its antioxidant activity), *M. cochinchinensis* (for jaundice, headache, cough treatment), *V. album* (immunological activity), *V. articulatum* (cardiovascular diseases, treatment of inflammation of liver and kidneys), *V. liquidambaricola* (used in oncology) (Kumal et al., 2021). Harvesting factors in the chemical composition of parasitic plants; changes in polyphenol and flavonoid composition and antioxidant activity have been seen. Climatic conditions such as temperature, seasonal variations and the place of collection also affect the content of secondary metabolites (Pietrzak & Nowak, 2021).

In the use of mistletoe, it should also be

No	Name of mistletoe	Host	Family	Part used	Extraction solvent	Seasons	Concentration of the extract/ compound	References
1	<i>Loranthus Micranthus</i>	<i>Kola Acuminata</i> Nigeria	<i>Loranthaceae</i>	Leaves	Aqueous methanol	January, April, July and October	In April, phytochemical test shows a higher (++++) concentration of Flavonoids and Alkaloids, followed by tannins and terpenoids. In October the alkaloids were in greater proportion. In January the reducing sugar were in high concentration. In July medium (++) concentration of flavonoids, alkaloids, terpenoids and reducing sugar were found.	(Osadebe <i>et al.</i> , 2021)
2	<i>Viscum album</i>	<i>Azadirachta indica</i> (Neem) <i>Psidium guajava</i> (guava) <i>Acacia albida</i> Nigeria	<i>Loranthaceae</i>	Leaves and stems	Distilled water	No mention	Alkaloids was absent in leaf of <i>V. album</i> obtained from <i>P. guajava</i> . Saponins had the highest scores (++++) in all the extracts followed by phenols and carbohydrates with moderate scores (++) Reducing and combined sugars had the lowest concentrations (+).	(Wasagwa <i>et al.</i> , 2018)
3	<i>Dendrophthoe pentandra</i> (L.) Miq	No mention Indonesia	<i>Loranthaceae</i>	Leaves	Methanol, n-hexane, ethyl acetate, and total flavonoid	No mention	The crude extract of <i>D. pentandra</i> (L.) Miq leaves exhibited the presence of flavonoids and terpenoid or steroid.	(Hardiyanti <i>et al.</i> , 2019)
4	<i>Loranthus Micranthus</i>	Egbo Area in Ilaro, Ogun State, Nigeria.	<i>Loranthaceae</i>	Leaf and Twig	Methanol	The dry season.	Thirteen of the compounds were commonly found in both leaf and twig of <i>L. micranthus</i> . The similar compounds are Cyclobutanol, 1,4- Dimethyl hexyl alanine, Piperazine, 4- Butyl phenol, N-(2-Hydroxy benzyl) alanine, Palmitic acid methyl ester, Ethyl hexadecanoate, 2- Undecyl phenol, Phytol, Methyl stearate, Methyl linoleate, Ethyl oleate and Squalene.	(Olakanmi <i>et al.</i> , 2020)
5	<i>Viscum album</i> L.	<i>Populus ciliata</i> L., <i>Ulmus villosa</i> L., and <i>Juglans regia</i> L.	<i>Loranthaceae</i>	Stem, leaf, and berry	Ethanol, methanol, and water	December	Phenolic compositions of <i>Viscum album</i> L. Hosted by <i>Populus ciliata</i> L.: Ethanolic berry 19.7 ± 0.38 mg/g/ Methanolic stem 17.6 ± 0.17 mg/g Leaf extracts 13.87 ± 0.03 mg/g, Flavonoids hosted by <i>Ulmus villosa</i> L. mEthanolic leaf 2.61 mg/g ± 0.15 Flavonoids hosted by <i>Juglans regia</i> L. Ethanolic leaf 2.38 ± 0.04 mg/g.	(Majeed <i>et al.</i> , 2021)
6	<i>Tapinanthus globiferus</i>	1. <i>Psidium guajava</i> 2. <i>Vernonia amygdalina</i> 3. <i>Moringa olifera</i> Lam. Nigeria	<i>Loranthaceae</i>	Leaves	Methanol	No mention	The phytochemicals present in abundance in the extracts were Alkaloids, Flavonoids, Phenolics, Saponins, Tannins.	(Oche <i>et al.</i> , 2019)

7	1. <i>Helixanthera ligustrina</i> (Wall.) Danser 2. <i>Macrosolen cochinchinensis</i> (Lour.) Tiegh 3. <i>Scurrula elata</i> (Edgew.) Danser	1. <i>Pyrus pashia</i> Buch.-Ham. ex D. Don 2. <i>Schima wallichii</i> Choisy 3. <i>Myrica esculenta</i> Buch.-Ham. ex D. Don	1, 2, 3 and 4: <i>Loranthaceae</i> 5, 6 and 7: <i>Santalaceae</i>	Whole	Methanol	No mention	The highest total flavonoid content was estimated as 31.5 ± 2.3 mg QE/g for <i>V. album</i> and lowest as 24.9 ± 2.3 mg QE/g for <i>M. cochinchinensis</i> . The highest amount of total phenolic content was found in <i>S. parasitica</i> (32.9 ± 2.5 mg GAE/g) while lowest found in <i>V. album</i> (20.6 ± 2.1 mg GAE/g),	(Kumal et al., 2021)
8	Viscum articulatum Burm. f. (CMC) and Viscum liquidambaricolom Hayata (CMP)	No mention China	<i>Loranthaceae</i>	No mention	70% (v/v) acetone	No mention	The total phenolic content of soluble, insoluble-bound and total phenolic extracts in CMs ranged from 8.65–9.91 mol FAE/g, 3.95–4.59 mol FAE/g and 12.59–14.50 mol FAE/g, respectively. The total flavonoid content of soluble, insoluble-bound and total flavonoids extracts in CMs ranged from 0.93–3.05 mol CE/g, 0.10–0.30 mol CE/g and 1.23–3.14 mol CE/g, respectively.	(Li et al., 2018)
9	<i>Viscum schimperi</i>	No mention, Saudi Arabia	<i>Santalaceae</i>	Aerial parts	Methanol extract as well as its chloroform, n-butanol and water fractions	May 2010	per gram plant dry wt (mean ± standard error of mean) 3-O-caffeoylquinic acid - 54 ± 9.0 µg/g 5-O-caffeoylquinic acid - 4401 ± 288.9 µg/g Feruloyl quinic acid - 327 ± 47.9 µg/g Sinapoylquinic acid - 163 ± 24.1 µg/g Eriodictyol - 56 ± 2.1 µg/g Naringenin - 45 ± 5.8 µg/g Eriodictyol hexoside - 74 ± 4.5 µg/g Isorhamnetin 3-O-glucoside - 142 ± 14.5 µg/g	(Abdallah et al., 2015)
10	<i>Dendrophthoe pentandra</i> (L.)	<i>Bauhinia purpurea</i> Indonesia	<i>Loranthaceae</i>	Leaves and flowers	Methanol	No mention	Contained alkaloids, phenolic compounds, flavonoids, saponins, and terpenoids	(Alharith et al., 2019)
11	<i>Tapinanthus bangwensis</i>	<i>Citrus sinensis</i> Nigeria	<i>Loranthaceae</i>	Leaves	No mention	No mention	Higher amount of compound detected: Cardiac glycosides Flavonoid Tannin	(Omoruyi et al., 2011)
12	1. <i>V. album</i> subsp. <i>album</i> 2. <i>V. album</i> subsp. <i>austriacum</i> 3. <i>V. album</i> subsp. <i>abietis</i>	1. Hosts from: <i>Populus nigra</i> L., <i>Populus nigra</i> L. 'Italica', 2. <i>Pinus sylvestris</i> L. 3. <i>Abies alba</i> Mill. Poland	<i>Santalaceae</i>	Leaves and stems	80% Methanol	Winter 2017-2018	In <i>Populus nigra</i> L. 'Italica' and conifer mistletoe was found the highest content of p-coumaric and syringic acids Protocatechuic acid was mainly present in the mistletoe extract collected from <i>Malus domestica</i> Borkh - 118.03 ± 0.86 g/g extract <i>Fraxinus pensylvanica</i> Marsh - 133.27 ± 1.20 g/g extract <i>Fraxinus excelsior</i> L. - 203.48 ± 9.16 g/g of extract <i>Tilia cordata</i> Mill. - 138.17 ± 1.17 g/g extract <i>Abies alba</i> Mill. - 114.29 ± 1.05 g/g extract	(Pietrzak et al., 2021)
13	<i>Phragmanthera capitata</i>	<i>Persea americana</i> , <i>Psidium guajava</i> , and <i>Podocarpus marnii</i> Cameroon.	<i>Loranthaceae</i>	Whole	n-hexane, ethyl acetate, ethanol, methanol, and water	During vegetative (January 2018), during flowering (March 2018), and during fruiting (April 2018).	HPLC profiles of ethyl acetate extracts showed a dynamic accumulation of phenolic compounds in <i>P. capitata</i> . Indeed, during the vegetative stage, quercetin appeared as the main constituent, while during flowering, rutin replaced quercetin as the main constituent.	(Feudjio et al., 2020)

Table 1. Potential antidiabetic active compounds extracted from different species of mistletoe

considered to study each part of the plant, since it has been found that the mistletoe *Dendrophthoe pentandra* (L.) Miq., from Indonesia showed to have difference in the number of components in leaves and flowers alkaloids, phenolic compounds, saponins, flavonoids and terpenoids. Flower extracts, having a higher number of phenols and flavonoids, have a correlation with antioxidant activity (Alharits et al., 2019). In addition, of the chemical compounds in mistletoe *Tapinanthus bangwensis* it has been reported that mistletoe leaves have minerals such as Ca, K, P, Mg, Fe, Zn and Na. These minerals play an important role in physiological activities that promote human health, which could be harnessed (Omoruyi & Onyeneke, 2019). Another study has found that the phytochemical composition of extracts from leaves and stems of *V. album* of *Azadirachta indica*, *Acacia albida* and *Psidium guajava*, contain high concentrations of saponins in all extracts, followed by phenols and carbohydrates in moderate concentrations, while reducing and combined sugars had low concentrations. Also, it was found that there is a higher concentration of alkaloids in the leaves (Wasagwa et al., 2018).

IN VITRO ANTIDIABETIC ASSAYS

Recent studies have found that polyphenols found in medicinal plants can inhibit amylolytic enzymes such as α -amylase and α -glucosidase, which could be relevant for the treatment of type 2 diabetes mellitus (Annunziata et al., 2020; Cao et al., 2019). **The α -glucosidase is an enzyme that participates in the digestion of carbohydrates, so its inhibition induces to reduce the absorption of carbohydrates in the small intestine and thus helps control blood glucose levels, so the use of inhibitors is ideal to prevent diabetes and obesity (Dirir et al., 2021; Usman et al., 2019). The α -amylase catalyzes starch,**

forming large, insoluble molecules; hydrolysis produces oligosaccharides or smaller molecules. On the other hand, α -glucosidase degrades oligosaccharides to glucose entering the bloodstream, leading to postprandial hyperglycemia. Therefore, inhibition of α -amylase and α -glucosidase reduces carbohydrate digestion in the small intestine and decreases postprandial hyperglycemia (Ohikhenana et al., 2018). In 2020, Oyeniran evaluated the inhibitory activity of α -amylase and α -glucosidase using moringa leaves (*Moringa oleifera* L.) infested with mistletoe *Tapinanthus bangwensis* L. using the fruit fly model *Drosophila melanogaster* M. the activity of α -amylase and α -glucosidase had a significant reduction ($P < 0.05$) compared to control flies and those that had sucrose feeding and were treated with moringa, infested moringa and mistletoe, these results attribute them to the phytoconstituents present (Oyeniran, Ademiluyi, Oboh, et al., 2021). In 2021, they evaluated mistletoe from moringa and almond host trees. The characterization carried out by HPLC, revealed that the mistletoe leaves that grew on the almond tree had significantly higher amounts ($p < 0.05$) of phenolic compounds. The phenolic content of mistletoe leaves could be modulated by host plants, which also modified the antioxidant capacity and inhibitory activity of α -amylase and α -glucosidase (Oyeniran, Ademiluyi, & Oboh, 2021).

α - GLUCOSIDASE INHIBITORY ACTIVITY

Methanolic extracts, with n-hexane, ethyl acetate and flavonoides extract; from the leaf of *Dendrophthoe pentandra* (L.) Miq, were shown to have antidiabetic activity by inhibiting the α -glucosidase. The mistletoes *Macrosolen* sp., *Dendrophthoe* (D.) sp. and *Scurulla* sp., currently used as herbal teas, have significant antidiabetic activity as α -glucosidase

inhibitors, notwithstanding mistletoe extract *D. sp.* has the highest inhibitory activity. Despite this, there is talk of the possibility of making an infusion with mistletoes, since it could have a synergistic effect (Artanti et al., 2018). One of the mechanisms of action of the antidiabetic activity of the extracts of leaves and stems of *Loranthus Micranthus* includes the reduction of glucose in the gastrointestinal tract since the inhibitory effect of the enzymes α -amylase and α -glucosidase was evaluated. Where stem extract was shown to have a greater inhibitory effect on enzymes ($p < 0.05$) compared to leaf extract (Olahanmi Bodun et al., 2020).

Using mistletoe *Phragmanthera capitata* (Sprengel) S. Balle, it was found that regardless of host and phenological stage, methanolic, ethanolic and aqueous extracts had better α -glucosidase inhibition activity, compared to ethyl acetate extracts. The greatest antidiabetic activity was with *P. capitata* extracts who grew up in *P. americana* and *Psidium guajava* (Feudjio et al., 2020). Mistletoe *L. begwensis* had no significant difference ($P > 0.05$) from cocoa tree mistletoe extracts (CCT); mistletoe from kola nut tree (KNT); and mistletoe from almond tree (AMT) ($EC_{50} = 1.94 \pm 3.1, 1.92 \pm 2.2, 1.96 \pm 3.5$, respectively). The activity may be due to the binding effect of the phenolic compounds of the extracts. There is a strong inhibition of α -glucosidase, but a slight inhibition of α -amylase activity by mistletoe extracts which could be useful for diabetes treatments (Oboh et al., 2018). Regarding the antidiabetic effects of *V. album* extracts of leaves, seeds and fruits, the best inhibition capacity of the α -glucosidase was observed by extracts obtained by ultrasound-assisted extraction (UAE), where the leaf presented the highest activity, followed by the leaf extract but obtained by homogenizer-assisted extraction (HAE) (0.98 mmol equivalent of acarbose (ACAE)/g extract) (Stefanucci et al.,

2020).

α -AMYLASE INHIBITORY ACTIVITY

The methanolic, ethanolic, aqueous and ketone extracts of *P. capitata*, which presented inhibitory activity of α -amylase at concentrations of 50, 100, 500 or 1000 $\mu\text{g/mL}$, but ketone and methanolic extracts had a greater inhibition of α -glucosidase, which had values of $IC_{50} 71.89 \pm 3.48 \mu\text{g/mL}$ and $91.98 \pm 2.24 \mu\text{g/mL}$ respectively. In contrast, the aqueous extract had the lowest inhibitory activity, IC_{50} of $952.87 \pm 9.87 \mu\text{g/mL}$ (Ohikhena et al., 2018).

The α -amylase inhibitory properties of *V. album* extracts. They show that the greatest inhibition capacity of α -amylase was found with the extract obtained by HAE. Clearly, the leaf extracts retained greater antidiabetic effects compared to the other extracts (Stefanucci et al., 2020).

Likewise, the inhibition of α -amylase has been negatively correlated with the yield of *P. capitata* (Sprengel) S. Balle using extracts with hexane ($r = -0.452, p < 0.05$), ethanolic extract ($r = -0.497, p < 0.01$), and methanolic extract ($r = -0.487, p < 0.01$). In the case of the hexane extract, it had no correlation with the phenolic content, so it was suggested that the active ingredients are not phenolic compounds (Feudjio et al., 2020). Not all extracts evaluated have considerable inhibitory activity of α -amylase, Ohikhena et al. (2018) also evaluated extracts of *P. capitata*; a mistletoe collected from rubber trees, where it was found that antidiabetic activity is not due to α -amylase inhibition, but to α -glucosidase inhibition (Ohikhena et al., 2018).

As for the host trees, the inhibitory activity of *L. begwensis* L. mistletoe has been evaluated of different hosts, where the bread tree (BFT) had the greatest inhibitory effect ($EC_{50} = 1.80 \text{ mg/mL}$) while that of the kola nut tree (KNT) had the lowest activity ($EC_{50} = 2.59 \text{ mg/mL}$).

In this study it is suggested that the inhibitory activity of α -amylase was by an extract rich in phenolic compounds of mistletoe, which indicates a reduction in the hydrolysis of carbohydrates and therefore glucose, which has been correlated with other studies where extracts of *Allium spp.*, tea (black or green) and extracts of *Gossypium herbaceum* or its phytochemicals in α -amylase activity were used in vitro (Oboh et al., 2018). On the other hand, when evaluating the methanolic extracts of *Helicanthus (H.) elasticus* hem a significant inhibition of the α -amylase was found compared to the acarbose reference standard. The results project high inhibitory activity of α -amylase, so *H. elasticus* hem can be developed as a potential remedy for diabetes (Lakzaei et al., 2011).

IN VIVO GLUCOSE LEVEL REGULATION STUDIES

Mistletoes of different species, found in a variety of host trees have been shown to have antidiabetic activity, such as *V. Album* (Table 2) (Abdallah et al., 2015; Adeeyo et al., 2013; Ahmed et al., 2019; Lakzaei et al., 2011; Onyenibe et al., 2019; Park et al., 2019), as it has been shown to help lower blood glucose.

Another important activity that has been detected in mistletoes is insulin resistance since secretion is favored in β -pancreatic cells. This activity could be evaluated by the homeostatic model of insulin resistance (HOMA-IR), demonstrating that aqueous extracts of *V. album* has dose-dependent activity to stimulate insulin secretion (Sanni et al., 2019).

ANTIOXIDANT ACTIVITIES IN VITRO

As a result of several studies, it is known that there is a close relationship between the content of phenolic compounds of medicinal plants with antioxidant activity (Negro et al., 2003). The use of antioxidants has been reported to be beneficial for various neurodegenerative, cardiovascular, diabetes and cancer diseases. The use of antioxidants in diabetes prevents the loss of cell function, therefore prevents cells from having insulin resistance and therefore vascular complications. The severity of diabetes has been seen to increase with increased oxidative damage (Pietrzak & Nowak, 2021).

The antioxidant capacity of mistletoes can be measured in various ways, ferric reducing antioxidant power (FRAP), hydrogen peroxide uptake activity (HPSA), DPPH radical-capturing activity (DRSA), 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) radical reduction capacity (ABTS), oxygen radical absorption capacity (ORAC) and equivalent antioxidant capacity of Trolox (TEAC) (Alharits et al., 2019; Feudjio et al., 2020; Kumal et al., 2021; Li et al., 2018; Pietrzak & Nowak, 2021).

In Chinese mistletoes *V. articulatum* Burm. f. housed in *Camellia assamica* (Mast.) Chang (CMC) and *V. liquidambaricolum* Hayata *parasitarium* in *Pyrus, i. f.* (CMP), soluble and insoluble phenolic compounds were found to have antioxidant activity, which has a correlation, as well as in many other plants. In FRAP, HPSA, DRSA and TEAC evaluations of CM-soluble phenolic extracts were significantly higher than their insoluble bonded phenolic counterparts ($p < 0.05$). CMP extracts with higher concentrations of phenolic compounds and flavonoids have higher antioxidant activity than CMC (Li et al., 2018).

On the other hand, the extraction solvent

No	Name of mistletoe	Period and concentration treatment	Bioactivity in relation to the chemical constituent	References
1	<i>Tapinanthus bangwensis</i>	500 mg/kg body weight 14 days	The blood glucose in the diabetic test (treated) group was significantly reduced to 163.75 ± 46.327 ($P < 0.05$) (mg/dl) compared to 377.50 ± 0.50 (mg/dl) in (STZ)-induced Diabetes mellitus in experimental animals rats.	(Ekhaise <i>et al.</i> , 2010)
2	<i>Helicantus elasticus</i>	For Anti-hyperglycemic effect 200mg/kg body weight Oral glucose tolerance test at the dose of 100, 200 and 400 mg/kg In sub-acute treatment for 21 days at 200 mg/kg	A concentration of 2g/kg body weight did not show any toxic reaction. The extract has antihyperglycemic activity. In blood glucose level at dose of 200mg and 400mg treated group are on par with glibenclamide treated group. In Methanolic extract of <i>H. elasticus</i> and Glibenclamide treated groups have shown significant decrease ($p < 0.01$) in blood glucose level.	(Rajesh <i>et al.</i> , 2015)
3	<i>Viscum album</i>	200 mg/kg 6 weeks	In the mistletoe treated diabetic group, there was a 3% increase in the average body weight of animals at week 3 and a 20.5% increase at week 6 when compared to their average body weight at week 0. The insulin level of mistletoe treated hyperglycemic groups were not significantly different from control ($P > 0.05$).	(Adeeyo <i>et al.</i> , 2013)
4	<i>Viscum schimperi</i>	75 and 150 mg/kg/day 4weeks	The fraction with chloroform (150 mg/kg) showed the highest antihyperglycemic effect. It could normalize fasting blood glucose values with a significant decrease of 78.3% compared with that of untreated diabetic group.	(Abdallah <i>et al.</i> , 2015)
5	<i>Loranthus micranthus</i>	200 and 400 mg/kg Single dose	The crude methanolic extract exhibited statistically significant hypoglycaemic ($P < 0.001$) and anti-hyperglycemic ($P < 0.001$) activities in normoglycemic and alloxan-induced diabetic albino rats, respectively.	(Osadebe <i>et al.</i> , 2004)
6	<i>Loranthus bengwensis</i>	100, 200 and 400 mg/kg 3 days	The extract antidiabetic activity is dose-dependent, i.e. its efficacy is more prominent at a high concentration as observed in the results obtained from the various assessments. It can therefore be said that the higher the concentration of <i>Loranthus bengwensis</i> , the more efficient its antidiabetic activity on diabetic patients.	(Ukpanukpong <i>et al.</i> , 2017)
7	<i>Loranthus micranthus</i> Linn	200 mg/kg 14 days	The extracts possess anti-hyperlipidemic activity. And they improved the hematological indices of the diabetic rats. This is reflected by the increases in the red blood cell count, packed cell volume, white blood cell count.	(Onoja <i>et al.</i> , 2017)
8	<i>Loranthus micranthus</i> Linn	500, 250 y 125 mg/kg 14 days	Treatment groups showed adequate glycemic control at all concentrations used <i>L. micranthus</i> leaf extract, <i>L. micranthus</i> twig extract, and glibenclamide.	(Olakanmi <i>et al.</i> , 2020)
9	<i>Phragmathera incana</i>	200, 400 and 800 mg/kg 14 days	Rats administered with <i>P. incana</i> harvested from <i>C. nitida</i> (kolanut) and <i>T. cacao</i> (cocoa) extracts showed significantly ($P < 0.05$) lower blood glucose levels compared to the diabetic control (417.2 ± 54.56 mg/kg) and glibenclamide treated rats (159 ± 58.00 mg/dl), but comparable to that observed in the normoglycemic control rats (81.4 ± 10.32 mg/dl).	(Ogunmefun <i>et al.</i> 2017)
10	<i>Tapinanthus globiferus</i>	200 and 400 mg/kg 21 days	The extract caused a dose dependent reduction of the levels of total cholesterol and triglycerides when compared with diabetic untreated rats whose levels were elevated by alloxan. These results are in consonance with available published evidence on the antihyperlipidemic, anti-hyperglycaemic potentials <i>Tapinanthus globiferus</i> .	(Atanu <i>et al.</i> 2019)

11	<i>Viscum album</i>	10 mg/kg 20 days	Diabetic rats have high blood glucose as 700,50 mg/dl and it was significantly decreased glucose level when treated with <i>V. album</i> to 514,64 mg/dl in only 20 days of experiment, this decline was statistically significant ($p \leq 0.05$).	(Ahmed <i>et al.</i> , 2019)
12	<i>Loranthus Micranthus</i>	200 and 400 mg/kg 1h 2h, 4h, 6h, 12h, 24h and 72h	The April extract exhibited optimum anti-diabetic activity at both dose levels. This was followed by the extracts sourced in October, July and January respectively	(Osadebe <i>et al.</i> , 2021)
13	<i>Helicenthus elasticus</i>	Anti-hyperglycemic effect: 200 mg/kg Oral glucose tolerance test: 100, 200 and 400 mg/kg. Sub-acute treatment: 21 days.	Anti-hyperglycemic effect: The fall was seen at 30min and remained up to 240min after administration of the extract which was statistically significant ($p < 0.01$). OGTT: The extract at the dose of 200mg and 400mg has significantly decreased blood glucose levels when compared to diabetic control. And they are on par with glibenclamide treated group showing significant decrease. After 21 days: The effect of extracts on parameters like cholesterol, triglycerides, liver glycogen and serum insulin shows significant effect ($p < 0.01$) at the dose of 200mg and 400mg/kg body weight.	(Rajesh <i>et al.</i> , 2015)
14	<i>Phragmanthera incana</i>	150 and 300 mg/kg 5 days	The administration of <i>P. incana</i> infusion significantly reduced the elevated blood glucose levels compared to the diabetic control group. The glucose tolerance ability of the animals in normal control groups was significantly ($p < 0.05$) better than the diabetic groups. The diabetic groups treated with hot water infusion of <i>P. incana</i> were significantly ($p < 0.05$) better than the diabetic control group.	(Sanni <i>et al.</i> , 2019)
15	<i>Plicosepalus acaciae and P. curviflorus</i>	250 mg/kg 4 weeks	Oral administration of pioglitazone hydrochloride, <i>P. acaciae</i> and <i>P. curviflorus</i> extracts, respectively, and solid lipid nanoparticle (SLN) formulations resulted in a significant reduction in the blood glucose and glycated hemoglobin levels as well as insulin resistance in comparison with the diabetic control group.	(Aldawsari <i>et al.</i> , 2014)
16	<i>Viscum album</i>	500 and 1000 mg/kg 24, 48 or 72 h	The administration of extracts significantly reduced the increase in serum glucose concentration induced by alloxan, was prominent 24, 48 and 72 h of alloxan injection. Both the extracts from <i>V. album</i> significantly enhance the serum insulin level as compared to control rats.	(Lakzaei, M. <i>et al.</i> , 2011)
17	<i>Viscum album var. coloratum</i> Ohwi	0–1000 µg/mL	The heat-treated mistletoe extract significantly inhibited α -glucosidase, and the effect increased at higher concentrations of the extract. The results showed that the stimulation of insulin secretion by the heat-treated mistletoe extract gradually increased between 0.25 and 0.5 h, plateaued at 1 and 1.5 h, and decreased thereafter.	(Park <i>et al.</i> , 2019)
18	<i>Viscum Album</i>	500 mg/kg 21 days	Blood sugar levels, HbA1c were significantly decreased and G6PDH significantly increased $p < 0.05$ in <i>V. album</i> , <i>C. longa</i> and pre-eminently <i>V. album</i> + <i>C. longa</i> treated group <i>visà-vis</i> negative control.	(Onyenibe <i>et al.</i> , 2019)

Table 2. List of mistletoes having antidiabetic activity

influences the antioxidant capacity. The total antioxidant capacity of *P. Capitata* extracts obtained by different solvents decreased significantly in the following order: ethanol and methanol, ethyl acetate and hexane. In general, in the reducing power a tendency to decrease was observed during the flowering of *P. Capitata* regardless of the host plant, on the contrary with ethanolic and methanolic extracts the reducing power was greater before and during the fruiting of de *P. Capitata* growing in *P. Guajava* and in *P. Mannii*. As for DRSA it was found that there is no influence according to the host plant. The ethanolic and methanolic extracts presented a stronger activity, regardless of the phenological stage and host plant. The excerpt from *P. Capitata* with hexane and ethyl acetate had the lowest activity with DPPH and in this case was observed to be significantly weaker at the flowering stage of the plant (Feudjio et al., 2020).

INFLAMMATION

Inflammation is a response to antigenic stimuli, infectious agents, and physical injury. The cellular elements involved in inflammation are endothelial and humoral tissue from damaged tissue or near the injured site. Effector cells (Leukocytes), regulated by cytokines or immune system cells, or those produced by plasma enzyme systems are also involved (Pérez & Núñez, 2007). The Korean mistletoe *Viscum album* (KM-110), prepared by the fermentation of two strains of *Lactobacillus* (FKM-110), improved the productivity of inflammatory cytokines such as TNF- α and IL-1 β (Lee et al., 2014). In another study, by evaluating the inflammatory response using mistletoe *Cladocolea loniceroides* in mice with induced diabetes, it was possible to reduce the concentration of inflammatory cytokines IL-6 and TNF- α in the group of diabetic mice (Ruiz et al., 2019). At the time, there is still very few

amount of studies carried out, so we still must delve into this point of study on mistletoes.

CONCLUSION

Research on mistletoes; mainly *Viscum album*, have focused on anticancer and immunomodulatory activities. Currently, *in vitro*, and *in vivo* studies have been carried out studying different pharmaceutical activities, including antidiabetic activity. Therefore, *Viscum album* and other mistletoe of the families *Loranthaceae* and *Santalaceae* have been found to have inhibitory activity of α -amylase and α -glucosidase. Within the different species, a greater inhibitory activity of α -glucosidase is sought, since when the inhibition of α -amylase is very strong, carbohydrates have an excessive fermentation in the colon, causing discomfort. As for phytoconstituents, it is known that the factors involved are the host plant, the season of the year, the type of extraction and the part of the plant. These results may be favorable due to the synergistic action between antioxidant compounds, which help reduce ailments, triggered by increased oxidative stress, such as inflammation. So, it is also necessary to delve deeper into research on the effects that mistletoe extracts have on inflammation. The variables are diverse, so it is necessary to establish an extraction method, if applicable a fraction process and purification method to identify the active components of the plant. Of the chemical groups that are most abundant are tannins, flavonoids, and alkaloids. Therefore, it is important to consider the mechanisms of action, evaluating the antidiabetic activities of the isolated compounds, as well as the extracts since the biological activity can be the result of the synergy of its components of the entire extract. As a result of this review, several species of mistletoe in different countries are used for different purposes, but different research shows that it may be a potential

source used as an adjuvant for diabetes. As it is known this chronic degenerative disease is increasing, and it is necessary to have a variety of medications to control it.

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