Biological activity of mistletoe: in vitro and in vivo studies and mechanisms of action

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Introduction

Mistletoe (Viscum L.) belongs to the family of Viscaceae. In Europe, Asia, Africa and Australia, about 100 species of mistletoe can be distinguished, of which the most known are in Santalaceae: Viscum album L. (European mistletoe), Santalaceae: Viscum album subsp. Coloratum Kom. (Viscum coloratum (Kom.) Nakai, Korean mistletoe), Santalaceae: Viscum articulatum Burm. f., Santalaceae: Viscum shimperi Engl., Santalaceae: Viscum capense L.f. and Santalaceae: Viscum cruciatum Sieber ex Boiss. Mistletoe is a semi-parasitic evergreen shrub, which means it depends on having water and some nutrients supplied from another plant (host tree) while it produces carbohydrates in a process of photosynthesis. Viscum species inhabit many types of wooded habitats and parasitize both deciduous and coniferous trees (Bussing 2000). For clinical applications, the most popular species are mistletoe parasitizing fir, maple, almond, birch, hawthorn, ash, apple, pine, poplar, oak, willow, lime and elm (Kienle et al. 2011).

Viscum species have been used in the traditional medicine of Europe for centuries. Hippocrates used mistletoe to treat diseases of the spleen and complaints associated with menstruation, while Pliny the Elder used it to treat epilepsy, infertility and ulcers. In the Middle Ages, Paracelsus recommended mistletoe as a treatment for epilepsy. Hildegard von Bingen described mistletoe as a treatment for diseases of the spleen and liver. Mistletoe was also applied for deworming children, to treat labour pains, gout, affections of the lungs and liver, leprosy, mumps, fractures and hepatitis. During the eighteenth century, mistletoe was applied for “weakness of the heart” and oedema (Bussing 2000). By the end of the nineteenth century, mistletoe was rejected by scientists as a folklore remedy. The scientific interest on mistletoe was awakened in the twentieth century, as Gaultier investigated the effect of oral or subcutaneous
applications of fresh *Viscum album* L. extracts on blood pressure in humans and animals (Bussing 2000; Committee on Herbal Medicinal Products 2012). In 1920, *Viscum album* L. was introduced as a cancer treatment by Rudolf Steiner who recommended a drug extract produced in a complicated manufacturing process combining sap from mistletoe harvested in the winter and summer (Bussing 2000). Mistletoe was also commonly used in other parts of the world. In Japan, mistletoe was used to treat hypertension, spasms of the heart, rheumatic pain, threatened abortion and locally to treat frostbite. In India, a tea prepared from mistletoe leaves was used to treat diabetes, while a preparation of *Viscum articulatum* Burm. f. was given in fevers with aching limbs. In Africa, *Viscum* species were a remedy to treat diarrhoea and an enema for stomach troubles in children. In Israel, *Viscum cruciatum* Sieber ex Boiss. was commonly used to treat constipation in young children and adults. Mistletoe was also used against general pain, backache and arthritis. In the traditional medicine of Egypt, the plant was used for the treatment of epilepsy, arteriosclerosis, and diseases of cardiac arteries, and as a hypotensive (Bussing 2000; Lev et al. 2011; Committee on Herbal Medicinal Products 2012). Such varied pharmaceutical applications result from the rich chemical composition of *Viscum* species, which largely depend on the host species. The main active compounds are lectins, viscotoxins, flavonoids, phenolic acids, sterols, lignans, terpenoids, phenylpropanoids, alkaloids and fatty acids (Szurpnicka et al. 2019). In this review, we would like to summarize the scientific data on the pharmacological activity of *Viscum* species and analyse the probable mechanisms of actions of mistletoe.

**Anticancer and immunomodulatory activity**

In German-speaking countries, mistletoe has been used as complementary anticancer therapy for more than 100 years. *Viscum album* L. preparations can be divided into phytotherapeutic extracts standardized on a certain lectin level (brand names such as Cefalektin, Eurixor, Lektinol) and anthroposophical/homeopathically produced extracts (brand names such as Abnoba*Viscum*, Helixor, Iscador, Isucin, Isorel) (Freuding et al. 2019). The main anticancer compounds isolated from *Viscum* species are lectins (Thies et al. 2005; Eggerschwiler et al. 2007) and viscotoxins (Schaller et al. 1996). Later studies have shown that other compounds, such as phenolic compounds (Melo et al. 2018), triterpene acids (Delebinski et al. 2015) and non-polar compounds (Čebović et al. 2008), have also shown antitumor properties. Furthermore, it was reported that complete mistletoe extract is more potent at inhibiting tumour cells than isolated compounds (Felenda et al. 2019), and there is synergistic action between different groups of mistletoe compounds (Twardziok et al. 2016; Kleinsimon et al. 2017). Mistletoe shows bi-directional activity in the treatment of cancer. Firstly, it affects the quality of life of cancer patients by the improvement of fatigue, sleep, exhaustion, nausea, vomiting, appetite, depression, anxiety, pain and side effects of traditional treatment (Kiene and Kiene 2010; Brandenberger et al. 2012; Kim et al. 2012). Secondly, it shows antitumor activity by cytotoxicity, induction of apoptosis (Čebović et al. 2008; Park et al. 2012; Han et al. 2015; Mishra et al. 2018) and inhibition of angiogenesis (Park et al. 2001; Elluru et al. 2009). The mechanism of action is shown in Fig. 1. In vitro studies on anticancer activity of mistletoe have confirmed that it modulates many different pathways, playing key roles in tumour proliferation, including MAPK (mitogen-activated protein kinase) (Park et al. 2012) and PI3K/AKT (phosphatiidylinositol 3-kinase/protein kinase B) (Fan et al. 2019). Furthermore, mistletoe can cause cell cycle arrest (Dela Cruz et al. 2015; Kim et al. 2017; Melo et al. 2018), loss of mitochondrial membrane permeability (MMP) (Mishra et al. 2018) and can activate caspases and regulate pro- and anti-apoptotic proteins (Fan et al. 2019) (Table 1). The anticancer activity of *Viscum* species is linked with their immunomodulatory activity (Oei et al. 2019), such as the increase of maturation and activation of dendritic cells (Elluru et al. 2008; Kim et al. 2014a; Steinborn et al. 2017), abrogation of tumour-induced immunosuppression of dendritic cells (Steinborn et al. 2017), increase of leukocytes, eosinophils, granulocytes (Huber et al. 2005, 2011) and lymphocytes (Semiglasov et al. 2004), increase of cytokines secretion (Hajto et al. 1990; Kovacs 2000; Elluru et al. 2008), increase of activity of natural killer cells (Hajto 1986; Tabiasco et al. 2002; Braedel-Ruoff 2010; Kim et al. 2018), increase of the activities of natural killer cells during surgery (Schink et al. 2007) and enhancement of cellular and humoral immune response (Yoon et al. 2001; Gardin 2009). Clinical studies were done on patients suffering from cancer diseases such as bladder cancer, breast cancer, colorectal cancer, glioma, lung cancer, melanoma and the results of these studies have been published in many articles. Those who are interested in the topic are invited to read review articles focusing on the anticancer properties of mistletoe (Ernst et al. 2003; Bar-Sela 2011; Bar-Sela et al. 2013; Steele et al. 2015; Kiene et al. 2016; Schlüppi et al. 2017; Freuding et al. 2019). Additionally, it is worth paying attention to studies regarding synergetic interactions of mistletoe preparations with other cancer treatments such as chemotherapy and radiotherapy (Siegle et al. 2001; Hong et al. 2014; Kleinsimon et al. 2017; Schöttler et al. 2019; Menke et al. 2019). Furthermore, we found research that Korean mistletoe lectin affected the self-renewal activity of placenta-derived mesenchymal stem cells (MSCs) (Choi et al. 2012; Kim et al. 2019), however its therapeutic use for cancer is still insufficiently investigated (Hmadcha et al. 2020).

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Cardiac activity

The cardiac activity of mistletoe has been confirmed in in vitro as well as in vivo studies (Committee on Herbal Medicinal Products 2012; Poruthukaren et al. 2014; Montero et al. 2016) (Table 2). Tenorio et al. (2005) and Tenorio-Lopez et al. (2006) studied the mechanism of vasodilator activity of aqueous extract of Viscum album L. leaves on the Langendorff’s isolated and perfused heart model. They showed that mistletoe induced nitric oxide synthetase-2 (NOS-2) and nitric oxide synthetase-3 (NOS-3) overexpression, which was connected with increases in nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) production. Therefore, the vasodilator activity of mistletoe might be mediated by the NO/sGC pathway. Soluble guanylyl cyclase (sGC) is an enzyme catalysing the conversion of GTP to cGMP and mediating several biological functions, such as the inhibition of platelet aggregation, smooth muscle relaxation and vasodilation. NO activates sGC by directly binding to heme to form a ferrous–nitrosyl–heme complex. Once sGC is activated by NO, GTP to cGMP conversion is triggered. Exogenous and endogenous compounds produce vasodilation through increases in cGMP, which in turn, relaxes vascular smooth muscle cells by both desensitising the contractile apparatus to Ca²⁺ and lowering intracellular Ca²⁺, with the consequent activation of a protein known as cGMP-dependent protein kinase. NO, synthesised by the enzyme nitric oxide synthase (NOS), maintains a vasodilator tone that is essential for the regulation of blood flow and pressure. NOS is a heme-containing enzyme that has three isoforms, designated as NOS-1, NOS-2 and NOS-3 (Tenorio-Lopez et al. 2006). Furthermore, studies on myocardial ischemia and reperfusion injury in rats as well as isoproterenol-induced heart failure in rats confirmed the cardioprotective effect of Viscum album L. might be mediated by the upregulation of the NO pathway (Karagöz et al. 2016; Suveren et al. 2017). Studies of Nω-nitro-L-arginine methyl ester (L-NAME)-induced hypertensive rats treated with methanolic extract of Viscum articulatum Burm. f. showed that mistletoe has an antihypertensive effect, which may be attributed to its diuretic, nephroprotective and hypolipidemic action. It was proposed the blood pressure lowering activity of this extract might have been due to the presence of triterpenoids, such as oleanolic acid and betulinic acid (Bachhav et al. 2012). Oleanolic acid isolated from the cuticular wax of Viscum articulatum Burm. f. significantly decreased the systolic blood pressures and cardiac lipid peroxidation levels in glucocorticoid (dexamethasone)-induced hypertensive rats, which might be connected with its antioxidant and nitric oxide releasing action (Bachhav et al. 2011). On the other hand, a study carried out in L-NAME-induced hypertensive rats treated with oleanolic acid showed that this compound did not affect nitric oxide levels, and its antihypertensive effect might be due to diuresis and nephroprotection (Bachhav et al. 2015). Another mechanism of the antihypertension activity of Viscum might be mediated by the calcium channel
| Mechanism of action | Preparation/compound (host tree) | Concentration of the extract/compound | Cell line | Observations | References |
|---------------------|----------------------------------|--------------------------------------|-----------|--------------|------------|
| Cell cycle          | *Viscum album* L. (apple tree)   | Extract containing 10 ng/mL lectin MLI | Human osteosarcoma cell lines 143B, Saos-2 and U2OS | G1 arrest in TP53 wild-type (U2OS) and null-mutant (Saos-2) cells, S arrest in TP53 mutant cells (143B), blockage of G1/S transition accompanied by downregulation of CDK4, CCND1, CDK2, CCNE, CCNA, investigations on the transcriptional level revealed secondary TP53 participation, cell cycle arrest was mediated by transcriptionally increased expression of GADD45A and CDKN1A and decreased SKP2 levels | Kleinsimon et al. (2018) |
|                     |                                  | Extract containing 60 µg/mL oleanolic acid |           |              |            |
|                     |                                  | Extract containing 5 ng/mL lectin MLI and 50 µg/mL oleanolic acid |           |              |            |
|                     | *Viscum album* L.                | 3% and 5% v/v                          | Murine melanoma cell line B16F10 | Increased Sub G0 population, probably associated with a consistent decrease in G1, and an increase in S or G2/M populations | Melo et al. (2018) |
|                     | *Viscum articulatum* Burm. f.   | 0.015–150 µg/mL                        | Human leukemia cell lines Jurkat E6.1 and THP1 | G2/M cell cycle arrest with a concomitant decrease in some cells at G0/G1 phase | Mishra et al. (2018) |
|                     | (*Dalbergia latifolia* Roxb.)    |                                       |           |              |            |
|                     | 1,7-Bis(4-hydroxyphenyl)-1,4-heptadien-3-one isolated from *Viscum coloratum* (Kom.) Nakai | 2.5–20 µM | Human lung cancer cell lines A549 and NCI-H292 | Cell cycle arrest in A549 and NCI-H292 cells at the S and G0/G1 phases, respectively | Fan et al. (2019) |
|                     | *Viscum coloratum* (Kom.) Nakai  | Lectin 10–1000 ng/mL Extract 10–1000 µg/mL | Mouse melanoma cell lines B16BL6 and B16F10 | G0/G1 cell cycle arrest | Han et al. (2015) |
| Mechanism of action | Preparation/compound (host tree) | Concentration of the extract/compound | Cell line | Observations | References |
|---------------------|---------------------------------|--------------------------------------|-----------|--------------|------------|
| MMP                 | *Viscum articulatum* Burm. f. (*Dalbergia latifolia* Roxb.) | 0.015–150 µg/mL | Human leukemia cell lines Jurkat E6.1 and THP1 | Loss of MMP, which is required for cytochrome c release | Mishra et al. (2018) |
|                     | *Viscum album* L (apple tree) | Extract containing 1.25–7.5 ng/mL lectin MLI | Human alveolar Rhabdomyosarcoma cell line RMS-13 | | Stammer et al. (2017) |
|                     |                                | Extract containing 30–45 µg/mL oleanolic acid | | | |
|                     |                                | Extract containing 1.25–7.5 ng/mL lectin MLI and 30–45 µg/mL oleanolic acid | | | |
|                     | *Viscum album* L (apple tree) | Extract containing 1–40 ng/mL lectin MLI | Human Ewing sarcoma cell lines TC-71 and MHH-ES-1 | | Twardziok et al. (2016) |
|                     |                                | Extract containing 10–60 µg/mL oleanolic acid | | | |
|                     |                                | Extract containing 1–40 ng/mL lectin MLI and 10–60 µg/mL oleanolic acid | | | |
|                     | *Viscum album* L (apple tree) | Extract containing 2–16 ng/mL lectin MLI | Human acute myeloid leukemia cell lines U937 and HL-60 | | Delebinski et al. (2015) |
|                     |                                | Extract containing 20–40 µg/mL oleanolic acid | | | |
|                     |                                | Extract containing 2–16 ng/mL lectin MLI and 20–40 µg/mL oleanolic acid | | | |
|                     | 1,7-Bis(4-hydroxyphenyl)-1,4-heptadien-3-one isolated from *Viscum coloratum* (Kom.) Nakai | 2.5–20 µM | Human lung cancer cell lines A549 and NCI-H292 | | Fan et al. (2019) |
|                     | *Viscum album* L (apple tree) | Extract containing 2.5–10 ng/mL lectin MLI | Human osteosarcoma cell lines 143B and Saos-2 | | Kleinsimon et al. (2017) |
|                     |                                | Extract containing 40–60 µg/mL oleanolic acid Extract containing 2.5–10 ng/mL lectin MLI and 40–60 µg/mL oleanolic acid | | | |
| Mechanism of action | Preparation/compound (host tree) | Concentration of the extract/compound | Cell line | Observations | References |
|---------------------|----------------------------------|--------------------------------------|-----------|--------------|------------|
| Cytochrome c and AIF | *Viscum album* L. (apple tree) | Extract containing 4–8 ng/mL lectin MLI | Human acute myeloid leukemia cell lines U937 and HL-60 | Release of cytochrome c | Delebinski et al. (2015) |
|                     |                                  | Extract containing 25–35 µg/mL oleanolic acid |                                      |              |            |
|                     |                                  | Extract containing 4–8 ng/mL lectin MLI and 25–35 µg/mL oleanolic acid |                                      |              |            |
|                     | 1,7-Bis(4-hydroxyphenyl)-1,4-heptadien-3-one isolated from *Viscum coloratum* (Kom.) Nakai | 2.5–20 µM Human lung cancer cell lines A549 and NCI-H292 | Release of cytochrome c and AIF | Fan et al. (2019) |
| MAPK/JNK, ERK and p38 | Lectin II isolated from *Viscum coloratum* (Kom.) Nakai | 100 ng/mL Human myeloid leukemia cell line U937 | Increased phosphorylation of the JNK1 substrate, GST-c-Jun N-terminal protein | Park et al. (2000) |
|                     | Abnoba*Viscum* F (ash) | 20 µg/mL Human myeloid leukemia cell line K562 | Increased phosphorylation of JNK1 and p38, reduced levels of phosphorylated ERK-1/2 | Park et al. (2012) |
|                     | *Viscum album* L. (apple tree) | Extract containing 1–40 ng/mL lectin MLI | Human Ewing sarcoma cell lines TC-71 and MHH-ES-1 | Increased phosphorylation of JNK1 and p38 | Twardziok et al. (2017) |
|                     |                                  | Extract containing 10–60 µg/mL oleanolic acid |                                      |              |            |
|                     |                                  | Extract containing 1–40 ng/mL lectin MLI and 10–60 µg/mL oleanolic acid |                                      |              |            |
|                     | *Viscum album* L. (apple tree) | Extract containing 10 ng/mL lectin MLI | Human osteosarcoma cell lines 143B, Saos-2 and U2OS | Activation of JNK1 with simultaneous inactivation of ERK-1/2 | Kleinsimon et al. (2018) |
|                     |                                  | Extract containing 60 µg/mL oleanolic acid |                                      |              |            |
|                     |                                  | Extract containing 5 ng/mL lectin MLI and 50 µg/mL oleanolic acid |                                      |              |            |
|                     | 1,7-Bis(4-hydroxyphenyl)-1,4-heptadien-3-one isolated from *Viscum coloratum* (Kom.) Nakai | 2.5–20 µM Human lung cancer cell lines A549 and NCI-H292 | Upregulation of the expression levels of p-ERK1/2 and p-P90RSK | Fan et al. (2019) |
| Mechanism of action | Preparation/compound (host tree) | Concentration of the extract/compound | Cell line | Observations | References |
|---------------------|---------------------------------|--------------------------------------|-----------|--------------|------------|
| PI3K/AKT            | 1,7-Bis(4-hydroxyphenyl)-1,4-heptadien-3-one isolated from *Viscum coloratum* (Kom.) Nakai  | 2.5–20 µM | Human lung cancer cell lines A549 and NCI-H292 | Downregulation of the phosphorylation of AKT and P70RSK | Fan et al. (2019) |
|                    | Lectin isolated from *Viscum coloratum* (Kom.) Nakai | 10 ng/mL | Human cancer cell line A253 | Dephosphorylation of AKT | Choi et al. (2004) |
|                    | Iscador Qu Spezial (oak) Iscador M (apple tree) | 0.3 mg/mL | Human tongue cancer cell lines SCC9 and SCC25 | Reduced pAKT | Klingbeil et al. (2013) |
|                    | Abnoba *Viscum* F (ash) | 20 µg/mL | Human myeloid leukemia cell line K562 | Reduced levels of phosphorylated AKT | Park et al. (2012) |
|                    | VA Qu Spez (oak) | 10–100 µg/mL | Human lung adenocarcinoma cell line A549 | Inhibition of the secretion of IL-1β-induced PGE2 associated with a reduced expression of COX-2 | Hegde et al. (2011) and Saha et al. (2015) |
| COX-2               | *Viscum album* L. (apple tree) | Extract containing 2–16 ng/mL lectin MLI | Human acute myeloid leukemia cell line HL-60 | Activation of caspase-8 and caspase-9 | Delebinski et al. (2015) |
|                    | *Viscum articulatum* Burm. f. (*Dalbergia latifolia* Roxb.) | 0.015–150 µg/mL | Human leukemia cell lines Jurkat E6.1 and THP1 | Activation of caspase-8 and caspase-3 | Mishra et al. (2018) |
|                    | *Viscum album* L. (apple tree) | Extract containing 1.25–7.5 ng/mL lectin MLI | Human alveolar Rhabdomyosarcoma cell line RMS-13 | Activation of caspase-9, caspase-8 and caspase-3 | Stummer et al. (2017) |
|                    | *Viscum album* L. (apple tree) | Extract containing 1–40 ng/mL lectin MLI | Human Ewing sarcoma cell lines TC-71 and MHH-ES-1 | Activation of caspase-9, caspase-8 | Twardziok et al. (2016) |
| Mechanism of action | Preparation/compound (host tree) | Concentration of the extract/compound | Cell line | Observations | References |
|---------------------|----------------------------------|-------------------------------------|-----------|-------------|------------|
| 1,7-Bis(4-hydroxyphenyl)-1,4-heptadien-3-one isolated from *Viscum coloratum* (Kom.) Nakai | | | Human lung cancer cell lines A549 and NCI-H292 | Activation of caspase-9 and caspase-3 | Fan et al. (2019) |
| Abnoba *Viscum* F (ash) | | 20 µg/mL | Human myeloid leukemia cell line K562 | Decreased expression of procaspase-9 but increased that of cleaved (active) caspase-9 | Park et al. (2012) |
| Lectin isolated from *Viscum coloratum* (Kom.) Nakai | | 10 ng/mL | Human cancer cell line A253 | Activation of caspase-3 | Choi et al. (2004) |
| *Viscum album* L. (apple tree) | Extract containing 2.5–10 ng/mL lectin MLI | Human osteosarcoma cell lines 143B and Saos-2 | Activation of caspase-8 and caspase-9 | Kleinsimon et al. (2017) |
| *Viscum Coloratum* (Kom.) Nakai | Lectin 10–1000 ng/mL, Extract 10–1000 µg/mL | Mouse melanoma cell lines B16BL6 and B16F10 | Activation of caspase-1, 3, 4, 5, 6, 7, 8, and 9 | Han et al. (2015) |
| Antiapoptotic proteins | Extract containing 40 ng/mL lectin MLI Extract containing 40 µg/mL oleanolic acid Extract containing 15 ng/mL lectin MLI and 30 µg/mL oleanolic acid | Human acute myeloid leukemia cell line HL-60 | Downregulation of BIRC5, XIAP, p53 and claspin | Delebinski et al. (2015) |
| *Viscum album* L. (apple tree) | Extract containing 1–40 ng/mL lectin MLI Extract containing 10–60 µg/mL oleanolic acid Extract containing 1–40 ng/mL lectin MLI and 10–60 µg/mL oleanolic acid | Human Ewing sarcoma cell lines TC-71 and MHH-ES-1 | Downregulation of BIRC5, XIAP, MCL1, and CLSPN | Twardziok et al. (2016) |
| *Viscum album* L. (apple tree) | Extract containing 2.5–10 ng/mL lectin MLI Extract containing 40–60 µg/mL oleanolic acid Extract containing 2.5–10 ng/mL lectin MLI and 40–60 µg/mL oleanolic acid | Human osteosarcoma cell lines 143B and Saos-2 | Downregulation of BIRC5, XIAP, BCL2, and CLSPN | Kleinsimon et al. (2017) |
Table 1 (continued)

| Mechanism of action | Preparation/compound (host tree) | Concentration of the extract/compound | Cell line | Observations | References |
|---------------------|-----------------------------------|---------------------------------------|-----------|--------------|------------|
| Viscum album L. (apple tree) | Extract containing 5 ng/mL lectin MLI Extract containing 40 µg/mL oleanolic acid Extract containing 5 ng/mL lectin MLI and 40 µg/mL oleanolic acid | Human alveolar Rhabdomyosarcoma cell lines RH-30 and RMS-13 | Downregulation of BIRC5, XIAP, BCL2, BCL2L1 and MCL1 | Stammer et al. (2017) |
| Viscum articulatum Burm. f. (Dalbergia latifolia Roxb.) Lectin isolated from Viscum coloratum (Kom.) Nakai | 0.015–150 µg/mL | Human leukemia cell lines Jurkat E6.1 and THP1 | Downregulation of BCL2 | Mishra et al. (2018) |
| | 10 ng/mL | Human hepatocarcinoma cells SK-Hep-1 and Hep3B | | Lyu et al. (2002) |
| | 20 µg/mL | Human myeloid leukemia cell line K562 | Downregulation of Mcl-1 | Park et al. (2012) |
| | 2.5–20 µM | Human lung cancer cell lines A549 and NCI-H292 | Upregulation of Bcl-2 and Bcl-xL | Fan et al. (2019) |
| Proapoptotic proteins | Viscum articulatum Burm. f. (Dalbergia latifolia Roxb.) Lectin isolated from Viscum coloratum (Kom.) Nakai | 0.015–150 µg/mL | Human leukemia cell lines Jurkat E6.1 and THP1 | Upregulation of Bax | Mishra et al. (2018) |
| | 10 ng/mL | Human hepatocarcinoma cells SK-Hep-1 and Hep3B | | Lyu et al. (2002) |
| | Extract containing 2.5–10 ng/mL lectin MLI Extract containing 40–60 µg/mL oleanolic acid Extract containing 2.5–10 ng/mL lectin MLI and 40–60 µg/mL oleanolic acid | Human osteosarcoma cell lines 143B and Saos-2 | | Kleinsimon et al. (2017) |
| | 2.5–20 µM | Human lung cancer cell lines A549 and NCI-H292 | Downregulation of Bax | Fan et al. (2019) |
| Mechanism of action | Preparation/compound (host tree) | Concentration of the extract/compound | Cell line | Observations | References |
|---------------------|----------------------------------|--------------------------------------|-----------|--------------|------------|
| STAT3               | *Viscum album* L. (apple tree)   | Extract containing 10 ng/mL lectin MLI, 60 µg/mL oleanolic acid, and 5 ng/mL lectin MLI and 50 µg/mL oleanolic acid | Human osteosarcoma cell lines 143B, Saos-2 and U2OS | Dephosphorylation of STAT3 at Tyr705 and Ser727, down-regulation of total STAT3 and its direct downstream targets BIRC5 and C-MYC | Kleinsimon et al. (2018) |
|                     | Abnoba *Viscum* F (ash)          | 5–20 µg/mL                            | Human hepatocellular carcinoma cell line Hep3B | Reduction of C-MYC protein levels which might be mediated by the ubiquitin–proteasome system | Yang et al. (2019) |
| Telomerase          | Lectin isolated from *Viscum coloratum* (Kom.) Nakai | 10 ng/mL | Human cancer cell line A253 | Inhibition of telomerase activity through downregulation of hTERT | Choi et al. (2004) |
| ROS                 | *Viscum articulatum* Burm. f. (*Dalbergia latifolia* Roxb.) 1,7-Bis(4-hydroxyphenyl)-1,4-heptadien-3-one isolated from *Viscum coloratum* (Kom.) Nakai | 0.015–150 µg/mL, 5–20 µM | Human leukemia cell lines Jurkat E6.1 and THP1 | ROS mediated DNA fragmentation, Promotion of ROS generation | Mishra et al. (2018), Fan et al. (2019) |
### Table 2 Pharmacological activity of *Viscum* species—in vivo studies

| Pharmacological activity | *Viscum* species/Product | Part       | Host tree                      | Extraction solvent     | Compounds Description               | Dose                          | Route of administration | Study duration | Experimental design                                                                 | Results                                                                                   | References                      |
|--------------------------|--------------------------|------------|--------------------------------|------------------------|--------------------------------------|-------------------------------|------------------------|----------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------|
| Antihypertensive activity| *Viscum album* L         | Fresh leaves| Citrus                         | Aqueous                |                                      | 150 mg/kg, daily              | Orally                | 6 weeks      | Normotensive, renal artery-occluded hypertensive and salt-induced hypertensive rats | Decrease in arterial blood pressure without alteration in heart rate, antihypertensive effect might involve sympathetic mechanism | Ofem et al. (2007)               |
|                          | *Viscum album* L         | Fresh steams|                               | Ethanol, ether, and ethyl acetate |                                      | 3.33 × 10⁻⁵, 1.00 × 10⁻⁴, 3.33 × 10⁻⁴, 1.00 × 10⁻³ mg/kg | Intraperitoneally         |                       | Ethanolic extract exhibited activity even on the lowest dose, the ether and ethyl acetate extracts exhibited activity only by higher doses, antihypertensive effect might involve muscarinic receptors |                                             | Radenkovic et al. (2009)         |
|                          | *Viscum album* L         | Dried leaves| Pear (*Pyrus communis auct. iber.*) | Aqueous                |                                      | 250 mg/kg, daily              | Orally by gavage       | 24 days      | Isoproterenol-induced heart failure in rats                                         | Improvement in all parameters of heart failure including left ventricular diameters, ejection fraction, serum NT-proBNP levels and histopathological changes; decrease in levels of NO, iNOS and hs-CRP | Karagöz et al. (2016)           |
|                          | *Viscum album* L         |             |                                |                        |                                      | 0.6–2.8 g, daily              | Orally                | 6 weeks      | An open study in 120 patients with light to moderate hypertension (WHO grade I-II) | Decrease in systolic pressure (in rest and during physical exercise) | Committee on Herbal Medicinal Products (2012) |
|                          | *Viscum album* L         |             |                                |                        |                                      | 5 drops of drug every 5 min up to 4 administrations | Sublingually           |                   | 264 patients with diagnosis of hypertension                                         | Time of arterial blood pressure reduction was less for the group of patients who received the natural treatment | Montero et al. (2016)           |
|                          | *Viscum album* L         |             |                                |                        |                                      | 10 drops of drug in 30 ml of distilled water, three times a day | Orally                | 12 weeks    | 37 newly diagnosed hypertensive patients                                             | Decrease in systolic and diastolic pressure, decrease in serum triglyceride                  | Poruthukaren et al. (2014)       |
| Pharma-activity | Viscum species/Product | Part | Host tree | Extraction solvent | Compounds | Dose | Route of administration | Study duration | Experimental design | Results | References |
|----------------|------------------------|------|-----------|-------------------|-----------|------|------------------------|----------------|--------------------|---------|------------|
| Table 2 (continued) | | | | | | | | | | | | |
| | Viscum articulatum Burm. f | Dried herb | Cordia macleodii Hook.f. & Thomson | Methanolic | | 200 and 400 mg/kg, daily | Orally | 4 weeks | L-NAM-induced hypertensive rats | | Bachhav et al. (2012) |
| | Viscum articulatum Burm. f | Cuticular wax | Oleanolic acid | | | 60 mg/kg, daily | Intraperitoneally | 15 days | Glucocorticoid (dexamethasone)-induced hypertensive rats | | | Bachhav et al. (2011) |
| | Viscum articulatum Burm. f | Cuticular wax | Oleanolic acid | | | 60 mg/kg, daily | | 4 weeks | L-NAM-induced hypertensive rats | | | Bachhav et al. (2015) |
| | Viscum album L | Fresh leaves | Citrus | Aqueous | | 150 mg/kg, daily | Orally | 6 weeks | High salt-fed rats | | | Ofem et al. (2009) |
| | Viscum album L | Dried leaves | Coffee (Coffee arabica), kola (Kola nitida) and cocoa (Theobroma cacao) | Aqueous | | 400, 800, 1600 and 3200 mg/kg, daily | Orally | 14 days | Healthy rats | | | Ladokun et al. (2015) |
| | Viscum album L | Dried leaves | Ethanol | | | 250, 500, 750, 1000 mg/kg | | 10 h | Normalglycemic and streptozotocin-induced diabetic rats | | | Nwaegene et al. (2007) |
### Table 2 (continued)

| Pharmacological activity | Viscum species/Product | Part | Host tree | Extraction solvent | Compounds | Dose | Route of administration | Study duration | Experimental design | Results | References |
|--------------------------|------------------------|------|-----------|-------------------|-----------|------|-------------------------|----------------|---------------------|---------|------------|
|                          | Viscum album L         | Dried herb | Apricot (*Armeniaca vulgaris* Lam.), pine (*Pinus nigra* J.F.Arnold), fir (*Abies bornmilleriana* Mattf.) | Aqueous and ethanolic | 500 mg/kg | Orally by gastric gavage | 8 days | Streptozotocin-induced diabetic rats | Antidiabetic effect of mistletoe depends on the host tree | Orhan et al. (2005) |
|                          | Viscum album L         | Fresh leaves | *Kola acuminate* | Aqueous | 100 mg/kg | Intravenously | 3 h | Normalglycemic and streptozotocin-induced diabetic rats | No effect on glucose level in normal rats but decrease of the blood glucose level in the diabetic rats, increase of the insulin secretion in normal rats and in the diabetic group | Eno et al. (2008) |
|                          | Viscum album L         | Dried herb | *Kola acuminate* | Methanolic | 100 mg/kg, daily | 3 weeks | Streptozotocin-induced diabetic rats | Reduction in fasting blood glucose level, HbA1c, serum triglyceride, urea, lactate dehydrogenase, α-amylase and low density lipoprotein cholesterol, increase of high density lipoprotein cholesterol | Adaramoje et al. (2012) |
|                          | Viscum album L         | Dried leaves | *Ethanol* | Ethanol | 100 mg/kg, daily | Orally by gavage | 10 days | Streptozotocin-induced diabetic rats | No significant difference in glucose level, reduction in oxidative stress | Turkkan et al. (2016) |
|                          | Viscum album L         | Dried leaves | Citrus | Aqueous | 150 mg/kg, daily | Orally with syringe and oro-gastric tube | 3 weeks | Streptozotocin-induced diabetic rats | Reduction in fasting blood glucose level | Nna et al. (2015) |
|                          | Viscum album L         | Dried leaves | Olh been (*Pentaclethra macrophylla* Benth.) | Aqueous | 200 mg/kg | Intraperitoneally | 4 h | Fasted normalglycemic rats | Decrease in blood glucose level | Ohri et al. (2003) |
|                          | Viscum album L         | Dried leaves | Oak | Aqueous | 500 and 1000 mg/kg, daily | Orally by gavage | 3 days | Alloxan-induced diabetic rabbits | Decrease in serum glucose concentration and increase in the serum insulin level | Shahabod-din et al. (2011) |
| Pharma-cological activity | Viscum spe-cies/Product | Part | Host tree | Extraction solvent | Compounds | Dose | Route of administra-tion | Study dura-tion | Experimental design | Results | References |
|---------------------------|-------------------------|------|-----------|-------------------|-----------|------|-------------------------|----------------|---------------------|---------|------------|
| Viscum album L            | Dried leaves            | Sweet orange (Citrus sinensis (L.) Osbeck), african pear (Diospyros edulis), guava (Psidium guajava L.) and pepper fruit (Dennettia tripetala Baker f.) | Aqueous | 100 mg/kg, daily | Orally by gavage | 14 days | Alloxan-induced diabetic rats | The strongest activity was exhibited by extracts of mistletoe growing on Citrus sinensis and Psidium guajava | Umoh et al. (2011) |
| Viscum album L            | Dried leaves            | Ethanolic | 2 mg/kg, 16 h | Intraperito-neally | 54 h | Alloxan-induced diabetic rats | Decrease in fasting blood glucose level | Ibegbulem and Chikezie 2013 |
| Viscum coloratum (Kom.) Nakai | Dried herb | Oak (Quercus variabilis Blume) | Protein frac-tion | 50—400 µg/ml | Intraperito-neally | 10 days | Alloxan-induced diabetic mice | Decrease in the blood glucose level and volume of drinking water | Kim et al. (2014b) |
| Viscum coloratum (Kom.) Nakai | Dried herb | Aqueous and ethanolic Betulin and oleanolic acid Diet containing 0.2 or 0.6% of extract | Orally | 8 weeks | Partial pancreatecto-mized rats | Ethanolic extract made β-cell mass greater by increasing β-cell proliferation and decreasing its apoptosis | Ko et al. (2016) |
| Viscum schim-pperi Engl | Dried herb | Methanolic | 500 mg/kg, daily | Orally by gavage | 4 weeks | Streptozotocin-induced diabetic rats | Reduction in the fasting blood glucose level; increase of the level of insulin, reduction of total cholesterol, triglyceride and low density lipoprotein cholesterol and increase of high density lipoprotein cholesterol | Abdel-Sattar et al. (2011) |
| Hepatoprotective activity | Viscum album L           | Leaves | Ethanolic | 1 g/kg | Orally | Paracetamol-induced hepatotoxicity in rats | Reduction of ALT, ALP levels, no influence on the levels of total bilirubin and total protein | Ogbonnanya et al. (2010) |
| Pharmaceutical activity | Viscum species/Product | Part | Host tree | Extraction solvent | Compounds | Dose | Route of administration | Study duration | Experimental design | Results | References |
|--------------------------|------------------------|------|-----------|-------------------|-----------|------|------------------------|---------------|---------------------|---------|-------------|
| **Viscum album L**       | Dried leaves           | Cocoa (Theobroma cacao L.) and cola (Cola nitida (Vent.) Schott & Endl.) | Methanolic | 1000–5000 mg/kg, daily | Orogastriically | 7 days | Paracetamol-induced hepatotoxicity in rats | No significant difference in AST, ALT and ALP for V. album growing on cocoa, significant increase in AST, ALT and ALP for V. album growing on cola at 4000 and 5000 mg/kg doses | **Yusuf et al.** (2015) |
| **Viscum album L**       | Dried leaves Citrus    | Aqueous | 150 mg/kg, daily | Orally (syringe and or gastric tube) | 6 weeks | High salt diet rats | Decrease in serum total bilirubin, serum conjugated bilirubin and serum unconjugated bilirubin | Ofem et al. (2014) |
| **Viscum album L**       | Dried leaves Citrus    | Aqueous | 150 mg/kg, daily | Orally (syringe and or gastric tube) | 3 weeks | Streptozotocin-induced diabetic rats | Decrease in serum total bilirubin, serum conjugated bilirubin and serum unconjugated bilirubin | Nna et al. (2014) |
| **Viscum Fraxini-2 (Viscum album L.)** | Ash | Aqueous | 0.1 and 0.2 ml/kg, once weekly | Subcutaneously | 30 days | Carbon tetrachloride-induced hepatotoxicity in rats | Decrease in ALT, AST and ALP levels, restoration of the normal architecture of the liver tissue with minimal fibrosis | Abdel-Salam et al. (2010) |
| **Iscador Qu (Viscum album L.)** | Fresh herb Oak (Quercus robur L. and Quercus petraea (Matt.) Liebl.) | Fermented, aqueous extract | Two 5 mg ampules, three times weekly | Subcutaneously | 12 months | 5 patients with chronic hepatitis C | 6–20 fold reduction in viral load (HCV-RNA) and complete remission of elevated AST and ALT in two out of five patients, an increase of HCV RNA in one patient | Tusenius et al. (2001) |
| **Iscador Qu (Viscum album L.)** | Fresh herb Oak (Quercus robur L. and Quercus petraea (Matt.) Liebl.) | Aqueous | 750 ng of lectins | Subcutaneously | 12 months | 21 patients with chronic hepatitis C | Decrease in ALT and AST during the 12 months treatment and slight increase after treatment end | Tusenius et al. (2005) |
| **AbnobaViscum (Viscum album L.)** | Fresh herb Oak | Aqueous | 1000 ng of lectins | 0.15 mg, three times weekly | | | | | |
### Table 2 (continued)

| Pharma-cological activity | Viscum species/Product | Part | Host tree | Extraction solvent | Compounds | Dose | Route of administration | Study duration | Experimental design | Results | References |
|---------------------------|------------------------|------|-----------|-------------------|-----------|------|-------------------------|----------------|---------------------|---------|------------|
| Abnoba Viscum Quercus (Viscum album L.) | Fresh herb | Oak | Aqueous | 65–3610 ng of lectins (mean weekly dose) | Three times a week | Subcutaneously | 9 months | 25 patients with chronic hepatitis C and elevated alanine aminotransferase (ALT) levels | None of the patients had complete or partial normalization of ALT or HCV-RNA levels during treatment period, mean ALT did not change during the study | Huber et al. (2001) |
| Viscum coloratum (Kom.) Nakai | Dried steams and leaves | Aqueous | Alkaloid fraction | 120 mg/kg, daily | Orally by gastric gavage | 8 weeks | Carbon tetrachloride-induced hepatic fibrosis in rats | Decrease of hepatic fibrosis; reduction in mRNA levels of TGF-β1, procollagen I and TIMPs; increase in TGF-β1, TGF-β1 receptor, phosphorylated Smad 2 and α-SMA proteins in liver tissues; increase in Smad 7 level | Jiang et al. (2014) |
| Antiepileptic activity | Viscum album L. | Fresh leaves | Citrus | Aqueous | 50 and 150 mg/kg | Orally | Maximum electro shock, isoniazid- and pentyleneetrazole-induced seizures in mice and rats | Reduction in various phases of epileptic seizures, increased latency to the first convulsion, increased convulsion onset and reduction in seizure duration | Gupta et al. (2012) |
| Viscum album L. | Dried herb | Maple (Acer platanoides L.) | Aqueous and aqueous-ethanolic | 100 mg/kg | Intragastrically | 2 days | Pentyleneetrazole-induced seizures in mice | Effective against pentyleneetrazole-induced seizures | Tsyvunin et al. (2016) |
| | | Willow (Salix alba L.) | Ethanolic | | | | | | |
| Viscum Mali e planta tota (Viscum album L.) | Apple tree | Initially given in strength D5, 10 granules BID, equivalent to a 1:100,000 dilution of the whole plant extract, later increased to D2, equivalent to a 1:100 dilution, 10 granules twice a day | 12 weeks | 4½-year-old girl suffering from childhood absence epilepsy | The dose increase of Viscum Mali, in addition to an existing combination with valproic acid and clobazam, may have played a key role in achieving seizure freedom for this child | von Schoen-Angerer et al. (2015) |
Table 2 (continued)

| Pharmacological activity | Viscum species/Product | Part | Host tree | Extraction solvent | Compounds | Dose          | Route of administration | Study duration | Experimental design | Results                                                                 | References                  |
|--------------------------|------------------------|------|-----------|-------------------|-----------|---------------|-------------------------|----------------|---------------------|--------------------------------------------------------------------------|-----------------------------|
|                          | Viscum capense L. f    |      |           |                   |           | 50 and 100 mg/kg | Intraperitoneally       |                |                     | Delayed the onset of pentylenetetrazole—bicuculline- and N-methyl-DL-aspartic acid-induced seizures and reduction in the number of convulsing animals; moderate effect against N-methyl-DL-aspartic acid-induced tonic seizures | Amabeoku et al. (1998)      |
|                          | Viscum articulatum Burm. f |      |           |                   |           | 100 and 200 mg/kg, daily | Orally 7 days | Maximum electro shock- and pentylenetetrazole—induced seizures in rats | Reduction in duration of hind limb extensor phase and increase in the latency to convulsions | Geetha et al. (2010)         |
|                          | Viscum articulatum Burm. f |      | Fresh herb | Chloroform and methanolic |           | 150 and 300 mg/kg for extracts, 10 and 20 mg/kg for isolated compound | Orally 7 days | Picrotoxin—induced seizures in rats | Extracts and syringaresinol delayed the onset of tonic convulsions, increase in the brain GABA levels in rats treated with the methanolic extract | Geetha et al. (2018)         |
|                          | Viscum album L         | Fresh leaves | Citrus | Aqueous |           | 50 and 150 mg/kg | Orally | Mice placed in actophotometer | Reduction in locomotor activity | Gupta et al. (2012)         |
|                          | Viscum album L         | Fresh leaves | Citrus | Aqueous |           | 50 and 150 mg/kg | Orally | Pentobarbital—induced sleeping time in mice | Increase in duration of sleeping time | Gupta et al. (2012)         |
|                          | Viscum album L         | Dried herb | Methanolic and its ethyl acetate and 1-butanol fractions |           |           | 200 and 400 mg/kg for extract, 25 and 50 mg/kg for fractions | Orally | Open field test on mice | Reduction in rearing and crossings | Kumar et al. (2016)          |
|                          | Viscum orientale Wildi | Dried leaves | Exoecaria agalloch | Methanolic |           | 300 and 500 mg/kg | Orally | Open field test and hole cross test in mice | Reduction in spontaneous motor activities | Khatri et al. (2016)         |
| Pharmacological activity | Viscum species/Product | Part               | Host tree                  | Extraction solvent                          | Compounds                                                                 | Dose                        | Route of administration | Study duration | Experimental design                          | Results                                                                 | References                |
|--------------------------|------------------------|-------------------|---------------------------|---------------------------------------------|-----------------------------------------------------------------------------|-----------------------------|-------------------------|----------------|---------------------------------------------|--------------------------------------------------------------------------|---------------------------|
| Hypnotic activity        | Viscum album L         | Dried herb        |                           | Methanolic and its ethyl acetate and 1-butanol fractions |                              | 200 and 400 mg/kg for extract, 25 and 50 mg/kg for fractions | Orally                   | Thyopentone sodium induced-sleeping time assay in mice | Increase in the duration of sleep in mice | Kumar et al. (2016) |
| Antipsychotic activity   | Viscum album L         | Fresh leaves      | Citrus                    | Aqueous                                     |                              | 50 and 150 mg/kg                                              | Orally                   | Apomorphine-induced stereotypy in mice and rats | Significantly reduction in the stereotyped behaviour | Gupta et al. (2012) |
| Antianxiety activity     | Viscum album L         | Fresh leaves      | Citrus                    | Aqueous                                     |                              | 50 and 150 mg/kg                                              | Orally                   | Haloperidol-induced catalepsy in mice and rats (bar test) | Enhancement in cataleptic effect of haloperidol                  | Gupta et al. (2012) |
| Antitussive activity     | Viscum album L         | Dried herb        |                           | Methanolic and its ethyl acetate and 1-butanol fractions |                              | 50 and 100 mg/kg for extract, 5 and 10 mg/kg for fractions   | Orally                   | Elevated plus-maze test on mice (EPM model) | The number of entries and time spent in open arms in the elevated plus-maze test were significantly increased | Kumar et al. (2016) |
| Antistress activity      | Viscum album L         | Dried herb        |                           | Methanolic and its ethyl acetate and 1-butanol fractions |                              | 200 and 400 mg/kg for extract, 25 and 50 mg/kg for fractions | Orally                   | Cold swim test on mice                      | Reduction in time spent by mice in the immobile state                  | Kumar et al. (2016) |
| Antidepressant activity  | Viscum album L         | Dried herb        |                           | Methanolic and its ethyl acetate and 1-butanol fractions |                              | 200 and 400 mg/kg for extract, 25 and 50 mg/kg for fractions | Orally                   | Despair swim test on mice                   | Reduction in the duration of immobility in mice                        | Kumar et al. (2016) |
| Analgesic activity       | Viscum album L         | Dried herb        |                           | Methanolic and its ethyl acetate and 1-butanol fractions |                              | 200 and 400 mg/kg for extract, 25 and 50 mg/kg for fractions | Orally                   | Tail immersion test was conducted by recording tail withdrawal from heat (flicking response) in mice | Significant analgesic activity                                         | Kumar et al. (2016) |
|                          | Viscum album L         | Dried leaves and stems | Apricot (Armeniaca vulgaris Lam.) | Ethyl acetate 2′-Hydroxy-4′,6′-dimethoxy-chalcone-4-O-[β-D-glucopyranosyl and 5,7-dimethoxy-flavanone-4′-O-[β-D-apiofuranosyl-(1 → 2)]-β-D-glucopyranoside |                              | 125 and 250 mg/kg for extract and 30 mg/kg for isolated compounds | Orally                   | p-Benzoxoquinone-induced writhing test in mice and carrageenan-induced hind paw edema model in mice | Ethyl acetate fraction and isolated compounds exhibited antinociceptive and anti-inflammatory activity | Orhan et al. (2006) |
|                          | Viscum orientale Wild | Dried leaves      | Eucoscinus agalloch | Methanolic                                     |                              | 300 and 500 mg/kg                                             | Orally                   | Acetic acid-induced writhing model in mice and formalin-induced paw licking in mice | Writhing and paw licking inhibition                                 | Khatun et al. (2016) |
| Pharmacological activity | Pharmaco-species/Product | Part | Host tree | Extraction solvent | Compounds | Dose | Route of administration | Study duration | Experimental design | Results | References |
|--------------------------|--------------------------|------|-----------|-------------------|-----------|------|------------------------|----------------|---------------------|---------|------------|
| Alzheimer's disease      | *Viscum album* L.        | Dried leaves | Orange tree | Aqueous | Aqueous | 100 mg/kg, daily | Orally | 21 days | Aluminum chloride-induced Alzheimer's disease in mice | Increase in the brain-derived neurotrophic factor (BDNF); reduction of aluminum chloride-induced memory impairment and oxidative damage | Ademola et al. (2016) and Ekpenyong et al. (2016) |
|                          | *Viscum coloratum* (Kom.) Nacai | Dried herb | Methanolic | 25 and 50 mg/kg, daily | 25 and 50 mg/kg, daily | Orally | 7 days | Intracerebroventricular injection of amyloid β protein in mice | Protection from memory impairment induced by intracerebroventricular injection of amyloid β protein | Jang et al. (2015) |
| Mood                     | Eurixor (*Viscum album* L.) | Fresh herb | Aqueous | Lectin (ML-1) | 1 ng/kg body weight, twice a week | Subcutaneously | 12 weeks | Breast cancer patients (n = 36) | Increased levels of plasma beta-endorphin | Heiny and Beuth (1994) |
|                          | Eurixor (*Viscum album* L.) | Fresh herb | Aqueous | Lectin (ML-1) | 0.5–1.0 ng & kg body weight, twice a week | Subcutaneously | 24 weeks | Breast cancer patients (n = 47) | Increased levels of plasma beta-endorphin | Heiny et al. (1998) |
| Antiobesity activity     | *Viscum coloratum* (Kom.) Nacai | Dried herb | Oak | Aqueous | 3 g/kg, daily | Orally | 15 weeks | High-fat diet-induced obesity in mice | Reduction in body and epididymal fat pad weights | Jung et al. (2013) |
|                          | *Viscum coloratum* (Kom.) Nacai | Dried herb | Oak | Aqueous | Betulin and oleanolic acid | Diet containing 0.2 or 0.6% of extract | Orally | 8 weeks | Partial pancreactectomy in mice | Reduction in epididymal fat mass by increasing fat oxidation | Ko et al. (2016) |
| Endurance capacity       | *Viscum coloratum* (Kom.) Nacai | Dried herb | Oak | Aqueous | 3 g/kg, daily | Orally | 15 weeks | Endurance test with treadmill in high-fat diet-induced obesity mice | Mistletoe treated mice run twice as far as high-fat diet mice | Jung et al. (2013) |
|                          | *Viscum coloratum* (Kom.) Nacai | Dried herb | Oak | Aqueous | 400 and 1000 mg/kg, daily | 1 week | Endurance test with treadmill in mice | Mistletoe treated mice run 2.5-times longer than control mice, plasma lactate levels of exhausted mice were significantly lower | Jung et al. (2012) |
|                          | *Viscum coloratum* (Kom.) Nacai | Leaves | Oak | Aqueous | 25—400 mg/kg, daily | Forced swim test in mice | The swimming time to exhaustion was prolonged by as much as 212% |  | Lee et al. (2014) |
|                          | *Viscum coloratum* (Kom.) Nacai | Whole plant | Aqueous | 500 mg/kg, daily | 500 mg/kg, daily | Orally | 2 weeks | Endurance test with treadmill in mice | Decreases in level of plasma lactate dehydrogenase, increase in the plasma FFA level | Jeong et al. (2017) |
Table 2 (continued)

| Pharma-cological activity | Viscum species/Product | Part | Host tree | Extraction solvent | Compounds | Dose | Route of administration | Study duration | Experimental design | Results | References |
|---------------------------|------------------------|------|-----------|-------------------|-----------|------|-------------------------|----------------|-------------------|---------|------------|
| Activity against muscle decline | Viscum coloratum (Kom.) Nacai | Whole plant | Aqueous | 200 and 500 mg/kg, twice a day | Orally by gavage | 15 days | Denervated mice | Decrease in denervation, decrease in the expression of Atrogin-1, no effect on Murf1 expression | Jeong et al. (2017) |
| Diet containing 0.3 and 1.5% of extract | | | | Diet containing 0.3 and 1.5% of extract | | 4 weeks | Mice | Increased whole body weights, a higher weight of quadricepses, increased grip strengths, increased swimming activity and elevated running times on the treadmill, increased skeletal muscle area and diameter | |
| Viscum coloratum (Kom.) Nacai | Whole plant | Aqueous | 1 and 2 g/d | Orally | 12 weeks | Randomized controlled trial with 67 patients aged 55–75 | Significant differences were found in atrogin-1 mRNA, myogenin mRNA and insulin growth factor 1 receptor phosphorylation | Lim et al. (2017) |
| Nephroprotective activity | Helixor M (Viscum album L.) | Fresh herb | Apple tree (Malus domestica Borkh.) | Aqueous | 5 mg/kg | Intraperitoneally | 10 days | Methotrexate-induced acute oxidative stress and nephrotoxicity in rats | Improvement in the glutathione peroxidase and superoxide dismutase activities, decrease in the NO and myeloperoxidase levels was not significant | Sakalli Çetin et al. (2017) |
| Viscum articulatum Burm. f | Cordia macleo-dri Hook.f. & Thomson | Oleanolic acid | 40, 60 and 80 mg/kg, daily | Orally | 8 days | Gentamicin-induced nephrotoxicity | Decrease in serum and urine levels of creatinine, albumin and urea | Patil et al. (2010) |
| Diuretic activity | Viscum angulatum B.Heyne ex DC | Dried herb | Randia dumetorum (Retz.) Lam | Methanolic | 100, 200 and 400 mg/kg | Orally | 24 h | Rats | Dose-dependent increase in urine excretion volume, significant saluretic and natriuretic activity, the Cl(-)/Na(+) + K(+) ratio, which indicates carbonic anhydrase mediated activity remained unaffected | Jadhav et al. (2010b) |
| Pharma-cological activity | Viscum species/Product | Part | Host tree | Extraction solvent | Compounds | Dose | Route of administration | Study duration | Experimental design | Results | References |
|--------------------------|------------------------|------|-----------|-------------------|-----------|------|-------------------------|----------------|---------------------|---------|------------|
| Wound healing            | Viscum album L         | Dried herb | Cordia macleodi Hook.f. & Thomson | Methanolic | 100, 200 and 400 mg/kg | Orally | 24 h | Rats | Dose-dependent increase in urine excretion volume, significant saluretic and natriuretic activity | (Jadhav et al. 2010a) |
| Antiulcer activity       | Viscum articulatum Burm. f | Whole plant | Ethanol | 1% extract ointment | Incision, excision and dead space wound model in rats | Reduction in wound area, faster re-epithelization rate | Garg et al. (2012) |
| Antibacterial activity   | Viscum album L         | Dried leaves | Cocoa | Methanolic | 200 and 400 mg/kg orally | Ethanol-induced ulcer model and pylorus ligation ulcer model in rats | Naganjaneyulu et al. (2011) |
|                          |                        |      |           |                   |           |      |                         | 7 days | Rats with infections of Staphylococcus aureus, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa, S. aureus + P. aeruginosa and infection of E. coli | Hematological and histopathological analyses showed therapeutic effects of the extract | Yusuf et al. (2013) |
blockade (CCB). The contractile mechanism in smooth muscle is activated by a rise in the concentration of free intracellular Ca\(^{2+}\) concentration, which activates the contractile elements. The increase in intracellular Ca\(^{2+}\) occurs via either influx from the extracellular fluid through voltage-dependent Ca\(^{2+}\) channels (VDCs) or its release from intracellular stores. Thus, vascular smooth muscle relaxant agents may produce their effects by inhibiting either or both sources of Ca\(^{2+}\) (Mojiminiyi et al. 2008; Khan et al. 2016). A study carried out in rat aortic rings showed that an aqueous extract of leaves of *Viscum album* L. growing on oil palm trees had vasorelaxant activity, which might be mediated by a non-specific non-competitive inhibition of Ca\(^{2+}\) influx as well as inhibition of Ca\(^{2+}\) mobilization from intracellular stores (Mojiminiyi et al. 2008). Furthermore, a study carried out in rabbit aortic rings showed that vasorelaxant activity of mistletoe is mediated through a voltage-dependent Ca\(^{2+}\) channel blockade (Khan et al. 2016). It was proposed that some of the actions on Ca\(^{2+}\) influx or mobilization from cellular stores observed in the study for *Viscum album* L. might be partly mediated by NO. This is because NO inhibits Ca\(^{2+}\) influx through ligand gated Ca\(^{2+}\) channels as well as release from cellular stores. Thus, it is probable that *Viscum album* L. might achieve vasorelaxation through dual mechanisms, the NO/sGC pathway as well as through Ca\(^{2+}\)-dependent mechanisms (Mojiminiyi et al. 2008) (Fig. 2). Ofem et al. (2007) suggested that the reduction in blood pressure without any alteration in heart rate by aqueous extract of leaves of *Viscum album* L. growing on citrus may be due to catecholamine-like blocking agent(s), showing predominantly alpha-1 adrenergceptor antagonist action or agonist-like agents that may be stimulating the beta-2 adrenergceptors to produce the depressor effect. In turn, Radenkovic et al. (2009) proposed that decreases in the blood pressure in rats treated with ethanolic extracts of *Viscum album* L. steams might be connected with muscarinic cholinergic receptors. In rat models of myocardial infarction, flavonoids isolated from *Viscum coloratum* (Kom.) Nakai reduced ischemic myocardial injuries by blocking the signalling pathway of platelet-activating factor (PAF). A PAF antagonist isolated from mistletoe might be a homoeriodictyol-7-0-β-D-glucoside (Chu et al. 2008). Additionally, *Viscum album* L. improved haematological parameters in rats. Mistletoe extracts reduced red blood cell count and packed cell volume (Ofem et al. 2009; Ladokun et al. 2015) and brought the elevated total plasma protein levels and reduced erythrocyte sedimentation rate in the high salt-fed rats to near control levels, indicating the ability of the extract to prevent marked changes in the blood viscosity (Ofem et al. 2009). Fig. 2 Mechanism of cardiac activity of mistletoe. Mistletoe compounds acting on receptor of endothelial cell might activate influx of Ca\(^{2+}\) ions leading to activation of NOS. NOS catalyzes formation of NO from L-arginine. NO diffuses to smooth muscle cell. Once sGC is activated by NO, GTP to cGMP conversion is triggered. cGMP activates PKG leading to reducing intracellular Ca\(^{2+}\) (by inhibition of Ca\(^{2+}\) influx through ligand gated Ca\(^{2+}\) channels and release from cellular stores). Proposed mechanism is confirmed by the fact that mistletoe induces NOS-2 and NOS-3 overexpression which is connected with increase in NO and cGMP production.

**Antidiabetic activity**

In vivo studies on rats showed that *Viscum* species exhibit antiglycemic and insulinotrophic activity by decreasing blood glucose level and increasing the insulin secretion (Ohiri et al. 2003; Nwaegerue et al. 2007; Enò et al. 2008; Shahaboddin et al. 2011; Abdell-Sattar et al. 2011; Adaramoye et al. 2012; Ibegbullem and Chikezie 2013; Kim et al. 2014b; Turkkan et al. 2016) (Table 2). Furthermore, the effects of mistletoe have been shown to be dependent on host trees (Orhan et al. 2005; Umoh et al. 2011). The antilipidemic activity of mistletoe was shown in the reduction in low density lipoprotein cholesterol (LDL) and the increase in high density lipoprotein cholesterol (HDL) (Abdel-Sattar et al. 2011; Adaramoye et al. 2012; Kim et al. 2015) as well as improvement of HOMA-IR (Homeostatic Model Assessment of Insulin Resistance), which is an indicator of insulin resistance (Kim et al. 2015). Gray and Flatt (1999) showed that aqueous extract of *Viscum album* L. exhibited dose-dependent activity to stimulate insulin secretion by rat clonal pancreatic β-cells, and the effect was not mediated by lectins. Furthermore, Kim et al. (2014b) showed that Korean mistletoe growing on oak increased the insulin secretion from the rat pancreatic β-cells (RINm5F cells) without any effects of cytotoxicity. The lectin-free protein fraction induced insulin secretion was similar to the Korean mistletoe extract. It was also reported that the protein fraction upregulated pancreatic and duodenal homeobox 1 (PDX-1) and beta2 (neuroD), which are transcription factors regulating the expression of insulin gene. An ethanolic extract of Korean mistletoe growing on oak also made β-cell mass greater by increasing β-cell proliferation and decreasing its apoptosis. An in vitro study showed that betulin potentiated insulin-stimulated glucose uptake by increasing PPAR-γ (peroxisome proliferator-activated receptor γ) activity and insulin signalling in 3T3-L1 adipocytes, whereas oleanolic acid enhanced glucose-stimulated insulin secretion and cell proliferation in insulinoma cells (Ko et al. 2016). Aqueous *Viscum coloratum* (Kom.) Nakai extract significantly increased the secretion of insulin and an insulin precursor, C-peptide, by RINm5F cells. In differentiated C2C12 cells, the extract enhanced the expression of glucose transporter type 4 (GLUT-4), insulin receptor substrate 1 (IRS-1), and protein kinase B (AKT), which are involved in the glucose uptake signalling pathway. Viscothion, a polypeptide isolated from mistletoe, increased the level of insulin secretion by more than 20-fold compared to...
that induced by the extract (Park et al. 2019). Furthermore, it was reported that mistletoe extracts inhibited α-glucosidase activity, an enzyme catalysing the cleavage of glucose from disaccharide, impeding the digestion and adsorption of glucose, eliciting attenuated postprandial plasma glucose levels (Önal et al. 2005; Park et al. 2019). The mechanism of action is shown on Fig. 3.

**Hepatoprotective activity**

Indicators of liver cell injury are increased levels of serum aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as well as alkaline phosphatase (ALP). Studies on rats with hepatic damage showed that *Viscum* species decreased levels of ALT, AST and ALP (Abdel-Salam et al. 2010; Ogbonnanya et al. 2010; Yusuf et al. 2015) (Table 2). Furthermore, aqueous extracts of leaves of *Viscum album* L. growing on citrus decreased levels of serum bilirubin in high-salt-fed rats and in streptozotocin-induced diabetic rats (Nna et al. 2014; Ofem et al. 2014). The results of studies on patients with chronic hepatitis C were ambiguous. Treatment with either Iscador or Abnoba *Viscum* caused significant improvement for AST and ALT (Tusenius et al. 2005). Furthermore, in two out of five patients treated with Iscodar, a 6–20 fold viral load reduction (HCV-RNA) and improvements for AST and ALT were observed (Tusenius et al. 2001). On the other hand, none of the patients with chronic hepatitis C and elevated ALT levels had complete or partial normalization of ALT or HCV-RNA levels during treatment with Abnoba *Viscum Quercus* (Huber et al. 2001). The mechanism of hepatoprotection by mistletoe is not clear, but it might be mediated by the TGF-β/Smad pathway (Fig. 4). It is accepted that hepatic fibrosis is characterized by an excessive accumulation of extracellular matrix (ECM) proteins. Transforming growth factor-β1 (TGF-β1) is a cytokine leading to the activation of hepatic stellate cells (HSCs), and it stimulates ECM production while inhibiting its degradation. Once activated, TGF-β1 binds its cognate receptors and functions in autocrine and paracrine manners to exert its activities via Smad-dependent and -independent pathways. Smads are signal transduction molecules transmitting signals directly from cell surface receptors to the nucleus. Smad signal transduction pathways...
are thought to mediate TGF-β1-induced collagen synthesis and to play a crucial role in the process of liver damage. Nine Smads have been reported and classified into three groups. When TGF-β1 binds to its receptor, Smad 2/3 is phosphorylated and binds with Smad 4 and together they move into the nucleus to regulate expression of target genes. Smad 7 is an inhibitory Smad that negatively regulates Smad 2/3 activation. In vivo study showed that mistletoe alkaloid fractions downregulate TGF-β1, TGF-β1 receptor, phosphorylated Smad 2 and α-SMA proteins as well as downregulate the mRNA levels of TGF-β1, collagen I and TIMP-1. In contrast, Smad 7 level is upregulated. In vitro study showed that mistletoe alkaloid fractions induce Smad 7 expression and inhibit the expression of α-SMA, TGFβ1, TGF-β1 receptor, Smad 2 and TIMP-1 (Jiang et al. 2014).

Neuropharmacological activity

The influence of *Viscum* species on the central nervous system (CNS) is differential, and it was reviewed by Szurpnicka et al. (2019) In vivo studies on mice and rats showed that *Viscum* species exhibited antiepileptic (Amabeoku et al. 1998; Geetha et al. 2010, 2018; Gupta et al. 2012; Tsyvunin et al. 2016), sedative (Gupta et al. 2012; Khatun et al. 2016; Kumar et al. 2016), analgesic (Orhan et al. 2006; Khatun et al. 2016), antianxiety, antidepressant, hypnotic, anti-stress (Kumar et al. 2016) and antipsychotic activity (Gupta et al. 2012) (Table 2). Several studies have proposed that the CNS activity of mistletoe is mediated by GABA (γ-aminobutyric acid) receptors. GABA is the most important inhibitory
neurotransmitter in the human central nervous system. GABA is involved in epilepsy, sedation and anxiolysis, and it works by binding to GABA_A receptors. GABA_A receptors are heteromeric GABA-gated chloride channels. The transmembrane ion channel is opened by a stimulus generated by GABA, which allows an influx of chloride ions and hyperpolarization leading to anticonvulsant, sedative and anxiolytic activity.

Channel opening frequency and have established efficacy in the treatment of anxiety, insomnia and epilepsy as well as muscle relaxant, sedative, hypnotic, and cognition impairing effects (Diniz et al. 2015) (Fig. 5). Furthermore, it has been reported that mistletoe extract standardized for galactoside-specific lectin (ML-1) increases the beta-endorphin plasma levels in breast cancer patients (Heiny and Beuth 1994; Heiny et al. 1998). Endorphins act through opiate receptors. Three major type of opioid receptors have been identified, mu (μ), delta (δ) and kappa (κ). Beta-endorphin has a relatively high affinity at mu and delta receptors. Mu (μ) (agonist morphine) receptors are responsible for supraspinal analgesia, respiratory depression, euphoria, sedation, decreased gastrointestinal motility and physical dependence (Sharma et al. 2015). Treatment with an aqueous extract of *Viscum album* L. might also increase brain-derived neurotrophic factor (BDNF) (Ademola et al. 2016; Ekpenyong et al. 2016). BDNF plays a prominent role in modulating cognition and memory. BDNF is a neurotrophin that belongs to a family of proteins that promote the survival, functions and development of neurons. BDNF enhances neurogenesis.

**Fig. 5** Mechanism of neuropharmacological activity of mistletoe, GABAergic signalling. Mistletoe compounds might be positive allosteric modulators of GABA_A receptor. They might bind to benzodiazepine site increasing the binding affinity of the receptor for GABA. This results in increased frequency of chloride ion channel opening, increased influx of chloride ions and hyperpolarization leading to anticonvulsant, sedative and anxiolytic activity.
and neurotransmission across the synapses, promotes synaptic growth and modulates synaptic plasticity (Fig. 6). BDNF also induces hippocampal long-term potentiation, which is important for memory formation. It was found that higher peripheral BDNF levels protect the older adults against Alzheimer’s disease (Ng et al. 2019).

**Antiobesity activity**

Treatment with mistletoe parasitizing oak might influence body and epididymal fat pad weights in vivo and inhibit adipogenic factors in vitro (Table 2). It is known that obesity is related with adipocyte differentiation and the extent of subsequent fat accumulation. Adipogenesis can be induced through the action of enzymes, such as fatty acid synthase (FAS), acyl-CoA synthase (ACC) and acyl-CoA synthetase (ACS). The expressions of these genes are regulated by transcription factors, including peroxisome proliferator-activated receptor γ (PPAR-γ), CCAAT/enhancer-binding protein-α (C/EBP-α) and sterol regulatory element binding element protein-1c (SREBP-1c), which are known to be crucial activators for adipogenesis and show early changes in gene expression during adipocyte differentiation (Jung et al. 2013). It has been shown that mistletoe treatment significantly decreased SREBP-1c, C/EBP-α, and PPAR-γ mRNA expression in cultured 3T3-L1 adipocytes and inhibited expression of adipocyte-specific proteins—FAS, ACC, ACS, and LPL (lipoprotein lipase) (Jung et al. 2013). Furthermore, in ovariectomized rats fed a high-fat diet, Korean mistletoe decreased FAS and SREBP-1c expression as well as increased carnitine palmitoyltransferase-1 (CPT-1) expression, a key regulator of fatty acid oxidation (Kim et al. 2015) (Fig. 7).
It was determined that the administration of an aqueous extract of Korean mistletoe might enhance exercise performance in mice (Jung et al. 2012, 2013; Lee et al. 2014) (Table 2). Jung et al. (2012) showed that an increase in endurance capacity might be mediated by improvement of mitochondrial biogenesis (Fig. 8). Korean mistletoe treatment increased the expression of PGC-1α transcriptional targets, such as PGC-1β, NRF-1 (nuclear respiratory factor-1), ERRα (estrogen-related receptor α), Tfam (mitochondrial transcription factor A), PPARβ/δ (peroxisome proliferator-activated receptor β/δ), MB (myoglobin) and TNNI2 (troponin I) in C2C12 cells. Additionally, Korean mistletoe decreased levels of plasma lactate and lactate dehydrogenase, parameters of tissue damage and muscle fatigue in exhausted mice (Jung et al. 2012; Lee et al. 2014). Furthermore, exercise training increases the muscular glycogen and plasma free fatty acid (FFA) level, and Korean mistletoe administration increased the plasma FFA level, indicating that Korean mistletoe administration alters the energy resources in muscle (Lee et al. 2014).

**Activity against muscle decline**

Supplementation with mistletoe might be effective against age-related decline in muscle mass (Table 2). An in vitro study showed that an aqueous extract of Korean mistletoe caused higher phosphorylation of AKT in C2C12 cells (mouse myoblast cell line), suggesting that mistletoe has an effect on the regulation of the muscle mass through the activation of the AKT/mTOR (protein kinase B/mammalian target of rapamycin) signalling pathway (Jeong et al. 2017) (Fig. 9). Furthermore, mistletoe showed increased phosphorylation of FoxO (forkhead box transcription factors of the class O) supporting the observation that mistletoe could induce the phosphorylation of AMPK (AMP-activated protein kinase), which is a repressor of FoxO. FoxO is a key molecule inducing muscle atrophy by stimulating the E3 ubiquitin ligases Murf1 and Atrogin-1. In C2C12 cells, as well as in denervated mice, mistletoe decreased gene expression of Atrogin-1. On the contrary, in C2C12 cells, mistletoe increased mRNA expression of PGC-1α, GLUT-4, and SREBP-1c genes related to the inhibition of muscle atrophy and related to the induction of muscle hypertrophy by regulating the expression of Atrogin-1 and Murf1 (Jeong et al. 2017). Lim et al. (2017) conducted randomized controlled trial confirming that supplementation with Korean mistletoe extract and exercise affects muscle mass and functional capabilities. Supplementation with tablets containing aqueous extracts of *Viscum coloratum* (Kom.) Nakai was effective for suppressing intracellular pathways related to muscle protein degradation, but stimulated those related to myogenesis. The mRNA expressions levels related to muscle protein degradation (REDD2, TSC2, FoxO1, and atrogin-1) and myogenesis (mTOR, S6K1/Rheb, c-Myc, myogenin, and MyoD) as well as the phosphorylation of proteins related to muscle protein degradation (GSK3β, GSK3α, TSC2, and PTEN) and myogenesis (IGF1R, IR, IRS-1, AKT, mTOR, P70S6K, RPS6 and ERK) were studied. Significant differences were found

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**Muscle mitochondrial activity**

It was determined that the administration of an aqueous extract of Korean mistletoe might enhance exercise performance in mice (Jung et al. 2012, 2013; Lee et al. 2014) (Table 2). Jung et al. (2012) showed that an increase in endurance capacity might be mediated by improvement of mitochondrial biogenesis (Fig. 8). Korean mistletoe treatment significantly increased the mitochondrial oxygen consumption rate (OCR) in L6 cells (rat myoblast cell line) as well as increased the mRNA expression of peroxisome proliferator-activated receptor γ coactivator (PGC-1α) and silent mating type information regulation 2 homolog 1 (SIRT-1), two major genes related to mitochondrial biogenesis and function in C2C12 cells (mouse myoblast cell line). Korean mistletoe treatment increased the expression of PGC-1α transcriptional targets, such as PGC-1β, NRF-1 (nuclear respiratory factor-1), ERRα (estrogen-related receptor α), Tfam (mitochondrial transcription factor A), PPARβ/δ (peroxisome proliferator-activated receptor β/δ), MB (myoglobin) and TNNI2 (troponin I) in C2C12 cells. Additionally, Korean mistletoe decreased levels of plasma lactate and lactate dehydrogenase, parameters of tissue damage and muscle fatigue in exhausted mice (Jung et al. 2012; Lee et al. 2014). Furthermore, exercise training increases the muscular glycogen and plasma free fatty acid (FFA) level, and Korean mistletoe administration increased the plasma FFA level, indicating that Korean mistletoe administration alters the energy resources in muscle (Lee et al. 2014).
in atrogin-1 mRNA, myogenin mRNA and insulin growth factor 1 receptor phosphorylation. A single administration of mistletoe induced decreases in atrogin-1 gene expression and PTEN (phosphatase and tension homolog) phosphorylation and an increase in myogenin gene expression. A 12-week treatment induced consistent changes in atrogin-1 and myogenin gene expression. Furthermore, the increase of REDD2 gene expression and a decrease of IGF1R phosphorylation shown by the placebo group were retarded in the mistletoe treated group at a 12-week administration. In patients treated with mistletoe, along with an endurance exercise program, the body composition was significantly changed, and knee strength and the dynamic balance ability were improved (Lim et al. 2017).

Antioxidative activity

Oxidative stress, defined as an imbalance between oxidants and antioxidants in favour of oxidants, leads to many biochemical changes in organisms and is an important contributing factor in several human chronic diseases, such as atherosclerosis and cardiovascular diseases, mutagenesis and cancer, several neurodegenerative disorders, and aging process (Frei 1999). It is suggested that increasing intake of dietary antioxidant may help to maintain a tolerable antioxidant status and help in the disease prevention (Nimse and Pal 2015). Numerous mistletoe extracts and isolated lectin showed radical-scaveging activity and protective effects against oxidative stress induced by free radicals, nitric oxide and superoxide anion (O2−) (Sengul et al. 2009; Papuc et al. 2010; Kim et al. 2010, 2016; Kusi et al. 2015). It was studied that the activity of the more polar extracts was higher in different antioxidant mechanism and might result from high level of phenolic and flavonoid compounds (Orhan et al. 2014; Khatun et al. 2016; Pietrzak et al. 2017). Furthermore, antioxidant activity of *Viscum* species depends on host tree (Vicas and Prokisch, 2009; Vicas et al. 2011; Orhan et al. 2014; Pietrzak et al. 2017) and the time of harvest (Önay-Uçar et al. 2006).
Nephroprotective and antiuretic activity

Helixor M, extract from Viscum album L. growing on apple tree, showed activity against methotrexate (MTX)-induced acute oxidative stress and nephrotoxicity in rats. The mechanism included antioxidant and anti-inflammatory properties, as evident from significant increase in the activities of the antioxidative enzymes, superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) (Şakalli Çetin et al. 2017). Oleic acid isolated from Viscum articulatum Burm. f. showed protective effects on gentamicin-induced renal damage in rats. Oleic acid decreased creatinine, albumin and urea levels in the serum and urine. It protected the rat kidneys from histological alterations induced by gentamicin and improved the glomerular filtration rate. The mechanism might be due to antioxidant and diuretic activity (Patil et al. 2010). Diuretic activity was tested for Viscum angulatum B. Heyne ex DC. and Viscum articulatum Burm. f. It was showed that mistletoe had a significant effect on the urine excretion volume. The higher natriuretic activity (Na+/K+) observed suggested a potassium-sparing diuretic effect. Furthermore, the extract showed less influence on the ion quotient (Cl−/Na+ + K+) which suggested no inhibition of carbonic anhydrase (Jadhav et al. 2010a, b).

Wound healing

Viscum articulatum Burm. f., extract showed reduction in wound area in an excision wound model in rats (Table 2). Furthermore, the re-epithelization rate was found to be faster and granuloma breaking strength as well as dry granulation tissue were significantly increased in extract-treated rats (Garg et al. 2012). Kunz et al. (2011) showed in a prospective case series study, wound healing promoting and anti-tumour effects by the topical treatment of basal cell carcinoma with ointment containing Viscum album L. lipophilic extract. More specifically, an achievement of haemostasis in bleeding tumour wounds, and after a prolonged treatment period, a wound epithelialization with a thin epithelial layer (Kuonen et al. 2013). It is known that, in wound healing processes, many different cell types are involved, including fibroblasts and keratinocytes. As fibroblasts are responsible for initiating angiogenesis, epithelialization, collagen formation and synthesis of extracellular matrix proteins an important step of the proliferative phase of wound healing is the activation of fibroblast migration into the wounded area. An in vitro study showed that Viscum album L. lipophilic extract and its predominant triterpene oleic acid significantly and dose-dependently promoted the migration of NIH/3T3 fibroblasts, thereby leading to an enhanced wound closure (Kuonen et al. 2013).

Antiulcer activity

We found a research regarding the antiulcer activity of mistletoe. Methanolic extract of Viscum articulatum Burm. f was tested in Pyrolus ligation ulcer and ethanol induced ulcer models in rats. The extract showed significant inhibition of the gastric lesions in both models. Significant reduction in gastric volume, free acidity and ulcer index was observed compared to control. The authors proposed that antiulcerogenic and ulcer healing properties might be due to antisecretory activity of mistletoe (Naganjaneyulu et al. 2011).

Antibacterial activity

In the need to find new potent antibacterial compounds, the activity of Viscum species was examined in vitro using wide selection of bacterial strains such as Staphylococcus aureus, Staphylococcus epidermidis, Bacillus subtilis, Bacillus atrophaeus, Enterococcus faecium, Escherichia coli, Bordetella bronchisiptica, Salmonella typhi, Pseudomonas aeruginosa, Pseudomonas syring, Enterobacter cloacae, Proteus vulgaris, Proteus mirabilis, Klebsiella pneumoniae. Streptococcus pyogenes, Mycobacterium tuberculosis, Erwinia carotovora, Agrobacterium tumefaciens, Propionibacterium acnes and Xanthomonas campestris (Satish et al. 1999; Deliorman et al. 2001; Erturk et al. 2003; Day et al. 2008; Sengul et al. 2009; Hussain et al. 2011; Turk et al. 2012; Assaf et al. 2013; Abualhasan et al. 2014; Kusi et al. 2015; Shah et al. 2017). The results obtained are difficult to compare, because researchers used different solvents and various extortion methods to obtain extracts. In addition, some extracts were obtained from the entire plant, and others were obtained from its individual parts such as fruits, leaves or steams (Hussain et al. 2011; Shah et al. 2017). Mistletoe was also obtained from various types of host trees (Deliorman et al. 2001; Turk et al. 2012). Those interested are invited to read the quoted articles. We found only one in vivo study carried out on rats infected by Staphylococcus aureus + Bacillus cereus, Escherichia coli + Pseudomonas aeruginosa, Staphylococcus aureus + Pseudomonas aeruginosa and Escherichia coli. Haematological and histopathological studies, after 7 days of treatment with methanolic extract of Viscum album L. parasitizing cocoa trees, exhibited its therapeutic effect (Yusuf et al. 2013) (Table 2). Researchers have noticed that antibacterial activity of the extracts was more effective against Gram-negative bacteria than against Gram-positive bacteria (Erturk et al. 2003; Hussain et al. 2011) and postulated that the antibacterial effects were through anti-biofilm activity (Kenar et al. 2016).
Antifungal activity

Antifungal activity was most often tested on *Candida* species, which are important pathogens causing substantial morbidity and mortality in hospitalized critically ill patients (Jahagirdar et al. 2018). Nacsa-Farkas et al. (2014) tested activity of ethanolic extract of *Viscum album* L. against twelve *Candida* species, of which the most sensitive was *Candida inconspicua* (MIC 5.65 mg/mL). A methanolic extract of *Viscum cruciatum* Sieber ex Boiss. leaves exhibited activity against *Candida albicans* with MIC 1.25 mg/mL (Assaf et al. 2013). Furthermore, an n-hexane extract of *Viscum album* subsp. *abiitis* (Wiesh.) Abrom. and its two fractions after flash column preparation were tested against *Candida albicans*. The first fraction was active at a concentration of 1 mg/mL (ZI (zone inhibition) 11 mm), whereas the second fraction showed activity at a concentration of 10 mg/mL (ZI 10 mm) (Erturk et al. 2003). Shah et al. (2017) compared the activity of different parts of *Viscum album* L. against *Candida albicans*. For steam distillations, the most active was the butanol extract, which showed 25.66 and 30.00 mm ZI at 1 and 2 mg/disc, respectively. For leaves, the methanol extract was the most active, reducing the growth of *Candida albicans* as 25.00 and 30.00 mm ZI at 1 and 2 mg/disc, respectively. For fruits, the most potent was the n-hexane extract, which reduced the growth of *Candida albicans* by 22.00 mm ZI at both concentrations (1 and 2 mg/disc). On the other hand, methanolic, dichloromethane and aqueous extracts of *Viscum capense* f. stems had no effect on the growth of *Candida albicans* (Amabeoku et al. 1998). Furthermore, Hussain et al. (2011) studied various extracts of *Viscum album* L. leaves and twigs and found that they were not effective against *Saccharomyces cerevisiae* and *Aspergillus flavus*. Methanolic extracts of leaves of *Viscum album* L. growing on cocoa and cola trees inhibited the growth of *Fusarium oxysporium*, *Penicillium oxalium* and *Fusarium solani*, *Sclerotinia sclerotiorum* and *Phytophthora infestans*. It was postulated that viscotoxin A3 might bind to membranes and form ion channels, leading to destabilization and disruption of the plasma membrane (Giudici et al. 2003, 2004, 2006).

Antiviral activity

So far, the antiviral activity of mistletoe has not been extensively investigated. The aqueous extract of leaves of *Viscum album* L. growing on lime trees was found to be effective against human parainfluenza virus type 2 (HPIV-2) growth in Vero cells. The extract, at a dose of 1 μg/mL, inhibited HPIV-2 replication and suppressed virus production by 99.7% (ED50 0.53 μg/mL) with no toxic effect on host cells (Karagöz et al. 2003). The methanolic extract of *Viscum album* L. leaves was active against measles virus growth in Vero cells at 0.063 μg/μL (IC50 0.031 μg/μL) and 0.031 μg/μL (IC50 0.039 μg/μL). On the other hand, the polio, yellow fever and simplex virus-1 (HSV-1) viruses were resistant to the same extract (Obi and Shenge 2018). Due to the strong impact of mistletoe on the immune system, it was proposed that it might be useful as a complementary treatment of patients with human immunodeficiency virus (HIV). Studies to confirm the induction of immunomodulation and possibility of the inhibition of the progression of HIV disease are needed (Gorter et al. 1996, 1999; Stoss and Gorter 1998; Stoss et al. 1999). An in vitro study revealed that a phenolic glycoside, homoeriodictyol-7-0-β-D-glucopyranoside-4′-0-β-D-apiofuranoside, isolated from *Viscum articulatum* Burm. f. growing on Fagaceae: *Lithocarpus variolosus* (Franch.) Chunex showed weak anti-HIV-1 activity with CC50 > 200 μg/mL and EC50 = 18.09 μg/mL. This compound exerted its weak protection of HIV-1IIIB-induced MT-4 host cell lytic effects with a TI > 11.06 (Li et al. 2008).

Conclusion

Traditionally mistletoe has been used in a treatment of many diseases. To date, the anticancer and immunomodulatory activities of *Viscum* species were the most studied. In Europe, mainly in German-speaking countries, this resulted in the launch of extracts for subcutaneous or intravenous administration to improve the quality of life and survival of cancer patients. Lately, an extensive number of in vitro and in vivo studies have been conducted to investigate the other pharmaceutical activities of mistletoe. The results of these studies (Table 2) showed that mistletoe might be a potential source of new drugs and complementary therapies to treat hypertension, diabetes, liver diseases, epilepsy and Alzheimer’s disease. Furthermore, it might be used to improve endurance and muscle strength, enhance wound healing and
as antibacterial and antifungal agent. Such a wide variety of pharmaceutical properties is due to the content of many biologically active compounds from various chemical groups. The chemical composition of mistletoe depends on part of the plant (stem, leaves, fruits) and host species as well as the place and time of harvest. To date, the active compounds responsible for the individual pharmacological activities of mistletoe have not been identified. Further studies on fractionation and isolation of main active compounds and the development of methods of standardization of the extracts are required. Such studies should be conducted for extracts prepared from mistletoe parasitizing various host trees, different harvesting periods and different parts of the plant. In the next step of research, the mechanisms of action need to be tested, not only for individual isolated active compounds, but also for the whole extracts. This is because the therapeutic effect of mistletoe might be a result of the synergistic interactions of various secondary metabolites. Those interactions might include both low-molecular weight compounds (such as phenolic acids, flavonoids and fatty acids) and high-molecular weight substances (such as viscoatoxines and lectins). Because of the diverse synergistic interactions, the mechanism of action of mistletoe might include many signalling pathways. Mistletoe might regulate either the same or different targets in various pathways, while acting on membrane receptors, enzymes, ion channels, transporter proteins and transcriptional targets. In this review, we summarized the existing studies on pharmacological activities of *Viscum* species and proposed possible mechanisms of action. Still, this is a new field for scientific research, and further studies on compound isolation and identification, synergistic interactions, metabolism, mechanisms of action and toxicity are required. We believe that due to this research, mistletoe will become a source of new complementary therapies supporting the treatment of many diseases.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare no conflicts of interest.

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