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## The bornean mistletoes as versatile parasites: A systematic review

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### Abstract

Natural parasites which grows on other trees also gives very effective benefits to humans. Although, the study and knowledge about the medicinal uses of mistletoes are still not in search. European mistletoes, *Viscum album* is most common species used in anticancer. Further, research reports 3 most precious species found in Borneo Island, namely *Scurrula ferruginea*, *Dendrophthoe curvata* and *Macrosolen cochinchinensis*. This borneo species belongs to Loranthaceae family. The phytochemicals present in mistletoes gives ethno medicinal uses. They are tannins, alkaloids, loranthin, gallic acid, flavonols, phenolics and terpenoids. Components which are present gives maximum therapeutic effects. Various components shows various action. The traditional and therapeutic uses of bornean mistletoes components includes Anticancer, Anti-microbial, Anti-oxidative, Anti-hypertensive, Anti-viral, Anti-hyperlipidemic, Anti-nociceptive, wound healing, and others activities.

**Keywords:** *Scurrula ferruginea*, *Dendrophthoe curvata*, *Macrosolen cochinchinensis*, flavonols, antinociceptive, tropical region, etc.

### Introduction

Mistletoes is a leathery-leaved parasitic plants which grows on host trees (apple, oak and other broadleaf trees) and bears white glutinous berries in winters. It's derived from two Anglo Saxon words "Mistel" meaning dung, and "Tan" meaning stick or branch. Mistletoes also called obligate hemiparasitic plants. They are attached to host trees or shrubs by a structure known as haustorium, which extract water and nutrients from host plant. They do perform photosynthesis for some period of life cycle [1]. The largest family of mistletoes is Loranthaceae, has 73 genera and over 900 species. But tropical and subtropical region have more mistletoes species.

### Taxonomy

- **Kingdom:** Plantae
- **Subkingdom:** Viridiplantae
- **Infra kingdom:** Streptophyta
- **Super division:** Embryophyta
- **Division:** Tracheophyta
- **Subdivision:** Spermatophyta
- **Order:** Santalales
- **Family:** Loranthaceae

Various chemical constituents are extracted from different mistletoes, which shows therapeutic and medicinal activities. Lipid, polysaccharide, proteins other chemical constituents extracted from mistletoes have many uses. In children, mistletoes used in treatment of stomach pain, diarrhea and schizophrenia. It helps to slow the pulse, which also reduce the exertion of heart. The hypertension reduction of mistletoes extract can help to prevent strokes, heart attacks and coronary heart disease [2]. By lowering blood pressure mistletoes extract is able to ease the strain and stress on cardiovascular system and also cutting down impact of atherosclerosis. Commonly mistletoes are able to treat cancer,

inflammation, diabetes, respiratory distress, low blood pressure, menstrual pain, consciousness and snoring [3]. It increases activity of immune system and act as immunity boosters. Indian people also use mistletoes in the form of tea against diabetes. There are many species which are native and cultivated in various regions of the world. Most common mistletoes found in India is *Dendrophthoe* belongs to Loranthaceae family. Also species found in Europe and China are *viscum album* and *Taxillus Chinesis*. Different mistletoes that are found in Southeast Asia are *Scurrula ferruginea*, *Dendrophthoe curvata*, *Scurrula atropurpurea*, *Macrosolen cochinchinensis*, *Loranthus parasiticus*, *Scurrulaoortiana* [3, 4]. Three Common species found on Borneo Island are *Scurrula ferruginea*, *Dendrophthoe curvata* and *Macrosolen cochinchinensis*.



Fig 1: *Scurrula ferruginea*



Fig 2: *Dendrophthoe curvata*



Fig 3: *Macrosolen cochinchinensis*

### History

- According to different cultures, mistletoes is the symbol of fertility, love, peace and friendship.

- Pagan cultures regarded white berries as symbol of male fertility, with the seeds resembling semen.
- Ancient Greeks referred to mistletoes as 'Oak sperm'. In
- Ancient Greek mythology mistletoes used by hero Aeneas to reach the underworld.
- Druidic mythology also plays an important role in 'Ritual of Oak and mistletoes'. Evidence taken from bog bodies make the Celtic use of mistletoes seem medical rather than ritual. It is possible that mistletoes was associated with human sacrifice [4].
- Norse mythology, Loki tricked the blind god Hodur into murdering his own twin brother Balder with an arrow made of mistletoes wood, being the only plant which Balder was vulnerable. From some stories, mistletoes becoming a symbol of peace and friendship [5].
- In Christian era, mistletoes used as decoration under lovers are expected to kiss, as well as with protection from witches and demons. It also associated with fertility and vitality through middle ages [6].
- In mid-19<sup>th</sup> century, Caribbean herbalists of Africa descent has referred to mistletoes as god-bush [7].
- In Nepal, diverse mistletoes are used for variety of medical purposes for treating broken bones.
- Every year, In UK Town of Tenbury wells hold a mistletoes festival and crowns a 'Mistletoes Queen'.

### Biology

All these three mistletoes are aerial hemiparasites and attached to the stems of trees through their haustoria. They derive nutrients and water from the host plants. The green leaves of mistletoes enable the parasitic plants to produce additional food through photosynthesis [1].

**Table 1:** Below table shows the information regarding the common host plants on which these 3 mistletoes parasites.

Mistletoes	Host trees	Reference
<i>Scurrula ferruginea</i>	<i>Tabebuia pallida</i> ( <i>T. pallida</i> )	(8)
	<i>Lagerstroemia speciosa</i> ( <i>L. speciosa</i> )	
<i>Dendrophthoe curvata</i>	<i>Vitex pinnata</i> ( <i>V. pinnata</i> )	(9)
	<i>Acacia auriculiformis</i> ( <i>A. auriculiformis</i> )	
	<i>Andira inermis</i> ( <i>A. inermis</i> )	
<i>Macrosolen cochinchinensis</i>	<i>Mangifera indica</i> ( <i>M. indica</i> )	(9)
	<i>Artocarpus heterophyllus</i> ( <i>A. heterophyllus</i> )	
	<i>Erioglossum rubiginosum</i> ( <i>E. rubiginosum</i> )	
	<i>Manilkara zapota</i> ( <i>M. zapota</i> )	
	<i>Mangifera indica</i> ( <i>M. indica</i> )	

### *Scurrula ferruginea*

*Scurrula ferruginea* has slender pendulous nature and rusty coloured leaves. Due to this nature it also named as slender busy mistletoes and rusty leaf mistletoes. The Rusty-leaf Mistletoe is not common to their members of other families like *Dendrophthoe pentandra* and *Macrosolen cochinchinensis*. *Scurrula ferruginea* is a very recognisable mistletoe from its rusty brown underside of the leaves. These brown hairs also extend through the plant, including the stem, branches and flowers. *S. ferruginea* is hemiparasitic shrub, which is able to grow about 1 m in length. It has leathery, reddish brown leaves. Arrangement of leaves is opposite and broadly elliptical to ovate. It has surface with short and verticillate hairs. Top surface is smooth [10]. Leaf stalk is about 2-6 mm. Grey coloured stem having lenticels on it. Axillary flowers having 4-6 in a cluster. Pear-shaped berries measuring about 8-10 in each cluster is about 3-4

mm. They are grows commonly on citrus trees in full sunlight. *S. ferruginea* is synonym with *Loranthus ferrugineus* belongs to Loranthaceae family [11]. In borneo, *S. ferruginea* also known as "benaluteh"

#### ***Dendrophthoe curvata***

*Dendrophthoe curvata* belongs to Loranthaceae family. It is also known as curved mistletoes or rainforest mistletoes. Leaves are arrange in scattered or subopposite manner. Leaf lamina is broadly ovate or obovate measuring 10-15 cm long, 3-5 cm wide and obtuse or rounded at the apex. Flowers born in raceme of 3-12 flowers [8]. Pedicels is about 2-4mm long. Inflorescence axis is about 5-30 mm long. Calyx and corolla clothed in stalked. Anther is 4 mm long. Staminal filament is about 3 mm long. Ovary is about 2.5-3 mm long. There are no ovules visible in ovary. Ellipsoidal fruits are 10-15 in number. It's surface is slightly scurfy. Seeds are with green radicals [8]. Seed germination time is about 18-146 days. *D. curvata* synonym as *Loranthus curvatus*, *Dendrophthoe falcata*, *Dendrophthoe discolor* and *Loranthus falcatus*.

#### ***Macrosolen cochinchinensis***

Another most common species is *Macrosolen Cochinchinensis* belongs to Loranthaceae family. It is found in

South India (Sigur plateau)-In Nilgiri district in Tamil Nadu. And Vogalkop (Tropical moist forest ecoregion in Indonesia)-Aru lowland rain forests. Leaves are broad, lanceolate to ovate measuring 2 cm wide and acute to rounded at apex.

Flowers of *M. cochinchinensis* are arranged in group of six petals with orange colour [12]. In some cases, change in host plant also changes the colour of flowers. *M. cochinchinensis* parasites on starfruit trees bears red flowers; whereas, on *Cartoxylum formosum* tree it bears yellow flowers. Long perianth tube which opens at tip into six highly reflexed lobes and six epiphyllous stamens. Ovary is inferior. Calyx is funnel shaped.

Corolla in mature bud is strongly 6-alate and inflated in middle is about 9-14 mm long. Anthers are 1-15 mm long. Fruits are globular in shape.

#### **Constituents Found In Mistletoes**

Every part of each mistletoes species contain different component with their specific action. Some parts of mistletoes shows it's action with different extraction solvents. Isolation of mistletoes gives proteins, fatty acids, glycosides, polysaccharides and steroids [13].

**Table 2:** All information about constituents and their activity is shown below.

Constituents	Activity	Reference
Flavonols(quercetin, quercitrin, 4 <sup>o</sup> -O-acetylquercitrin)	Anticancer, Cytotoxic, Anti-proliferative, Anti-inflammatory	[14]
Alkaloids	Antibacterial, Vasodilatory, Anti-asthmatic, Anti-microbial	[15]
Terpenoids	Antibacterial, Anti-microbial	[16]
Gallic acid	Neuroprotective	[17]
$\beta$ -phenylethylamine, Tyramine	Degenerative joint disease, In malignant tumors	[18]
Tannins	Anticancer, antiviral and antibacterial	[19]
Loranthin	Antiviral, Antibacterial	[20]
Phenolics and Lectins.	Immune system modulator, anticancer, antiviral, antioxidant, and proapoptotic effects	[21]

#### **Pharmacological and Medicinal Uses of Mistletoes**

##### ***Scurrula ferruginea***

On the basis of number of research and experimental studies it is explained that every Bornea mistletoes has different therapeutic activities in various complications. *S. ferruginea* also possess some important activity against diseases. *S. ferruginea* is also used for wounds, snakebites, beriberi, and fever [22]. *S. ferruginea* found to have anticancer, antimicrobial, antioxidant and antihypertensive properties [23]. Plants from the genus *Scurrula* were found to inhibit cancer growth due to presence of phytoconstituents such as quercetin and fatty acid chains. Similar to plants from the genus *Viscum*; *Scurrula* also possesses TNF $\alpha$  activity to strengthen the immune system to combat cancer [24].

In line with its anticancer activity, both mistletoes are rich in antioxidants that confer protection against cancer as well as neuro-degeneration. Extracts from plants of both genera showed evidence of validation. Other therapeutic effects such as weight loss, postpartum and gastrointestinal healing from different plants of the genus *Scurrula* are documented. As the therapeutic effects of plants from *Scurrula* are still in exploration stage, there is currently no known clinical trial on these plants. *Viscum album* extract has been studied in clinical trials and is being used in Europe as an adjuvant therapy for cancers of breast, malignant ascites and pancreas [23].

As *Scurrula* research is still in its early stage, phytoconstituents isolation, structure activity relationship of phytoconstituents, mechanism of action of the bioactive compound and clinical trials are in the research.

#### **1. Anticancer/ Cytotoxic effects**

*S. ferruginea* inhibit cancer cell growth due to presence of quercetine and fatty acid. From few studies, It is identified that Flavonols are isolated and elucidated from *Scurrula ferruginea* [25]. subsequently reported their cytotoxicity on human cancer cell lines (DU145, K562 MCF-7, (U251) [26]. It mainly affect on glioma cells of U251. 3 Flavonols are isolated named as: quercetin, quercitrin and 4-O-acetylquercitrin. Quercitrin has found to mediate the protective effects on endothelial progenitor cells that repair damage endothelium & have anti- atherosclerosis effects [27]. Quercetin exerts anti-proliferative effects on cancer cells by growth arrest of HepG2 cells as well by targeting micro RNA-21 signalling in BEAS-2B cells. Therefore both have much more therapeutic effect [28]. Isolation of *Scurrula* plants reports the flavonoids to determine relation between structural and biological activity [29]. It act as inhibitors of various enzymes in cellular processes (Protein kinase to poisomerase) [29]. Degranulation of enzymes has been closely linked to different diseases. Inhibition of these enzymes be useful in cancer therapy & other diseases.

### Anti-microbial effect

Indonesian plants has main source of infectious diseases. Brunei Darussalam species of mistletoe, researchers found the antibiotic activity of Gentamycin and Ampicillin for *Staphylococcus aureus* while Sulphamethoxazole was used for *Escherichia coli* [30, 31]. Antibacterial effect on *Staphylococcus aureus* ATCC 25923 strain shows no inhibition against *Escherichia coli*. Further investigation which includes Minimum Inhibition Concentration (MIC) and Minimum Bactericidal Concentration (MBC) has been initiated to confirm the antibacterial effect. Also several *Scurrula* plant members have been shown to possess promising anti-microbial activity. The leaf, flower & stem of *S. ferruginea* crude acetone extract have good anti-bacterial activity against a range of Gram +ve and -ve bacteria [32]. The extract of leaves & stems of *S. ferruginea* has potent anti-microbial activity against Clinically relevant skin pathogen; *Staphylococcus aureus* [32]. *Scurrula* plants have an intrinsic anti-microbial activity against a broad spectrum of different types of bacteria. Ethno pharmacological study shows that indigenous people of Indonesia could diagnose viral infections [33] Crude methanol extract of *S. ferruginea* inhibited replication of poliovirus with remarkable IC50 of 62µg/ml. In Ovo injection of crude *S. oortiana* extract preparation into embryonated chicken eggs was shown to be protective when challenged with Marek's Disease Virus (MDV), highly contagious virus cause poultry disease. Given evidence shows that some of *Scurrula* plants can be effective against range of viruses.

### 3. Antioxidant Activity

Preliminary findings of researchers that the study suggests that *S. ferruginea* extract can be considered as a new source of antioxidant agents. Researchers of Teknologi University found the antioxidant properties of *S. ferruginea*. They obtained the results and suggest that antioxidant capacity of *S. ferruginea* slightly differ depending on the plant part used. According to scientists, stem extract exhibited higher phenolic content which shows antioxidant and metal chelation activities, based on Folin-Ciocalteu. In given research study, stem, leaf and flower extracts contains more phenolic content of *S. ferruginea*. Stem extract contains highest amount of phenolic Content rather than leaves and flowers. Highest phenolic content; highest is anti-Oxidative activity. In recent, it was also observed that mature leaves extract of *S. ferruginea* exhibited higher anti-oxidant activity than dried tender leaves. In addition, methanolic leaf extract of *S. ferruginea* shows higher anti-oxidant activity in comparison to aqueous extraction. Common forms of free radicals i.e., Reactive Nitrogen Species (RNS) and Reactive Oxygen Species (ROS). ROS-ex. Hydroxide radical, peroxide radical, Superoxide anion (O<sup>-</sup>), peroxy radical (HO<sup>2-</sup>). RNS-ex. NO<sup>2-</sup> nitrogen dioxide radical, NO- Nitric oxidase. Any atom or molecule with one or more unpaired electron is a free radicals [34].

It is generated as normal by-products of aerobic metabolism (mitochondrial respiration) [35] also derived from externally alcohol, smoking, medication, pollution radiation. (36) Excess ROS capable of lipid denaturation, change in protein shapes, oxidative stress leads to some diseases such as ageing, cancer, cataract, rheumatoid arthritis, autoimmune disorder, neurodegenerative disease, cardiovascular diseases. An endogenous anti-oxidant defenses

insufficiency to prevent free radical damage completely, diet derived antioxidants (vit. E and C) are crucial to combat ROS-induced oxidative damage for optimal health [37] As free radicals may induce initiation of cancer through DNA damage and mutation, it can be postulated that scavenging free radicals with antioxidants is anti-cancerous (cytotoxic) [38] Recent study explore that Neuroprotective control of antioxidants. All these shown that antioxidant therapy is an attractive option for both Cancer & Neuroprotective disease. *S. ferruginea* Stem extracts elicit higher anti-oxidant activity (due to their higher phenolic) content compared to leaf extract. Identification of bioactive plant constituents helps to maintain antioxidant status and confer protection against free radical damage induced diseases including cancer and neurodegeneration. The overall free radical scavenging activity might be attributed to the presence of phenolic compounds in the extracts. According to their work is under way to confirm the antioxidant activity of various parts of *S. ferruginea*, using other types of solvents. In addition, more *in vitro* study investigating the effect of *S. ferruginea* extracts on breast cancer cell lines is under progress.

### 1. Anti-hypertensive effects

Cardiovascular disease are most observed complication among people by stress or severe problems. Hypertension is risk factor of CVD. The methanolic extract of *S. ferruginea* helps in hypertension. The vasorelaxant properties of *S. ferruginea* explained using both *in vitro* and *in vivo* animal experimental studies. It effects via reversible noncompetitive, antagonism. The aerial parts of plants (leaves, fruits, flowers) were collected, dried and pulverized into Powder. Then extract it in hot water with chloroform petroleum ether, methanol, ethyl acetate, ect. carried out generative 5 different extracts. Then various responses of isolated rat aortic ring towards different doses of noradrenaline in presence of extracts has measured. The methanolic extract produced a dose dependent inhibition (prevents) in maximum response. This *in vivo* experimental study is most potent extract for blood pressure lowering activity in anesthetized normotensive Sprague Dawley (SD) rat model [39] This study is limited to vasoconstriction or dilation with respect to noradrenaline in presence of extract [40] The extract of *S. ferruginea* was obtained using Soxhlet extraction method.

On other hand, Hypotensive effect of extract was reduced in presence of atropine. This dose dependent effect of methanolic extract of *S. ferruginea* together with reduction of effect in presence of atropine, was replicated in guinea pig ileum. Conversely, neostigmine (Ach inhibitors) enhanced contraction of guinea pig ileum. This experiment leads to hypotensive effect of *S. ferruginea* methanolic extract via stimulation of muscarinic receptor/ stimulation of NO release. Chemical analysis of n-butanolmethanolic extract of *S. ferruginea* reported 0.4% of flavonoids, 6.3% phenolic compounds, 0.3% total antioxidants 40.04% free radical scavenging activity with antihypertensive activity.

### Gastrointestinal activity

Various herbal preparation are mostly used for gastrointestinal disorders. Herbal medicines are widely used for their efficacy, ease of use and most importantly for lesser side effects. The flowers & leaves of *S. ferruginea* reported for therapeutic purpose, as a purgative while the haustorium noted for effect on ulcer. The study of *S.*

*ferruginea* methanolic extract on gastrointestinal effects exhibited dose-dependent Spasmogenic activity [41]. To determine MOA of contractile responses, in isolated guinea pig, graded addition of extracts. The extract inhibited the contraction by atropine while opposite was true of Neostigmine. It was recorded that the extract mimics Ach, works directly on ileal muscarinic receptors and act as a substrate for Acetylcholine esterase enzyme. Ach is excitatory neurotransmitter regulating gut motility, it activates M3 receptor in smooth muscles. The extract act through activation of muscarinic receptor achieving choline mimetic activity [42].

### ***Dendrophthoe curvata***

*Dendrophthoe curvata* is used as traditional medicine. It possesses remarkable potential as a medicinal plant, as is evident from the wound healing, anti-microbial, antioxidant, antihypertensive, antihyperlipidemic and antinociceptive properties of its ethanolic extracts [43, 44, 45, 46]. Medicinal properties of this hemiparasite may vary in effects respective to different hosts it establishes a relation with. The whole plant is used in indigenous system of medicine as cooling, bitter, astringent, aphrodisiac, narcotic and diuretic and is useful in treating pulmonary tuberculosis, asthma, menstrual disorders, swelling wounds, ulcers, renal and vesical calculi and vitiated conditions of kapha and pitta. Also, the decoction of plant used by women as an anti-fertility agent has been evidenced to possess anticancer activity [47]. The leaf ethanolic extract significantly and dose dependently inhibits the acetic acid induced writhing in mice and has indicated a low level toxicity in the brine shrimp lethality assays. Besides, a more recent work shows significant tumor reduction in induced mammary carcinogenesis in Wistar female rats when fed with hydro alcoholic extracts of *D. falcata* [48]. *Dendrophthoe falcata* Ettingsh is a popular hemi parasitic plant and is used in folklore medicine for ailments including importance, paralysis, skin diseases, menstrual troubles, and wounds. Scientific evidence suggests its versatile biological functions such as it's potentiality in immunomodulation, reducing the tumor volume, male contraception, urolithiasis and wound healing. A comprehensive account of the morphology, tissue culture, phytochemical constituents, ethno botany and biological activities, are included in view of the recent findings of importance on the plant, *Dendrophthoe falcata*.

### ***Macrosolen cochinchinensis***

*Macrosolen cochinchinensis* is a parasite grows in Indonesia and is known to possess the anticancer activity. This study was published in Journal of Applied Pharmaceutical science explained the anticancer activity of the extracts and the fractions of jackfruit mistletoe leaves describe the cell cycle inhibition and induction of apoptosis on T47D breast cancer cell line. The jackfruit mistletoe is extracted using the maceration method. The extract is then separated by liquid-liquid partition method with n-hexan, chloroform, ethyl acetate, and water solvent. MTT method is used to determine the anticancer activity of crude extract and fractions. Cell cycle inhibition test is conducted using flow cytometry with PI marker. The induction of apoptosis is determined by flow cytometry method using PI-Annexin V and PI double staining acridine orange-ethidium bromide. The results indicated that the IC50 value of the ethanol extract., Chloroform fractions and ethyl acetate fractions of

jackfruit mistletoe leaves showed a higher anticancer activity with IC50 which respectively are 362.8, 356.8, 314.8µg/ml. The treatment of n -hexan and water fraction show no signs of anticancer activity because it has a great value of IC50 which are respectively 926.0 and 2243 µg/ml. Cell death caused by treatment of ethyl acetate fraction of jackfruit mistletoe leaf (*Macrosolen cochinchinensis*) is due to the induction of cell apoptosis and cell cycle inhibition in G0-G1, S and G2-M phase. *Macrosolen cochinchinensis* (Lour.) Tiegh. that grows in the host star fruit inhibited breast cancer cells growth *in vitro*.(49) There study showed the effect of water extract of *M. cochinchinensis* leaves (MCE) on Balb/c mice hepatocyte after initiation of 7,12dimethylbenz anthracene (DMBA) as a liver cancer model inducer. *In vitro* antioxidant potential was determined by DPPH free radical scavenging activity and reducing power capacity. Leaves extract of *M. cochinchinensis* have excellent anti-nociceptive activity and moderate antioxidant property. That study showed on leaves extract of *M. cochinchinensis* revealed that the plant has significant anti-nociceptive activity against both chemical and physical heat induced pain in mice and exhibits moderate antioxidant properties. But for demonstration the mechanisms of this crude extract and their biological active component (s) needed more investigations.

### **Conclusion**

Mistletoe species in Borneo Island found effective in various disease such as cancer treatment, inflammation, diabetes, respiratory distress, low blood pressure, menstrual pain, consciousness which is impressive as a hemiparasitic plant but it's still lack of research and clinical trials, Although, mistletoe's used as medical aliment has been known from ancient era's. There are three species of mistletoe found in Borneo. The most common is *Scurrula ferruginea* which has different activities as anticancer, antioxidant, antihypertensive and antimicrobial. Second species is *Dendrophthoe curvata* which has significant action in pulmonary tuberculosis, asthma, menstrual disorders, swelling wounds, ulcers, renal and vesical calculi. *Macrosolen cochinchinensis* is 3rd species found in borneo specially in Indonesia has anticancer also have free radical scavenging activity. It also found effective as anti-nociceptive activity. Mistletoe searched species are found in worldwide, but each species has different activities according to regions and their host plants. Mistletoe could be drug which in new way can fight cancer cell according to their free radical scavenging ability and also have many versatile effect on different disease. On *Scurrula ferruginea*, there is a well-known research work has been done. But other two species are somehow need a more research on the components and their special activities.

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