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REVIEW ARTICLE

A Hidden Treasure: The Borneo Mistletoes

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ABSTRACT

The European mistletoe, *Viscum album*, is the most common consumed adjuvant among cancer patients in Europe. Its success warrants a report on three most apparent mistletoes found in Borneo Island, namely *Scurrula ferruginea*, *Macrosolen cochinchinensis,* and *Dendrophthoe curvata*. The traditional and pharmacological uses of these mistletoes include antibacterial, anticancer, antiviral, antihypertensive, antioxidative, and cytotoxic effects. Phytochemicals such as flavonols, alkaloids, tannins, and gallic acid have been reported in one of these mistletoes. This review discusses the potential of these mistletoes as therapeutic agents.

Key words: Cancer, *Dendrophthoe curvata*, *Macrosolen cochichinensis*, plant, *Scurrula ferruginea*, traditional medicine, tropical

INTRODUCTION

Mistletoes are often associated with Christmas decorations in cold climate regions. The success of European mistletoe, *Viscum album,* as a source of anticancer drug has prompted us to look into the tropical mistletoes. There is not only a dearth of knowledge regarding tropical mistletoes but also a lack of awareness even among the local people in the region. Mistletoes are obligate parasitic plants which grow on stems of trees with the aid of a sophisticated structure called haustorium. Mistletoes may encounter varying responses from host plants for their haustorial penetration.[1] Taxonomically, mistletoes are from the order of Santalales and are found in three families: Santalaceae (inclusive of the Viscaceae), Loranthaceae, and the Misodendraceae.[2] The species under the various genera are mentioned in Table 1.

The most common mistletoe known as *V. Album* (English name: *mistle*), belongs to the Santalaceae (Viscaceae) family. This hemiparasitic plant is native to Europe.[3] The most common mistletoe found in India is *Dendrophthoe falcata*, one of the seven species of *Dendropthoe* and belongs to the Loranthaceae family. Mistletoe commonly found in China is *Taxillus chinensis Danser* (mulberry mistletoe). The different mistletoes that are found within Southeast Asia include *Scurrula atropurpurea, Scurrula ferruginea, Macrosolen cochinchinensis, Dendrophthoe curvata, Loranthus parasiticus,* and *Scurrula oortiana*.[4-8]

Brunei Darussalam, a Southeast Asian nation rich in flora and fauna, has more than 70% of its country made up of primary rainforests, rendering it an excellent resource of a great diversity of plants and wildlife. Three common species of mistletoes found in Brunei are *D. curvata, S. ferruginea,* and *M. cochinchinensis*.[9]

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BOTANY

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.[10] Table 2 summarizes the common host plants that these mistletoes parasitize on.

SCURRULA FERRUGINEA

S. ferruginea is a semi-woody plant with slender, pendulous branches that grows up to 70 cm in length. The branches have brown hair on its bark. Being a hemiparasitic plant, it attaches itself to different types of trees such as citrus trees that grow in full sunlight and at times, penetrates into the host plant.[11] The leaves are arranged opposite and elliptically, up to 7 cm by 2.5 cm with a glossy upper surface and lower brownish fuzzy surface.[12] The flowers are inflorescences and arranged in clusters of 4–7, emerging from the axils. Each flower consists of four small petals with brown hair on its 1.5 cm long tubular corolla with dark brown interior. The brown hairy ovary is found within the flower. Due to its slender pendulous nature and rusty colored leaves, *S. ferruginea* has earned its name as slender busy mistletoe. It is also referred as rusty mistletoe or even scurfy mistletoe. Figure 1a illustrates the parasitic nature of *S. ferruginea* on a tree along the roadside in Brunei Darussalam. A stalk of *S. ferruginea* with its brown flower is shown in Figure 1b. *S. ferruginea* is synonymous with *Loranthus ferrugineus* and belongs to the Loranthaceae family.[13] In Brunei, *S. ferruginea* is known as "*benalu teh*."

DENDROPHTHOE CURVATA

Similar to *S. ferruginea*, *D. curvata* belongs to the family of Loranthaceae and is known as rainforest mistletoe or curved mistletoe. The leaves of *D. curvata* are elliptical. The flowers are usually 3–4.8 cm long of red buds with narrow club-shaped necks that broadened as the flowers

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curved upward. Within the flower buds, there are flower tubes of about 1.8–3 cm long while the petals curve to one split side of the flower.[7]

MACROSOLEN COCHINCHINENSIS

Another most common species of mistletoe in Brunei Darussalam is *M. cochinchinensis*. Similarly, this mistletoe belongs to the Loranthaceae family. The flowers of *M. cochinchinensis* are arranged in groups of six with orange corollas that are straight but inflated in the middle. The flower buds are recognizable by their yellow tips. This shrub mistletoe has gray scattered branches. The leaves are arranged opposite each other and are broadly elliptic, pointed at the ends, and bend upward.[14] Figure 2 displays *M. cochinchinensis* on a tree.

Table 1: The three families of mistletoes within the order of *Santalales*

	Order of *Santalales*		
	Family		
	Santalaceae (Viscaceae)	Loranthaceae	Misodendraceae
Genus	*Viscum*	*Scurrula*	*Misodendrum*
Species	*V. album*	*S. ferruginea*	*M. punctulatum*

V. album=Viscum album, *S. ferruginea=Scurrula ferruginea*, *M. punctulatum=Misodendrum punctulatum*

Table 2: Common host plants of the mistletoes

Parasite	Host tree(s)	Reference
D. curvata Blume	A. auriculiformis A. Cunn. Ex Benth	[7]
	A. inermis (W. Wright) DC.	
	M. indica L.	
	V. pinnata L.	
M. cochinchinensis	*A. heterophyllus*	[6]
	E. rubiginosum	
	M. indica	
	M. zapota	
	T. calamansanai	
S. ferruginea	*T. pallida*	[6]
	L. speciosa	

D. curvata=Dendrophthoe curvata, *M. cochinchinensis=Macrosolen cochinchinensis*, *S. ferruginea=Scurrula ferruginea*, *A. auriculiformis=Acacia auriculiformis*, *A. inermis=Andira inermis*, *M. indica=Mangifera indica*, *V. pinnata=Vitex pinnata*, *A. heterophyllus=Artocarpus heterophyllus*, *E. rubiginosum=Erioglossum rubiginosum*, *M. zapota=Manilkara zapota*, *T. calamansanai=Terminalia calamansanai*, *T. pallida=Tabebuia pallida*, *L. speciosa=Lagerstroemia speciosa*

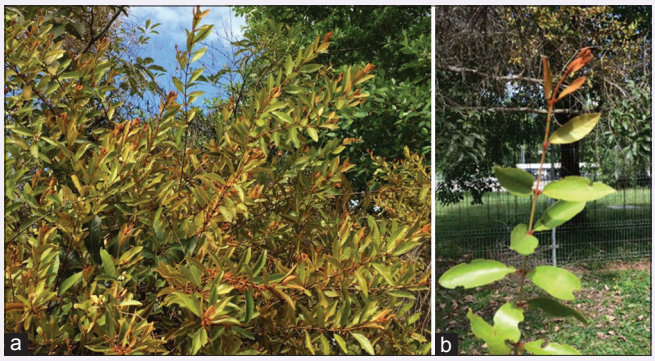

Figure 1: (a) Luscious bush of *Scurrula ferruginea* on a tree alongside the road in Brunei Darussalam. (b) A stalk of *Scurrula ferruginea* with the brown flower

TRADITIONAL AND PHARMACOLOGICAL USES OF MISTLETOES

Although the pharmacological effects of these mistletoes are understudied at the moment, traditional folklore has been using mistletoes for muscle swelling and sprains, bone dislocations and fractures, headaches, postpartum, suspected cancer, and other illnesses.[15] In Nepal, *M. cochinchinensis* is used for curing headaches.[15] Both *M. cochinchinensis* and *S. ferruginea* have been found to have antihypertensive effects exhibited vasorelaxing effects in isolated rat thoracic aorta[16,17] and childbirth.[18] *S. ferruginea* is also used for wounds, snakebites, beriberi, and fever.[18] There is currently no documentation of usage of *D. curvata* for traditional treatment, but a sibling *Dendrophthoe falcata* has been documented to possess anticancer, antifertility, antimicrobial, antioxidant, antidiabetic, antihypertensive, antihyperlipidemic, wound healing, and diuretic properties.[19-23] Nevertheless, there is a thesis published in the Malay language from Indonesia on the effects of *D. curvata* on breast cancer cell line T47D which postulated that terpenoids from the plants' extract contributed to the antiproliferative effects.[24] Similarly, there is a lack of documentation on the pharmacological use of *M. cochinchinensis,* but a recent paper published positive cytotoxic effects of *Macrosolen parasiticus* on the growth of breast cancer cell line (MCF-7).[25]

Incidentally, among the three mistletoes, most research work has been done on *S. ferruginea*, which exerted antibacterial, antiviral, antihypertensive, antioxidative, and cytotoxic effects.[26] Table 3 summarizes the various extracts of *S. ferruginea* and the actions observed from these extracts. The most documented effect of *S. ferruginea* is its antihypertensive effect. Various (crude methanol, chloroform, and ethyl acetate) extracts of whole plant of *S. ferruginea* were found to possess vasorelaxant properties on rat thoracic aorta.[16] Applying the methanolic extract of *S. ferruginea* on Guinea Pig Ileum resulted in hypotensive and spasmogenic effects on the intestinal tract. This observed effect was found to be due to norepinephrine-induced vasoconstriction on the vascular system.[27] Further work by Ameer *et al.* illustrated that the n-butanol fraction of the methanolic extract is responsible for this antihypertensive effect and this team observed that the rat thoracic aorta relaxed in a dose-dependent hypotensive action by acting on the vascular smooth muscle.[28] In addition, the methanolic extracts also showed antiviral properties against poliovirus.[29] The acetone extract, especially from the stem component of *S. ferruginea*, contains the most antioxidative property as it scavenges DPPH free radicals[30] The

Figure 2: *Macrosolen cochinchinensis* parasitizing on a tree

Table 3: Summary of the plausible effects of different extracts of *Scurrula ferruginea* from the experimental observations

Types of extract(s)	Parts of plants used	Observation(s)	Effect(s)	Reference
Methanolic extracts	Leaves Stems Flowers	Antiviral activity against poliovirus active on poliovirus and activity on the U251 glioblastoma cells	Antiviral	[29]
Acetone extract	Stem Leaves Flowers	DPPH free radical scavenging assay	Antioxidant	[32]
Crude methanol extract, chloroform extract, ethyl acetate extract	Whole aerial plant	*In vivo* experiment: Vasorelaxant using rat thoracic aorta	Antihypertensive	[16]
Methanolic extract	Whole aerial plant	Hypotensive and spasmogenic effects The vascular effects by norepinephrine-induced vasoconstriction	Antihypertensive	[17]
Methanolic extract and by n-butanol fraction	Whole aerial plant	Rat thoracic aorta rings: vascular smooth muscle relaxation *in vitro* a dose-dependent hypotensive action *in vivo*	Antihypertensive	[27]
Methanolic extract and then successively fractionated using chloroform, ethyl acetate and *n*-butanol of LFME	Whole aerial plant	Isolated rat thoracic aorta	Antihypertensive	[28]
Extracted with petroleum Ether followed by isolation from ethyl acetate fraction	Leaves Stems Twigs Flowers	Quercetin was found to be the most active in the following four human cancer lines U251 (NCI strain) K562 (CCL-243, ATCC) DU145 (HTB-81, ATCC) MCF-7 (HTB-22, ATCC)	Cytotoxic	[29]
Aqueous extract	Leaves Stems Flowers	Antibacterial activity against (MIC) *S. aureus* *B. subtilis* *E. coli* *P. putida*	Antimicrobial	[32]

S. aureus=Staphylococcus aureus, *B. subtilis=Bacillus subtilis*, *E. coli=Escherichia coli*, *P. putida=Pseudomonas putida*, DPPH=2,2-diphenylpicrylhydrazyl, MIC=Minimal inhibitory concentration, LFME=*Loranthus ferrugineus methanol extract*

anticancer effects of *S. ferruginea* are documented using its ethyl acetate fraction of its petroleum ether extract. Quercetin, the active compound in this extract, exerts its anticancer properties against U251, K562, DU145, and MCF-7 cells.[29,31] The antimicrobial effects of *S. ferruginea* aqueous extract against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli,* and *Pseudomonas putida* were observed by Marvibaigi *et al*.[32] Thus, the extracts of *S. ferruginea* have shown to exert a wide range of health benefits.

COMPOUNDS FOUND IN MISTLETOES

All these three mistletoes, native Bruneian plants, belong to the family of Loranthaceae. Table 4 summarizes the currently known constituents and their pharmacological studies of Loranthaceae plants. In addition to the chemical constituents stated in Table 4, building blocks such as polypeptides, polysaccharides, glycosides, and steroids that are important for signaling pathways were found in Loranthaceae plants.[17,33,34]

Isolation of the ethyl acetate fraction of *S. ferruginea* yielded three flavonol compounds namely: quercetin, quercitrin, and 4”-O-acetylquercitrin. Quercetin was found to kill human glioblastoma cells with an IC50 of 35 μM.[31] A flavanol, quercetin glycosylated with three sugars, was identified from *Ligaria cuneifolia* Tiegh from Argentina, of the Loranthaceae family. Although the chemical structure of this flavonoid was not reported, the extract consisting of this flavonoid has been found to exert antiproliferative effect on activated cells and enhanced the production of macrophage nitric oxide, an immunomodulant.[35] Therefore, with three different flavonols found in *S. ferruginea* and a different flavonol component in mistletoe from Loranthaceae family, it is plausible that *M. cochinchinensis* and *D. curvata* would possess different types of flavonols.

Table 4: Constituents found in Loranthaceae mistletoes and their plausible actions

Constituent	Plausible actions	Reference
Flavonols (quercetin, quercitrin, 4”-O-acetylquercitrin)	Anti-inflammatory, protection against infectious agents and anti-cancer	[35]
Alkaloids	Antimalarial, antiasthma, anticancer, vasodilatory, antiarrhythmic, analgesic, antibacterial and anti-hyperglycemic	[36]
Tannins	Anticancer, antiviral and antibacterial	[33,37,38]
Terpenoids	Antibacterial	[39,40]
Gallic acid	Neuroprotective	[41,42]
Loranthin	Antioxidative and antimicrobial	[43]

Alkaloids have been isolated from different mistletoes of the Loranthaceae family, specifically African mistletoe (*Tapinanthus dodoneifolius* [DC] Danser).[36] However, of the three mistletoes mentioned, isolation of alkaloids has not yet been documented. This is most likely attributed to the lack of studies on these three mistletoes. Another chemical found in a South American Loranthaceae mistletoe, *Struthanthus vulgaris*, in Southeast Brazil is tannin, a natural polyphenol.[33] Tannins have been found to exert anticancer and antiviral effects.[37,38] Another compound

found in Loranthaceae mistletoes is terpenoid, an antimicrobial essential oil, which is also used as a food preservative.[40] An example of the mistletoe, in which terpenoids are found in is *Loranthus micranthus* (Linn) from eastern Nigeria.[39] Gallic acid, a weak carbonic anhydrase inhibitor, is another chemical identified from one of the Loranthaceae mistletoes, *Psittacanthus calyculatus,* a mistletoe from South America.[41] Gallic acid protects the neurons by its antioxidative activity and consequentially by alpha-synuclein modification leading to amyloid fibrils inhibition alleviates Alzheimer's and Parkinson's diseases.[42] A new flavanocoumarin named loranthin was identified from *Plicosepalus acacia*, also known as *Loranthus acaciea*. This compound was found to significantly scavenge free radicals and acts against microbes.[43] Therefore, Loranthaceae mistletoes consist of a wide range of constituents that provide health benefits. Therefore, *Loranthaceae* mistletoes consist of a wide range of constituents that provide health benefits similar to other medicinal plants and remain a potential niche for cancer therapies.[44].

CONCLUSION AND FUTURE PROSPECTS

The deficiency of research on both *M. cochinchinensis* and *D. curvata* has left pervasive documentation lacuna. Although there are few research articles mostly on antihypertensive effect of *S. ferruginea,* more research needs to be done to elucidate various constituents and their effects. The web of cross-relationships needs to be carefully studied both qualitatively and quantitatively. The compounds identified and isolated from these plants are keys for the exploration of biological activities of their extract, which are clues given by nature about their potential in health care. Extrapolation of results from other species of these genera may also assist in the identification and exploration of various pharmacological effects, as it is presumed that similar genera would have identical effects. Constituents-based research and documentation would pave the way for identifying and quantifying the beneficial uses of the extracts leading to clinical trials. Thus, the need of the hour for these plants is high-quality research to benefit humanity. In conclusion, the three Loranthaceae mistletoes found in Borneo region are still awaiting further studies for exploration of the health benefits they bring. There is potential in the medicinal values of these plants.

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Conflicts of interest

There are no conflicts of interest.

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