

Scurrula ferruginea (Jack) Danser: Therapeutic Applications and Future Opportunities

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ABSTRACT

Scurrula ferruginea (Jack) Danser from Loranthaceae is one such mistletoe that grow in tropical countries and has been used as therapeutic agent for curing of diseases, such as anticancer, antihypertensive, antiviral, antimicrobial, antiasthma, anti-hyperglycemic, and analgesic. Regardless of *S. ferruginea* various kinds of health benefits, their available data and literature review are still limited, especially in Indonesia. The scientific studies existence in this review can promote the potency development of *S.ferruginea*. We suggest critical future opportunities and research directions of *S.ferruginea* that could improve understanding toward evidence-based medicinal herbs.

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Introduction

Medicinal herbs have been widely used worldwide as traditional medicine. These herbs were chosen as alternative related to their relatively low-price, availability, and use depends on ancestral experience (Ameer et al., 2009). Medicinal plant constitutes a great deal of unused reservoir of drugs. It uses for medicinal and therapeutic purpose for curing of diseases and improve human health (Harvey, 1999; Shakya, 2016). However, several medicinal plants have been used in the treatment of numerous diseases and dietary supplement without proper knowledge of their function. Thus, there is a growing interest in the utilization of medicinal plant which recently researcher intensifying efforts regarding the evaluation of these valuable treasures.

The mistletoes have been recently studied due to their widespread uses as traditional medicine (Hong, Mat Isa, Fakurazi, & Safinar Ismail, 2020). As hemi-parasitic plants, mistletoes possess a distinctive way of life by growing on dicotyledonous plant and attaching to the plant stem with their modified roots called haustorium (Lim et al., 2016). They can survive through their sophisticated system to obtain water and nutrients from the host plants and the

ability to do their own photosynthesis (Moghadamtousi, Kamarudin, Chan, Goh, & Kadir, 2014). Mistletoes may confront variety of responses from their hosts for their haustorial penetration (Okubamichael, Griffiths, & Ward, 2016). Therefore, it should not be abandoned issue on the medicinal values of hemi-parasitic plant which might be positively or negatively influenced by its host nature. The type and level of chemical compounds and the biological activities of the mistletoe significantly depended on the different host species (Le, Tennakoon, Metali, Lim, & Bolin, 2016).

Scurrula ferruginea (Jack) Danser, a member of the Loranthaceae family, is one of the mistletoe species. *S.ferruginea* have been proven to possess several health benefits. Marvibaigi et al. (2014) reported the potent antioxidant activity of *S. ferruginea* which related to treat diseases associated with oxidative stress. Other reports have found that the *S. ferruginea* extract obtained from methanolic extraction shown the result on lowering blood pressure activity, (Ameer et al., 2009). Moreover, phytochemical investigation of *S. ferruginea* has indicated the presence of components from the group of flavonols including quercetin, quercitrin, dan 4-O-

acetylquercitrin. They performed that quercetin contained in *S. ferruginea* is an active antioxidant responsible to cytotoxic activity which could be further developed on its anticancer activity (F. Lohézic-Le Dévéhat, S. Tomasi, D. Fontanel, & J. J. Z. f. N. C. Boustie, 2002b).

Other studies investigated other phytochemicals from different mistletoes of Loranthaceae family including alkaloids from African Loranthaceae mistletoe (*Tapinanthus dodoneifolius*) as antimalarial, antiasthma, vasodilatory, analgesic, anti-hyperglycemic, and antibacterial (Deeni & Sadiq, 2002), tannins from South American Loranthaceae mistletoe (*Struthanthus vulgaris*) as anticancer and antiviral (Cai et al., 2017; Liu et al., 2016), terpenoid from *Loranthus micranthus* as an antimicrobial agent (Ogechukwu, Ogoamaka, Sylvester, Kawamura, & Proksch, 2011), and gallic acids from *Psittacanthus calyculatus* to treat Alzheimer's and Parkinson's diseases (Mansouri et al., 2013). The reports suggesting the future opportunities of *S. ferruginea* on its phytochemical investigation.

Despite *S. ferruginea* wide range of health benefits, there is limited data and literature review available investigated *S. ferruginea*, especially from Indonesia. Thus, there is a need to review information that can describe this plant and analyze the relevant scientific publication to add up our knowledge about *S. ferruginea*. Furthermore, from this review we suggest critical future opportunity and research direction of *S. ferruginea* that could improve understanding toward evidence based medicinal herbs.

***Scurrula ferruginea* (Jack) Danser**

Scurrula ferruginea (Jack) Danser, one of the mistletoes species in the Loranthaceae family. *S. ferruginea* is synonym with *Loranthus ferrugineus* Roxb. is a plant of a hemi-parasitic mistletoe which adheres to branches or twigs on the various plant, such as coffee, manalagi apple, and jengkol. In Indonesia, *S. ferruginea* is known as kemladen, benalu, pasilan, ambai-ambai, and tahi burung (De Padua, Bunyapraphatsara, & Lemmens, 1999)

S. ferruginea is a cylindrical woody plant, slender branches that can grow up to 70 cm in length around the branches have brown hairs. The shape of the leaves is elliptical, which are arranged opposite, the upper of the leaves are glossy, and the lower is brownish fuzzy. The flowers are consist of 4-7 located from the axils. The ovary of brown hairy is found in the flower (Lim et al., 2017). The structural appearance and physical may be slightly different

depending on the plant's natural habitat and age. The physical of *S. ferruginea* described in figure 1 (Lim et al., 2016).



Figure 1. (a) The mistletoe of *Scurrula ferruginea* attached on a tree (b) A stalk of *Scurrula ferruginea* mistletoe

S. ferruginea is epiphyte plants that absorb minerals and water from their host causing damage through their complex endophyte system. The type of mineral taken reported including Mg, K, Ca, and Na. However, the level proportion of minerals was permeated depends on the Loranthaceae species and its host (Didier et al., 2009). The taxonomical classification of *S. ferruginea* presented in Table 1 (Lim et al., 2016).

Table 1. Taxonomical classification of *Scurrula ferruginea* (Jack) Danser

Kingdom	Plantae
Phylum	Spermatophyta
Class	Magnoliopsida
Order	Santalales
Family	Loranthaceae
Genus	<i>Scurrula</i>
Species	<i>Scurrula ferruginea</i>
Scientific Name	<i>Scurrula ferruginea</i> Danser

Therapeutic Applications of *Scurrula ferruginea* (Jack) Danser

A. Antioxidant Activity

In recent years, there are many diseases associated with oxidative stress, including certain type of cancer, diabetes, coronary heart disease, and the other cardiovascular disease such as high blood pressure, atherosclerosis, and stroke. Those conditions occur from the imbalance between free radical production and neutralization of free radical by antioxidant defense (Liguori et al., 2018). Plant-based

antioxidants which are derived from natural resources, have been widely used to overcome the problems of oxidative damage. These group of antioxidants have also some advantages including have slight side effects, being reached easily and moderately-priced (Vicas, Socaciu, & Rugina, 2012). *S. ferruginea*, one such mistletoe which mainly distributed in tropical country, have been investigated on its antioxidant activity which potential to counterbalance the effect of free radical production.

A study reported by Ameer et al. (2009), investigated the potential antioxidant activity of *S. ferruginea* extract on blood pressure reduction. The study found that the extract obtained from methanolic extraction shown the best result on lowering blood pressure activity. They also mentioned for possibility of further study to analyze bioactives compounds from *S. ferruginea* that can directly used to treat high blood pressure in human. Another study by Lohézic-Le Dévéhat et al. (2002b) investigated the phytochemical compounds of *S. ferruginea*. The main antioxidant contain in *S. ferruginea* is the group of flavonoids including quercetin, quercitrin, dan 4-O-acetylquercitrin, which were isolated from the ethyl acetate extract. The study also carried out the cytotoxic glycoside evaluation on different cancer cell and found that quercetin shows the most potential cytotoxic activity on U251 (human glioblastoma cells cancer cell line) with IC₅₀ of 35µm. Findings from this study performed that quercetin contained in *S. ferruginea* is an active antioxidant which could be further developed on its anticancer activity.

Based on DPPH (2,2-diphenyl-1-picrylhydrazyl) method reported by Marvibaigi et al. (2014), the antioxidant activity of *S. ferruginea* extract varied depending on parts of plant, solvent polarity, and concentration of extracts. Results from this study show that the stem methanol extract exhibited the strongest DPPH radical scavenging (IC₅₀=27.8 µg/mL), highest phenolic (273.51 ± 4.84 mg gallic acid/g extract) and flavonoid contents (163.41 ± 4.62 mg catechin/g extract). They also reported that methanol extract influenced an increase in ROS generation and the depolarization of mitochondrial, suggesting its potential apoptotic activity. Another study from Marvibaigi reported that the extracts of different parts of *S. ferruginea* especially the stem extract, have a potent antioxidant activity. The stem extract showed a significant antioxidant activity to scavenge free radicals with IC₅₀ value of 19.5 µg/mL. Results from those studies give straight evidence that *S. ferruginea* has a potential antioxidant

activity that can be further developed to treat several types of disease associated with oxidative stress.

B. Cytotoxic Activity on Cancer Cell

The study on the potential of *S. ferruginea* mistletoe to inhibit cancer cell has been done by F. Lohézic-Le Dévéhat, S. Tomasi, D. Fontanel, and J. Boustie (2002a) shown the *S. ferruginea* extract containing flavonols natural compounds such as glycoside 4-O acetylquercitrin, quercitrin, and quercetin which had the cytotoxic activity on different human cancer cell lines. Quercetin has been found to have the highest cytotoxic activity with IC₅₀ of 35µM on U251 cells (human glioblastoma cell line).

Some studies have been reported that quercetin are anticancer agent. Xavier, Lima, Rohde, and Pereira-Wilson (2011) found the quercetin could induce the activity of p53 and Bax on HCT15 cells (colorectal cells). The increase of Bax expression suggesting the apoptosis activation via the intrinsic pathway. Tanigawa, Fujii, and Hou (2008) also found the quercetin could delay the cycle of HepG2 cells (liver cancer cells) in the G₂/M phase and induce the apoptotic markers of caspase-3. Apoptosis is a subfamily of cysteine proteases that programmed cell death. Increased apoptotic activity on patients is expected because capable to eliminate cancerous cells or harmful cells thus so as to maintain body tissue homeostasis and control cell proliferation (Safrida, Budijanto, Nuraida, & Priosoeryanto, 2020). In another study had been reported by Marvibaigi et al., (2016), *S. ferruginea* v mistletoe extracted by methanol and aqueous had cytotoxic activity on human breast cancer (MDA-MB-231), with IC₅₀ of 19.27 and 50.35 µg/mL respectively. It was capable to inhibit the migration and colony formation of cells. *S. ferruginea* extract by methanol could induce mitochondria of depolarization and an increase in ROS generation thus result in apoptosis.

Similar to *S. ferruginea* extract, *S. atropurpurea* also possess anticancer activity. Ohashi et al. (2003) evaluated the cytotoxic of *S. atropurpurea* extract. The bioactive compound of octadeca-8,10,12-triynoic acid was found the most potential to inhibit the invasion of the tumour cells in rats.

C. Antihypertensive

Hypertension referred to as high arterial blood pressure abnormally which associated with cardiovascular and kidney disease. It has been identified as the risk factor leading for global mortality. Around 10.4 million deaths per years occur due to hypertension (Unger et al., 2020).

One of the assorted mistletoes that have been common used in herbal medicine is the family of Loranthaceae. Even though there is a slightly published paper of *S. ferruginea* supporting a lowering activity of blood pressure (Ameer et al 2009; Marvibaigi et al. 2016), within other Loranthaceae family which related species have been many reported for their activity of antihypertensive. Earlier preliminary identification undertaken by Iwalokun, Hodonu, Nwoke, Ojo, and Agomo (2011) that *L. micranthus* have antihypertensive effects. Here, it was found that extract methanol of *L. micranthus* was partitioned with n-butanol shown the highest antihypertensive activity ($EC_{50} = 0.65$ mg/mL and smooth muscle relaxation (R_{max}) of 75.2%) on rat aorta contracting with norepinephrine, then followed by water, chloroform, and ethyl acetate fractions. Additionally, on n-butanol fraction, the cardiac arginase shown reduced by 11.7%, and serum nitric oxide elevated by 55% in mice with steroids, terpenoids, and tannins assumed to promote these mechanisms. The studied of nitric oxide and cardiac arginase was found that has responsibility for the hypertensive activity.

In Africa, the potency mistletoe herbs of the Loranthaceae family claimed to have antihypertensive activity. It was reported by Obatomi, Aina, and Temple (1996) that given an aqueous *L. Bengwensis* extract (1.32 g/kg daily) orally to male spontaneously hypertensive rats effectively lowering blood pressure. It was confirmed that *L. Bengwensis* was an antihypertensive agent.

Conclusion and Future opportunities

S. ferruginea have been used traditionally as medicinal herb to treat variety of human diseases in tropical countries. Despite its application as traditional medicine, there was a limited study investigated its application directly to a specific disease.

Previous studies reported the potent therapeutic applications of *S. ferruginea* on its antioxidant activity (Marvibaigi et al., 2014), blood pressure reduction activity (Ameer et al., 2009), and cytotoxic activity (Lohézic-Le Dévéhat et al., 2002b). However, the details about bioactive compounds related to those therapeutic effects were not mentioned in detailed from the studies. Thus, further analysis on specific bioactive compounds from *S. ferruginea* that can directly use to treat a disease need to be studied. There was a study by Lohézic-Le Dévéhat et al. (2002a) reported bioactive compounds of *S. ferruginea* which responsible to cytotoxic

activity from the group of flavonoids including quercetin, quercitrin, dan 4-O-acetylquercitrin. They performed that quercetin contained in *S. ferruginea* is an active antioxidant which could be further developed on its anticancer activity.

Other studies investigated other bioactive compounds from different mistletoes of Loranthaceae family including alkaloids, tannins, terpenoid, and gallic acids. However, isolation of those bioactive compounds from *S. ferruginea* have not yet been reported. Alkaloids have been isolated from African Loranthaceae mistletoe (*Tapinanthus dodoneifolius*) (Deeni & Sadiq, 2002). Tannins have been isolated from South American Loranthaceae mistletoe (*Struthanthus vulgaris*) and have been found to exert anticancer and antiviral activity (Cai et al., 2017; Liu et al., 2016).

Terpenoids are found in *Loranthus micranthus* from eastern Nigeria and reported as an antimicrobial agent (Ogechukwu et al., 2011). Gallic acids are found in *Psittacanthus calyculatus*, a mistletoe from South America and reported to exert Alzheimer's and Parkinson's diseases (Mansouri et al., 2013). Therefore, there are positive opportunities of *S. ferruginea* as one type of mistletoes from Loranthaceae family to be further studied on its wide range of constituents that provide health benefits.

In the future, when the study on the bioactive compounds contained in *S. ferruginea* have been clinically proven, it could be further emphasize to its application for supplements or functional food that promote several health benefits.

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