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A perspective review of phytochemistry and pharmacology of the *Syzygium* genus

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Abstract

Syzygium is a genus of the Myrtaceae family consisting of large and widespread species from Africa, Asia, Australia, and throughout Oceania and the Pacific region. Some have been cultivated for bearing fruit, ornamental plants and used as traditional medicine. This article excavated Syzygium genus which was focused on traditional uses, chemical compounds and biological activities related to treatment of syndrome metabolic. All information was obtained from the scientific literature such as Science Direct, Google Scholar, Scopus and PubMed. Several species were known to have therapeutic potential and used in traditional Chinese medicine, Ayurveda, and herbal medicine in Indonesia. Traditionally, Syzygium is known for its therapeutic purposes such as coughing, diarrhea, colds, dysentery, inflammation, pain, skin, and mouth infections. Only a few species have been scientifically studied to verify their usage as traditional medicine. There were many reports on the traditional uses and medicinal effects of Syzygium plants, but only a few review articles mainly about phytochemical constituents and their role in pharmacological activities. The present reviews highlight the phytochemical and pharmacological activity of various species of the Syzygium genus. The pharmacological activities were discussed in this article focused to metabolic syndrome treatment, such as antidiabetic, antihyperlipidemic, antioxidant and antihypertensive activities. Chemical components isolated mainly flavonoid, terpenoids/sesquiterpenoid, sterols, and lignan. Several bioactive compounds have been identified correlated with pharmacological activity, but the chemical compounds were different for each species.

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INTRODUCTION

Syzygium is a genus that belongs to Myrtaceae family containing more than 1200 species spread worldwide. Syzygium species were found from Asia, Africa, Australia, and New Caledonia, commonly found in Southeast Asia. The Syzygium genus is an evergreen tree and generally has essentials oil. They have aromatic leaves that are rough, shiny and produce flowers, usually pink, yellow, red, or white. *Syzygium cumini*, *Syzygium samarangense*, *Syzygium aromaticum*, and *Syzygium polyanthum* are examples of prevalent species in the community. Syzy-

gium genus has been cultivated for medicine, fruit-bearing, and ornamental plants (Mudiana, 2016).

Syzygium genus has been known in many traditional treatments as in Ayurveda, Chinese traditional medicine, and herbal remedy in Indonesia. For example, *S. cumini* is used to treat diabetes, diarrhea, dysentery, and digestion disorders in India (Nahid *et al.*, 2017). In Indonesia, *S. polyanthum* is known to have properties for treating diabetes mellitus, diarrhea, hypertensive, wounds and bacterial infection (Ramadhania *et al.*, 2018). Commonly, several species of Syzygium have been used traditionally to treat non-infectious diseases such as diabetes, hypertension, pain, and inflammation. Several species of Syzygium have been reported in recent studies to treat conditions which associated with metabolic syndrome such as diabetes, hypertension, dyslipidemia, heart disease and as an antioxidant to reduce the progression of this syndrome. Phenolic compounds are common as phytochemical constituents in Syzygium species. This paper reviews a recent study of the phytochemical compounds of the genus Syzygium and pharmacological activity which focused to the metabolic syndrome treatment.

MATERIALS AND METHODS

Data and information in this article were collected from scientific literature database such as Science Direct, Google Scholar, Scopus and PubMed.

RESULTS AND DISCUSSION

Phytochemical Content

There are few species of Syzygium that have been explored phytochemically. Some of these chemical compounds have been known to be responsible for the pharmacological activities of Syzygium. Table 1 reviewed the chemical compounds of different species of Syzygium.

Isolated compounds comprise mainly flavonoid, phenolic compound, terpene/sesquiterpenoid, sterols, and lignan. Some of the same compounds are found in several plants in this genus such as myricetin and myricitrin derivatives were found in *S. aqueum*, *S. forrestii*, *S. grande*, and *S. samarangense*. They were known to have antihyperglycemic and antioxidant activities. β-sitosterol was found in six Syzygium species, namely *S aromaticum*, *S cumini*, *S. grande*, *S.kusukusense*, *S. polycephalum*, and *S siamense*. β-sitosterol was identified to have cytotoxicity activity. Ursolic acid was detected in 4 types of Syzygium, *S. corticosum*, *S. polycephalum*, *S. grande*, and *S. kusukusense*. Like β-sitosterol, ursolic acid also displayed cytotoxic activity. No literature mentions specific or marker compounds from Syzygium species.

Pharmacological Activities

Metabolic syndrome is a condition which characterized by increasing in risk of heart disease, diabetes, and other health problems that can be co-occurred. Other conditions that give rise to metabolic syndrome are elevated blood pressure and cholesterol and triglyceride abnormalities. The Syzygium genus has been extensively studied for the treatment of metabolic syndrome. Many species in this genus are effective against more than one disease accompanying metabolic syndrome.

Antidiabetic Activity

Different antidiabetic mechanisms have been reported in this plant, including a-amylase and a-glucosidase inhibitors, increasing insulin secretion, acting as an insulin-like effect, or controlling adipocyte metabolism hormones. Flavonoid and phenolic compounds were recognized from the several plant species which contributed to the antidiabetic activity. Furthermore, myricetin derivative from *S. malaccense* and *S. aqueum* was found to be bioactive against diabetes mellitus. Vescalagin from *S. samarangense* and europetin-3-O-rhamnoside from *S. aqueum* were reported as compounds that actively contribute as antidiabetic. This information confirmed the antidiabetic potential of the Syzygium genus. Numerous species of the Syzygium genus have not been explored yet for their antidiabetic potential. Therefore, an examination of other species of Syzygium genus as hypoglycemic is still needed.

Mechanistic action indicated that fruit of *S.cumini* could inhibit a-amylase that is responsible for restraining starch breakdown and lower the levels of postprandial hyperglycemia (Gajera *et al.*, 2017). Myricetin derivatives from *S. malaccense* play a role in antihyperglycemic activity by inhibiting a-glucosidase and a-amylase that are responsible for carbohydrate hydrolysis. Another mechanism of myricetin derivatives to control blood glucose is by exhibiting insulin-like effects (Arumugam *et al.*, 2020). Vescalagin is an active component that is isolated from *S. samarangense* fruit. It had mechanism action as antihyperglycemic effects by enhancing glucose uptake in type 2 diabetic mice. Fasting blood glucose decreased by 44.7% after vescalagin administration for four weeks in diabetic rats (Shen and Chang, 2013).

S. densiflorum extract was given for 28 days can lower blood glucose level and HbAi1c in non-fasting

Table 1: Phytochemical content of different species of Syzygium

Species	Compounds	Properties	Ref
S. aqueum	Europetin-3-O-rhamnoside Myricetin-3-O-rhamnoside 4-hydroxybenzaldehyde Myrigalone-B and G, Phloretin	Antihyperglycemic Unknown	(Manaharan *et al.*, 2012)
S. aromaticum	β-sitosterol, Oleanolic acid lacton β-sitosterol, Oleanolic acid lactone 3β-hydroxy-11-oxo-olean-12-en-28-oic acid, Flavaellagic acid, Nigricin 3-O-β-D-glucopyranoside 2α-hydroxyoleanolic acid	Unknown	(Begum *et al.*, 2014)
S. corticosum	Fouquierol Ursolic acid	Unknown Cytotoxicity	(Ren *et al.*, 2018)
S. cumini	Lupeol, β sitosterol, Stigmasterol 12-oleanen-3-ol-3 β-acetate	Antidiabetic	(Alam *et al.*, 2013)
S. forrestii	Myricitrin Myricetin 3-O-(300-Oacetyl)-α-L-rhamnopyranoside Myricetin 3-O-(3”-O-acetyl)-α-L-rhamnopyranoside Myricetin 3-O-β-D-galactopyranoside	Unknown	(Tian *et al.*, 2011)
S. grande	Myricetin 4’-methyl ether 3-O-β-D-xylopyranoside, Grandoside 4’-methyl ether 3-O-α-L-rhamnopyranoside, Myricetrin Myricetin 3-O-β-D-glucopyranoside β-sitosterol, β-sitosterol glucoside, Botulin Friedelin, Quadranoside IV, Crotalionoside C, Ursolic acid	Antioxidant: Myricetrin ; Myricetin 3-O-β-D-glucopyranoside	(Samy *et al.*, 2014)
S. kusukusense	Ursolic acid, 2α-hydroxybetulinic acid Platanic acid, Betulinic acid, Hyptatic acid A	Cytotoxic Unknown	(Bai *et al.*, 2014)
S. polyanthum	Hentriacontane, Palmitic acid, Squalene, Phytol, Linalool, α-tocopherol, β-tocopherol, α-pinene, Nerolidol	Unknown	(Rahim *et al.*, 2017)
S. polycephalum	Ursolic acid, Squalene, Oleanolic acid β-sitosterol	Unknown	(Ragasa *et al.*, 2014)
S. samarangense	Sysamarins A-E; Myricitrin	Unknown Antioxidant	(Hu *et al.*, 2018; Sobeh *et al.*, 2019)
Syzygium siamense	Stigmast-5-ene-3β,17α-diol Stigmast-5-ene-3β,7α-diol Stigmast-5-ene-3β-ylformate Stigmast-5-ene-3-one, Stigmast-5-ene-7amethoxy-3β-ol, 3β-sitostanol, 3β-sitosterol	cytotoxicity	(Chumkaew *et al.*, 2010)
S. szemaoense	Syzygiumursanolides	Antimicrobial	(Xu *et al.*, 2020)

diabetic rats model. This study also revealed the regeneration of β-cells islets of Langerhans in diabetic group was treated by the extract (Krishnasamy *et al.*, 2016). The antidiabetic effect of *S. aqueum*, as a result, enhances adipogenesis, improves glucose uptake, and increases adiponectin secretion in 3T3-L1 adipocytes. Europetin-3-O-rhamnoside and myricetin-3-O-rhamnoside were bioactive compounds from *S. aqueum* that exhibited insulin-like and insulin-sensitizing effects on adipocytes (Manaharan *et al.*, 2012).

Hypolipidemic Activity

The hypolipidemic effect of Syzygium showed a close relationship with antidiabetic effects. Some plants that have antihyperglycemic effect can also lower cholesterol levels such as *S. cumini*, *S. densiflorum*, *S. aromaticum*, *S. malaccense* and *S samarangense*. The mechanism of reducing lipid profile is unknown. This information indicated that Syzygium not only could treat diabetes but also prevent diabetes complications that were related to metabolic syndrome.

Two studies indicated that *S. cumini* declined triglyceride and cholesterol levels, also increased serum HDL (High-Density Lipoprotein) concentration in diabetic rats (Nahid *et al.*, 2017). *S. densiflorum* extract also has an antihyperlipidemic effect at level 800 mg/kg bw (Krishnasamy *et al.*, 2016). Vescalagin which was isolated from *S. samarangense* had a therapeutic value anti-hypertriglyceridemia effect. The earlier report showed that vescalagin also has a beneficial effect on the diabetic disease (Shen and Chang, 2013).

Administration of clove bud powder (*S. aromaticum*) at dose 20-40 g/kg bw decreased lipid concentration serum in diabetic rat. Calculation of the atherogenic index exhibited an increase in value in the diabetic rat group related to the group given by clove bud powder (Adefegha *et al.*, 2014). *S. malaccense* ethanol extract significantly affected the lipid profile by decreasing total cholesterol level and raising HDL cholesterol. The total serum cholesterol was 57.23 mg/dl in *S. malaccense* group and 95.08 mg/dl in the diabetic control. The HDL value was 66.90 mg/dl in *S. malaccense* group and 42.45 mg/dl in the diabetic group (Bairy *et al.*, 2005).

Cardioprotective and Thrombolytic Activity

Cardiomyopathy is one of the risks for diabetic patients caused by up-regulation of reactive oxygen species (ROS). *S. cumini* ethanolic extract exhibit 34% clot lysis from clotted blood in the thrombolytic activity test. This result showed that *S. cumini* possessed moderate thrombolytic activity (Barbhuiya and Godiya, 2019). The effect of the thrombolytic and cardioprotective activity of *S. cumini* was beneficial for diabetic patients to prevent complications of heart disease.

Antioxidant and Hepatoprotective Activity

Syzygium genus had antioxidant activity through scavenging free radicals and improving metabolism and activity enzyme. Several bioactive compounds have been isolated from Syzygium species was indicated to have antioxidant activity. The flavonoid, phenolic compounds, anthocyanin, and essential oils from Syzygium species inhibited free radicals. Some of Syzygium species have been investigated, potential preventing diabetic retinopathy due to the antioxidant activity.

S.calophyllifolium extract could maintain antioxidant levels in vivo (superoxide dismutase; glutathione reductase and glutathione levels) compared to normal control. Antioxidant levels in vivo in type-2 diabetic rats showed declining in values after 28^{th} days of the examination (Chandran *et al.*, 2016). Administration of *S. densiflorum* extract in diabetic rats revealed rising in SOD (superoxide dismutase), CAT (catalase), and GSH (glutathione) activity (Krishnasamy *et al.*, 2016).

As an active component of *S. malaccense*, myricitrin indicated the potent antioxidant and was useful for controlling diabetes mellitus and its related problems. Myricetin derivatives could prevent diabetic retinopathy in ARPE-19 (retinal pigment epithelium) cellsby reducing intracellular reactive oxygen species (ROS) (Arumugam *et al.*, 2020).

Research by Sobeh *et al.* (2019) displayed that 3,5-di-O-methyl gossypetin from *S. samarangense* had antioxidant activity. This compound worked as an antioxidant by activating the nuclear transcription factor-2 (Nrf-2) pathway, increasing antioxidant proteins expression, for example, HO-1 and Mn-SOD-3.

Antihypertensive Activity

One of the uses of traditional medicine Syzygium was for treating hypertension. *S. polyanthum* and *S. guineense* have been evaluated for antihypertensive activity. *S. polyanthum* leaves extract induced hypotension by involving α, β- adrenergic. Cholinergic receptors (Ismail *et al.*, 2013) and *S. guineense* played a major role in antihypertension by dilating blood vessels (Ayele *et al.*, 2010). *S. gratum* could decrease blood pressure in rat model after two weeks of treatment with the extract. It due to the extract had ability to improve endothelial vascular function (Bunbupha *et al.*, 2020), and didn't state

which compound play a role in causing the antihypertensive effect of the Syzygium species.

CONCLUSION

In conclusion, only a few species have been examined for the phytochemical compounds from the Syzygium genus. The therapeutic effect that was often reported from the Syzygium genus as antidiabetic. This effect was also supported by research on antioxidants, hypolipidemia, cardioprotective and antihypertensive. Among the Syzygium genus, *S. cumini*, *S. aromaticum*, *S. malaccense*, *S. aquaeum*, and *S. samarangense* are the most studied species for the treatment of metabolic syndrome. The research showed that the Syzygium species played a role in the antidiabetic treatment and prevented the development and complications of diabetes. Myricetin derivates were known to be responsible for antihyperglycemic and found in several species of Syzygium. Only a few pharmacological analysis categories have been carried out to support the potential traditional uses of the Syzygium genus. The Syzygium genus needs further investigation regarding other pharmacological activities, bioactive compounds, and its mechanism of action.

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Conflict of Interest

The authors declare no conflict of interest for this study.

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