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Review article

Potential of *Syzygium polyanthum* (Daun Salam) in Lowering Blood Glucose Level: A Review

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ABSTRACT

Syzygium polyanthum is a herb widely used in Malaysia and Indonesia in cuisines. Traditionally, the herbal decoction of *S. polyanthum* (daun salam) leaves is often used by diabetic patients in Indonesia. Therefore, our objective is to evaluate the scientific evidence available for *S. polyanthum* in lowering blood glucose levels (BGL). We systematically searched Pubmed, Google Scholar, Scopus, CENTRAL. LILAC and clinicaltrials.gov databases up to 23rd October 2020 using the keywords "*Syzygium polyanthum*" and "antidiabetic". From the selected 413 articles, eight studies involving rodents were included. All results showed a significant effect in lowering BGL without any adverse effects. The possible underlying mechanism of action is attributed to inhibiting intestinal glucose absorption and enhancing glucose uptake by the muscles. Chemical families responsible for the effect were determined as flavonoids, alkaloids and terpenoids. Thus, *S. polyanthum* leaves showed potential antidiabetic properties, but further research is required to identify the active compounds followed by the safety evaluation of this compound.

Keywords: Blood glucose level, daun salam, diabetic, *Syzygium polyanthum*

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INTRODUCTION

Diabetes mellitus (DM) is described as a deficiency of insulin production secreted by the pancreas or the inability of the body to use the insulin it produces (WHO, 2019). There are currently 420 million people globally with diabetes, with a mortality rate of 1.6 million in 2016 (Loke, 2020). This increase will occur due to population

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growth, ageing, unhealthy diets, obesity and sedentary lifestyles (WHO, 2019). Asian countries make up more than 60% of the world's diabetic population (Ramachandran et al., 2012). This situation is due to a few factors, such as urbanisation and socioeconomic transition. Hence, they are prone to have more intra-abdominal fat accumulation and low muscle mass (Ramachandran et al., 2012).

According to the National Health and Morbidity Survey 2019 (NHMS, 2019), almost one in five Malaysian adults has diabetes. In addition, the survey found that 3.9 million Malaysian adults were diagnosed with diabetes, surpassing the 2014 prediction by Health Ministry that figure would not be reached until 2020 (Rashid, 2017).

There are two types of diabetes: Type 1 and Type 2. Type 1 diabetes (or juvenile/ childhood-onset diabetes) is defined as the failure of the pancreas to produce insulin caused by hereditary factors or damage to the immune system (Berawi et al., 2017; WHO, 2019; & Widyawati et al., 2015a). Type 2 diabetes (non-insulin-dependent or adult-onset diabetes) is defined as the body's inability to respond appropriately to the action of insulin. Type 2 diabetes is much more common worldwide, accounting for around 90% of all diabetic patients, due to food intake habits, obesity, smoking and lack of physical activity (Berawi et al., 2017; WHO, 2019; & Widyawati et al., 2015a).

Despite using insulin and oral medications to control blood glucose, diabetes remains among the world's top 10 causes of death (Waly et al., 2010; WHO, 2019; & Widharna et al., 2015). In addition, DM is a risk factor for kidney, liver, and also contributes to the two-fold increase of coronary heart disease and vascular damage, which lead to 50% to 80% of the diabetes patient mortality (Emerging Risk Factors Collaboration, 2011; Duncan et al., 2003; Nwaneri et al., 2013; Rashid, 2017; & Whiteley et al., 2005).

Syzygium polyanthum belongs to the Myrtaceae family (The Plant List, 2012; Quattrocchi, 2012). Among others, species included in the genus *Syzygium* are *Eugenia atropunctata*, *Eugenia holmanii*, *Eugenia balsamea*, *Syzygium cymosum*, *Syzygium micranthum*, and *Syzygium pamatense* (The Plant List, 2012; Quattrocchi, 2012). *S. polyanthum* is widely distributed throughout Myanmar, Indo-China, Thailand, Malaysia, and Indonesia (Azwar, 2010), with a few familiar names, such as Indian laurel, Indonesian bay leaf, *daun salam*, *kelat samak*, *samak*, *serah*, *serai kayu*, *kelat putih*, *kelat merah*, *palong* (Malaysia), *manting*, *salam*, and *ubar serai* (Indonesia) (Malaysian Herbal Monograph Committee, 2017; The Plant List, 2012; & Quattrocchi, 2012).

Traditionally, *S. polyanthum* is widely used as a food ingredient in Indonesian and Malaysian cuisine and used to treat diabetes in Indonesia (Azwar, 2010). It is usually dried, crushed and extracted through soaking in boiled water (Dewijanti et al., 2018).

Other traditional uses include using the leaf and bark extracts of *S. polyanthum* for treating diarrhoea (Burkill, 1935). In addition, the poultices of the bark, root and leaves relieve itching (Burkill, 1935). The leaves contain polyphenols (flavonoids, terpenoids,

tannins) and saponin (Hikmah et al., 2016; Liem et al., 2015; Wahjuni et al., 2018; Widharna et al., 2015; Widyawati et al., 2015a & Yuliana, 2014). In medicinal plants. These polyphenols, saponins and coumarins have been reported to exhibit antidiabetic properties (Hikmah et al., 2016; Wahjuni et al., 2018; Yuliana, 2014).

Since *S. polyathum* leaves are ethnobotanically used in treating diabetes in Indonesia and Malaysia (Dewijanti, 2018 & Burkill, 1935), the National Agency for Drug and Food Control in Indonesia highly regards this medicinal plant. Therefore, we conducted this study to evaluate the scientific evidence available for *S. polyanthum* in lowering blood glucose levels (BGL).

MATERIALS AND METHODS

This review was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Liberati et al., 2009).

Search Strategy

A literature search was conducted to identify relevant studies on *S. polyanthum* in lowering blood glucose. The following six electronic databases were searched for this purpose: Pubmed, Google Scholar, Scopus, CENTRAL, LILAC, and clinicaltrials.gov with two keywords (*Syzygium polyanthum* and antidiabetic) and their combinations (Table 1). The bird's eye view strategy was applied to identify all the antidiabetic properties of *S. polyanthum*. Relevant studies were further identified by going through the citations and lists of references in the related articles. All related articles found in English and Indonesian were included. Two authors independently conducted the literature search by dividing the databases list and followed by cross-checking to avoid redundancy. The search was done up to 23rd October 2020. The tentatively selected articles were reviewed for the inclusion criteria, peer-reviewed, and the articles that best met the criteria were carefully selected. The extensive literature search brought about 413 published articles (Table 1).

Study Selection

The PICOS (participants/patients, interventions, comparators, outcomes, study design) formula for the literature search was pre-determined through discussion by the authors. The selection of search terms was centred on participants and interventions for maximum sensitivity, as shown in Table 1. The search and inclusion/exclusion criteria are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and presented in a PRISMA flow chart in Figure 1. The abstract of the searched articles was screened, followed by full-text reading for articles fulfilling the inclusion criteria. The inclusion criteria were based on samples, intervention, outcomes and study design. Articles published in English and Indonesian were reviewed and extracted.

Two authors conducted the screening process. Any disagreement was discussed with the third author, and a decision is agreed on. Both authors worked independently in analysing the eight studies and tabulated the extracted data (Table 2), and subsequently critically appraised the chosen papers together to reduce bias.

Selection of Samples and Intervention

1. Types of study sample: This review included using *S. polyanthum* as an intervention in animals induced with diabetes.
2. Types of intervention selected for this review include studies using any form/dosage of *S. polyanthum* intervention comparing it with diabetic medications.
3. Types of comparison: The comparison groups included (a) group with *S. polyanthum* compared with glibenclamide, (b) group with *S. polyanthum* compared with metformin, and (c) group with a combination of *S. polyanthum* with glibenclamide.

Selection of Outcomes

The outcome selected was the intervention ability and the comparators of *S. polyanthum* for lowering BGL in Type 2 diabetes in experimental studies.

Selection of Study Model

In vivo and human trials (if any) that evaluated the effectiveness of *S. polyanthum* in lowering BGL were included in this review.

Quality Assessment of Included Studies

The risk of bias (RoB) tool for animal intervention studies, i.e. SYRCLE's RoB tool, was used to assess the risk of bias of all included studies (Hooijmans et al., 2014b). Two independent authors performed a quality assessment of all included studies. Disagreements were resolved by discussion.

RESULTS

The search initially produced 413 potentially relevant studies (Table 1). However, 22 review articles were excluded immediately from these articles, as these contributed no additional data besides the original studies, which were already included. Another 111 studies were excluded based on duplication, vague references and unpublished work. Of the remaining 280 studies, 75 did not include antidiabetic studies, 120 did not use *S. polyanthum* species, and 77 involved other than in vivo studies. Conclusively, eight articles that fulfilled the inclusion criteria were included in this review (Hikmah et al., 2016; Liem

et al., 2015; Sutrisna et al., 2016; Wahjuni et al., 2018; Widharna et al., 2015; Widyawati et al., 2015a; Widyawati et al., 2015a; & Yuliana, 2014), as shown in the process of study selection (Figure 1).

The selected studied all used leaves extract of *S. polyanthum* in the form of extracts or decoction (Hikmah et al., 2016; Liem et al., 2015; Sutrisna et al., 2016; Wahjuni et al., 2018; Widharna et al., 2015; Widyawati et al., 2015a; Widyawati et al., 2015b; & Yuliana, 2014) and had comparable designs: in lowering BGL (Hikmah et al., 2016; Liem et al., 2015; Sutrisna et al., 2016; Wahjuni et al., 2018; Widharna et al., 2015; Widyawati et

Table 1
Search strategies used

Databases	Year of search	Keyword used	No. of studies in search
Pubmed	2015 – 2020	*Syzygium polyanthum* AND antidiabetic	3
Google scholar	2005 – 2020	*Syzygium polyanthum* AND antidiabetic	295
Scopus	2005 – 2020	*Syzygium polyanthum* AND antidiabetic	71
CENTRAL	2019	*Syzygium polyanthum* AND antidiabetic	1
LILAC	(No hit)	*Syzygium polyanthum* AND antidiabetic	0
Clinicaltrials.gov	2009 – 2020	*Syzygium polyanthum* AND antidiabetic	43
TOTAL SEARCH =			413

Note. As of 8th September 2020

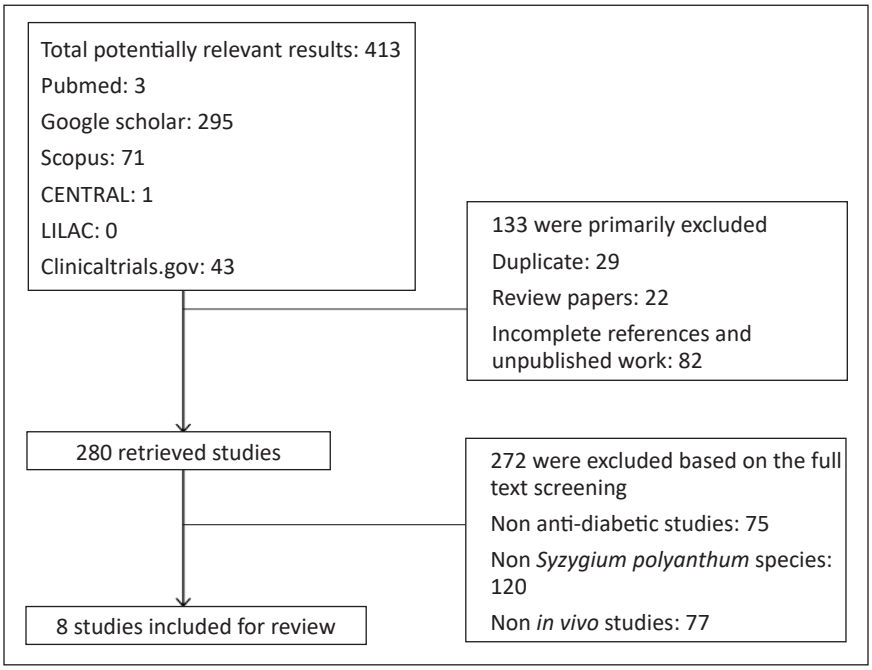

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of study selection

al., 2015a; Widyawati et al., 2015b; & Yuliana, 2014), fasted animals were first induced with diabetes using alloxan (Hikmah et al., 2016; Liem et al., 2015; Sutrisna et al., 2016; Wahjuni et al., 2018; Widharna et al., 2015; Widyawati et al., 2015a; & Yuliana, 2014) or streptozotocin (Widyawati et al., 2015a & 2015b) followed by *S. polyanthum* mixture with glibenclamide (Hikmah et al., 2016 & Liem et al., 2015), different dosages of *S. polyanthum* extract alone (Sutrisna et al., 2016; Wahjuni et al., 2018; Widharna et al., 2015; Widyawati et al., 2015b; & Yuliana, 2014) or different extracts of *S. polyanthum* (Widyawati et al., 2015a) supplementation for a duration of 6 to 56 days. Only one study had a test period of seven hours (Widyawati et al., 2015a).

The results showed that oral administration of methanol extract of *S. polyanthum* leaves (1000 mg/kg body weight) did not significantly alter BGL in normal or intraperitoneally glucose-loaded male Sprague Dawley rats. However, in streptozotocin-induced (55 mg/kg b.w.) diabetic male Sprague Dawley rats (180 g to 250 g), administration of the extract in three doses (250, 500, 1000 mg/kg b.w.) twice daily for six days significantly ($p < 0.05$, $p < 0.01$, $p < 0.001$) and dose-dependently reduced fasting BGL compared to the control (normal saline, 10 mL/kg b.w.) (Widyawati et al., 2015b).

The aqueous extract of *S. polyanthum* leaves (200 mg/kg b.w.) administered orally to intravenous glucose-loaded average male Wistar rats (100 g to 150 g) showed a significantly ($p < 0.01$) reduction in BGL after 30 minutes. Glibenclamide administered at 0.45 mg/kg b.w. on the other hand, significantly ($p < 0.01$) reduced the BGL after 90 minutes compared to the regular control group (received drinking water) (Widharna et al., 2015).

Aqueous extract of *S. polyanthum* leaves (200 mg/kg b.w.) administrated orally to alloxan-induced (150 mg/kg b.w.) diabetic male Wistar rats (100 g to 150 g) for 14 days significantly ($p < 0.01$) reduced their fasting BGL to 45% compared to untreated diabetic rats that received drinking water. However, oral administration of metformin (63 mg/kg b.w.) reduced fasting BGL to 48%, which showed no significant difference with the S. *polyanthum* extract (Widharna et al., 2015).

The combination of ethanol extract of *S. polyanthum* leaves (500 mg/kg b.w. and 750 mg/kg b.w.) with glibenclamide (0.65 mg/kg b.w.) administrated orally to alloxan-induced (120 mg/kg b.w.) diabetic mice (*Mus musculus*) for 14 days significantly ($p < 0.05$) lowered fasting BGL by 230 ± 23.69 and 233.75 ± 9.93 mg/dL. This result is significant compared to the negative control (Na carboxymethyl cellulose (CMC) 0.5%) by 4 ± 6.82 mg/dL, positive control (glibenclamide alone) by 150.75 ± 11.34 mg/dL, combination of ethanol extract of *S. polyanthum* leaves (250 mg/kg b.w.) with glibenclamide (0.65 mg/kg b.w.) by 170 ± 10.51 mg/dL, and ethanol extract of *S. polyanthum* alone of 250, 500 and 750 mg/kg b.w. at 134 ± 4.61, 151.25 ± 6.72, and 158.75 ± 17.64 mg/dL, respectively (Liem et al., 2015).

The leaf decoction of *S. polyanthum* (1800 mg/kg b.w.) administrated orally to alloxan-induced (120 mg/kg b.w.) diabetic male Wistar rats (180 gm to 200 g) for ten days

significantly ($p < 0.05$) lowered fasting BGL on hyperglycaemic rats as well as Kupffer cell count. However, it is not likely to give significant results in lowering pancreatic and kidney haemorrhage scores (Yuliana, 2014).

Petroleum ether, chloroform, and methanol extract of *S. polyanthum* leaves at a dose of 1000 mg/kg b.w. administrated orally to intraperitoneal glucose-loaded average male Sprague Dawley rats (180 g to 250 g) for 30 minutes did not significantly alter the increase of BGL within 120 minutes after glucose loading (Widyawati et al., 2015a).

Aqueous extract of *S. polyanthum* leaves at a dose of (1000 mg/kg b.w.) administrated orally to intraperitoneal glucose-loaded average male Sprague Dawley rats (180 g to 250 g) for 30 minutes significantly ($p < 0.05$) increase BGL (9.3 ± 0.38 mmol/L) compared to the control (normal saline, 10 mL/kg b.w.). Metformin with the administration of 500 mg/kg b.w. dose, on the other hand, significantly displayed better BGL inhibition after 90 minutes ($p < 0.01$) (5.3 ± 0.14 mmol/L) and 120 minutes ($p < 0.05$) (5.1 ± 0.19 mmol/L) compared to the control (normal saline, 10 mL/kg b.w.) with 6.4 ± 0.23 mmol/L after 90 minutes and 5.9 ± 0.13 mmol/L after 120 minutes (Widyawati et al., 2015a).

Methanol extract of *S. polyanthum* leaves (1000 mg/kg b.w.) administrated orally to streptozotocin-induced (55 mg/kg b.w.) diabetic male Sprague Dawley rats (180 g to 250 g) for seven hours significantly ($p < 0.01$) decrease the fasting BGL compared to the diabetic control (normal saline, 10 mL/kg b.w.). Metformin, on the other hand, significantly reduced the blood glucose from the first hour ($p < 0.01$) to the seventh hour ($p < 0.001$) of the study (Widyawati et al., 2015a).

Ethanol extract of *S. polyanthum* leaves (62.5, 125, and 250) mg/kg b.w. administrated orally to alloxan-induced (150 mg/kg b.w.) diabetic male Wistar rats for ten days significantly ($p < 0.05$) reduced BGL (114.3 ± 9.4, 119.3 ± 23.4, 119.3 ± 11.3) mg/dL (Sutrisna et al., 2016).

The combination of ethanol extract of *S. polyanthum* leaves (750 mg/kg b.w.) and glibenclamide (0.65 mg/kg b.w.) administrated orally to alloxan-induced (70 mg/kg b.w.) diabetic male mice (*Mus musculus*) for 14 days shows significant ($p > 0.05$) mean difference of lowered fasting BGL (287.4 ± 65.05 mg/dL) compared to the negative control (Na CMC 0.5%) showing -78.8 ± 115.12 mg/dL, positive control (glibenclamide alone) (173.6 ± 60.55 mg/dL), ethanol extract of *S. polyanthum* leaves alone at (250, 500 and 750) mg/kg b.w. with 135.4 ± 28.89, 163.2 ± 47.99, 190.2 ± 46.98 mg/dL mean difference respectively, and the combination of ethanol extract of *S. polyanthum* leaves (250 and 500) mg/kg b.w. with glibenclamide (0.65 mg/kg b.w.) (237.4 ± 75.11, 246 ± 23.09) mg/dL (Hikmah et al., 2016).

Aqueous extract of *S. polyanthum* leaves (5.0 mg/kg b.w./day) administrated orally to alloxan-induced (125 mg/kg b.w.) diabetic Wistar rats for 56 days significantly ($p < 0.05$) lowered BGL (110.56 ± 1.68 mg/dL) than the control group (105.76 ± 2.53 mg/dL) (Wahjuni et al., 2018).

Figures 2 and 3 show the risk of bias assessment results of the eight studies included in this review. Six (75%) of the studies stated the studies have baseline characteristics based on this assessment. Since the backgrounds of the animals were essentially homogeneous,

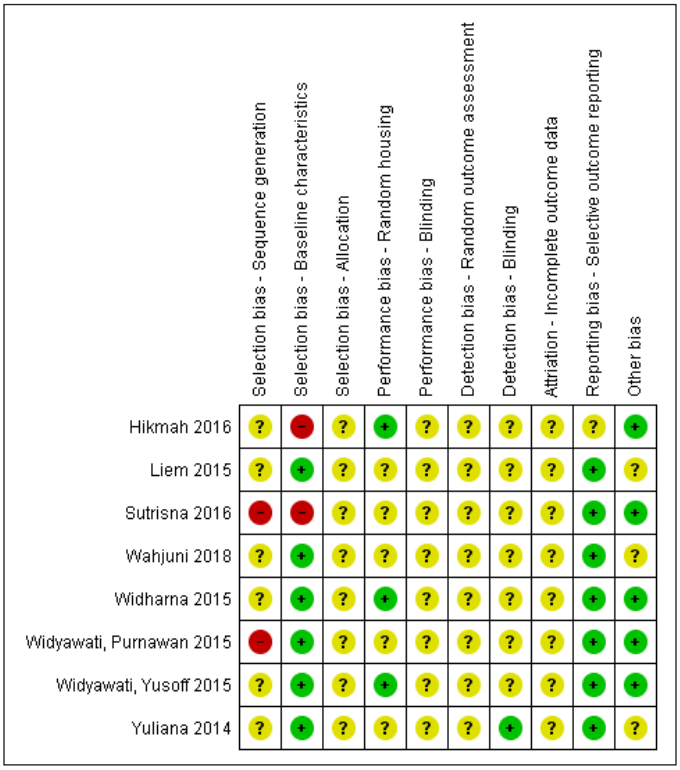

Figure 2. Risk of bias assessment of included studies using SYRCLE tool

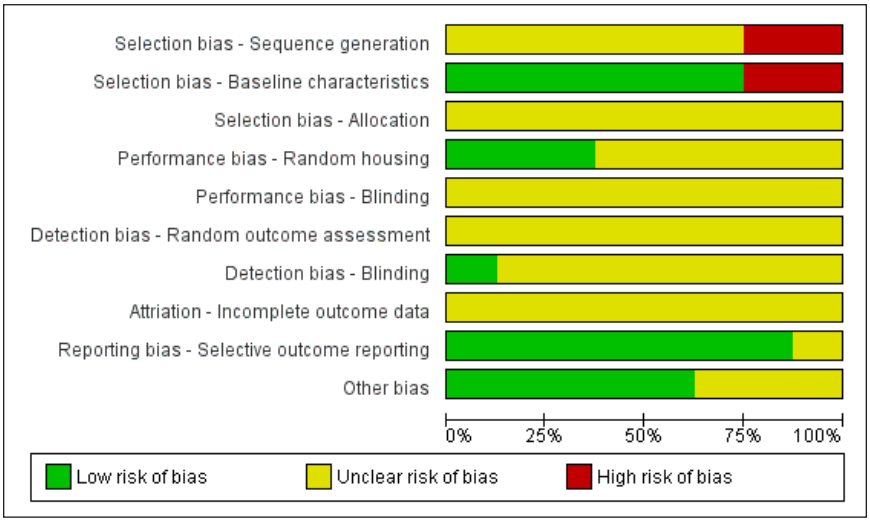

Figure 3. Risk of bias summary

Table 2
Data extraction table

Author, Year	*Plant part*	*Type of extraction*	*Study subject*	*Induction of diabetes*	*Dosage*	*Comparison*	*p-value*	*Finding (s)*
(Widyawati et al., 2015b)	Leaves	Methanol	Eighty-two healthy male Sprague Dawley rats weighing between 200 to 250 g	Streptozotocin-induced at 55 mg/kg b.w. intraperitoneally	125–1000 mg/kg b.w.	Glibenclamide, 10.00 mg/kg b.w. Metformin, 500.00 mg/kg b.w.	$p < 0.01$	Methanol extract of *S. polyanthum* leaves did not significantly alter the BGL in average and intraperitoneal glucose loaded rats, respectively. However, glibenclamide and metformin significantly reduced the BGL in normal and intraperitoneal-loaded glucose rats, respectively. Both methanol extract of *S. polyanthum* leaves and metformin, on the other hand, significantly reduced the fasting BGL in diabetic rats.
(Widharna et al., 2015)	Leaves	Aqueous	Eighty-four healthy male Wistar rats weighing between 100 to 150 g	Alloxan-induced at 150 mg/kg b.w. intravenously	200 mg/kg b.w.	Glibenclamide, 0.45 mg/kg b.w. Metformin, 63.00 mg/kg b.w.	$p < 0.05$	Both aqueous extract of *S. polyanthum* leaves and glibenclamide significantly lowered the BGL in intravenous glucose-loaded average rats. Aqueous extract of *S. polyanthum* leaves significantly reduced the fasting BGL while metformin did not significantly reduce the fasting BGL in diabetic rats.
(Liem et al., 2015)	Leaves	Ethanol	Thirty-two mice (*Mus musculus*)	Alloxan-induced at 120 mg/kg b.w. intraperitoneally	250–750 mg/kg b.w.	Glibenclamide, 0.65 mg/kg b.w.	$p < 0.05$	Combination of ethanol extract of *S. polyanthum* leaves with glibenclamide significantly lowered the fasting BGL in diabetic mice compared to glibenclamide alone.
(Yuliana, 2014)	Leaves	Aqueous	Twenty-four male Wistar rats weighing between 180 to 200 g	Alloxan-induced at 120 mg/kg b.w. intraperitoneally	900–2700 mg/kg b.w.	Untreated hyperglycemic rats	$p < 0.05$	Aqueous leaf decoction of *S. polyanthum* significantly lowered the fasting BGL in hyperglycemic rats.

Table 2 (*continue*)

Author, Year	*Plant part*	*Type of extraction*	*Study subject*	*Induction of diabetes*	*Dosage*	*Comparison*	*p-value*	*Finding (s)*
(Widyawati et al., 2015a)	Leaves	Petroleum ether, chloroform, methanol, aqueous	Seventy-five healthy male Sprague Dawley rats weighing between 180 to 250 g	Streptozotocin-induced at 55 mg/kg b.w. intraperitoneally	1000 mg/kg b.w.	Metformin, 500.00 mg/kg b.w.	$p < 0.05$ $p < 0.01$	Petroleum, chloroform, and methanol extract of *S. polyanthum* leaves did not significantly alter the increase of BGL in intraperitoneal glucose-loaded average rats. Aqueous extract of *S. polyanthum* leaves significantly altered the increase of BGL in intraperitoneal glucose-loaded average rats. Metformin significantly inhibited the BGL in intraperitoneal glucose-loaded average rats. Both methanol extract of *S. polyanthum* leaves and metformin, on the other hand, significantly reduced the fasting BGL in diabetic rats.
(Sutrisna et al., 2016)	Leaves	Ethanol	Forty healthy male Wistar rats	Alloxan-induced at 150 mg/kg b.w.	60–250 mg/kg b.w.	Glibenclamide, 0.63 mg/kg b.w.	$p < 0.05$	Ethanol extract of *S. polyanthum* leaves reduced BGL in diabetic rats.
(Hikmah et al., 2016)	Leaves	Ethanol	Forty healthy male mices	Alloxan-induced at 70 mg/kg b.w. intravenously	250–750 mg/kg b.w.	Glibenclamide, 0.65 mg/kg b.w.	$p > 0.05$	Combination of ethanol extract of *S. polyanthum* leaves and glibenclamide significantly lowered the BGL in diabetic mice compared to *S. polyanthum* leaves and glibenclamide alone.
(Wahjuni et al., 2018)	Leaves	Aqueous	Forty healthy Wistar rats	Alloxan-induced at 125 mg/kg b.w.	0.5–5.0 mg/kg b.w.	Glibenclamide, 0.18 mg/200g b.w.	$p > 0.05$	Aqueous extract of *S. polyanthum* leaves significantly reduced BGL in diabetic rats.

most of the studies did not describe the method of randomisation. None of the studies indicated whether the allocation was adequately concealed. As shown clearly in Figure 2, many items were scored as "unclear", indicating that these animal studies' reporting and presumably experimental design can be improved. Three (38%) of the studies did not state the source of the plant or extract, which gives a score of "unclear" in other bias.

DISCUSSION

Of the total eight studies we analysed, we found that different extracts of *S. polyanthum* leaves (aqueous, methanol, and ethanol) positively impact lowering the BGL in animal subjects. Out of the eight studies, the *S. polyanthum* leaves extract were conducted in average and diabetic rats to examine the hypoglycaemic (three studies) (Widharna et al., 2015; Widyawati et al., 2015a; & Widyawati et al., 2015b), intraperitoneal glucose tolerance test IPGTT (two studies) (Widyawati et al., 2015a & 2015b) and antihyperglycaemic (eight studies) (Hikmah et al., 2016; Liem et al., 2015; Sutrisna et al., 2016; Wahjuni et al., 2018; Widharna et al., 2015; Widyawati et al., 2015a; Widyawati et al., 2015b; & Yuliana, 2014). In addition, Sutrisna et al. (2016) reported that the most optimum dosage of ethanol extract of *S. polyanthum* leaves (62.5 mg/kg b.w.) administered to male Wistar rats reduced the BGL to 114.3 ± 9.4 mg/dL.

The phytochemical screening of *S. polyanthum* leaves extract contains tannins, flavonoids, alkaloids, and terpenoids (Hikmah et al., 2016; Liem et al., 2015; Wahjuni et al., 2018; Widharna et al., 2015; Widyawati et al., 2015b; & Yuliana, 2014). Each of these compounds has been shown to have a potential antidiabetic effect. A study reported that administering tannin from *Syzygium mundagam* bark significantly reduced the BGL of an STZ-induced diabetic rat model. It has been shown to have the antioxidant effect of tannin on reducing oxidative stress in diabetic animals supplemented with tannin fraction (TF) 200 mg/kg due to its hydrogen donating ability, which reduces the radical scavenging activity (Chandran et al., 2017; & Velayutham et al., 2012).

Flavonoids have been reported to possess antihyperglycaemic activity in STZ-induced diabetic rats through a few mechanisms of action attributable to the inhibition of α-glucosidase and the elevation of blood insulin levels (Khamchan et al., 2018; & Mohamed et al., 2015). Flavonoid compound (quercetin) present in *Syzygium cumini* seed (Chagas et al., 2015) and phenolic compound (gallic acid) present in *Syzygium samarangense* fruit (Khamchan et al., 2018) have been reported to regenerate pancreatic β-cells, thus may increase the secretion of insulin (Brahmachari, 2011; Jananie et al., 2011; & Yang & Kang, 2018). In addition, the animal study showed that flavonoids played similar functions to vitamin E by inhibiting peroxidation to liver microsomes in mice that experienced vitamin E efficiency (Duthie & Morrice, 2012). It is due to the stimulation of antioxidant enzymes catalase (CAT) and superoxide dismutase (SOD) activities or chemical structure where

double bond at two to three position conjugated with a 4-oxo function and hydroxyl groups at positions 3 and 5 in flavonoid contributes to its antiradical activity (Khamchan, 2018; Duthie & Morrice, 2012).

Alkaloid from *S. polyanthum* leaves has shown antidiabetic potential in STZ-induced diabetic rats (Widyawati et al., 2015b). Alkaloid compounds, namely polyhydroxyalkaloids (PHA), specifically casuarine 6-O-α-glucoside that are present in most Myrtaceae species such as *Syzygium malaccense*, *Syzygium oleosum*, *Syzygium paniculatum*, and *Syzygium cumini*. They could be induced in relatively high glucose uptake in mouse (β-TC6) pancreatic cell line and mouse (C2C12) myoblast skeletal muscle cells (Bhaskar et al., 2011; Jung et al., 2006; Kumar et al., 2013; & Porter et al., 2000). Alkaloid compounds play a role in reducing blood glucose transportation in the blood, stimulates glycogen synthesis and inhibits glucose synthesis by inhibiting enzyme glucose 6-phosphatase, fructose 1, 6-bifosfatasen and increase glucose oxidation through glucose 6-phosphate dehydrogenase (Kooti et al., 2016).

Oral administration of triterpenoid from *Syzygium malaccense* for 15 days results in a significant decrease of fasting BGL in STZ-induced diabetic rats (Bairy et al., 2005). Squalene, a triterpene that belongs to the terpenoid family present in *S. polyanthum* (Widyawati et al., 2015b) and *Mucuna pruriens* (Bhaskar et al., 2011), is responsible as an α-glucosidase inhibitor (Hou et al., 2009), which delay the absorbance of carbohydrates in the intestine subsequently decreasing the postprandial insulin level and also increase insulin insensitivity (Li et al., 2010; Nazaruk & Borzym-Kluczyk, 2014) and may increase insulin secretion (Li et al., 2010). Another underlying mechanism of *S. polyanthum* in reducing BGL may be inhibiting intestinal glucose absorption and enhancing glucose uptake by the muscles (Kooti et al., 2016).

However, few references suggest or deny the use of *S. polyanthum* leaves as a potential antidiabetic agent. The available articles have limitations in many aspects, and the results lack implications. Besides, no human studies are available, and only animal studies were included. Therefore, it is not easy to conduct any measure of consistency or subgroup analysis due to the more diverse nature of the animal studies, such as species used, design, and study characteristics (age, dose, schedule of administration). The risk of bias assessment of the animal studies conducted in this paper is vital to show the need to reduce the biases through methodological quality since most of the assessments gave "unclear" scores. Although safety data on *S. polyanthum* is limited, the only study by Widharna et al. (2015) revealed that combination of *S. polyanthum* and *Andrographis paniculata* leaves extract were free of acute oral toxicity up to 2000 mg/kg body weight and did not cause a change in behavioural activities of the animals. Other toxicity tests reported previously suggested that the extract of *S. polyanthum* was practically safe and non-toxic when tested on Wistar rats (Sumiwi et al., 2019). Therefore, based on the current empirical evidence, the potential

of *S. polyanthum* leaves alone or combined with glibenclamide has shown a significant lowering of blood glucose levels. However, this paper showed the need to improve the methodological quality of animal studies. It can be done by minimising or standardising the biological study characteristics of animal studies and reducing bias sources. By performing this, the original research can be applicable with high quality to be used for meta-analysis with reduced impact of bias (Hooijmans et al., 2014a).

CONCLUSION

In conclusion, the extract of *S. polyanthum* leaves alone or combined with glibenclamide may potentially exhibit a significant antidiabetic effect. However, although the leaves extract of *S. polyanthum* may be a promising agent for diabetes mellitus, further studies with a comprehensive methodology and results are needed to determine the phytochemicals involved, possible mechanisms of action, and safety assessment so that the results can be translated into clinical trials.

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