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Gambier for Diabetes: Comparison of the Antidiabetic Potency between Two Types of Extracts from *Uncaria gambir* (W. Hunter) Roxb.

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ABSTRACT

Gambier is a dry extract obtained from both the leaves and twigs of the *Uncaria gambir*. It is an agricultural product produced by the local community through traditionally unique methods. The main objective of this study was to evaluate the antidiabetic potency of gambier. The study used two types of gambier, namely traditional aqueous gambier (TAG) from traditional extraction and maceration ethanol gambier (MEG) from maceration extraction. The phytochemical compound, alpha-glucosidase inhibition, and antioxidant activity were analyzed. Moreover, in vivo hypoglycemia activity study was carried out. The results showed that both TAG and MEG contained flavonoids, tannin, and triterpenoids, while saponins were detected in TAG and steroids in MEG only. Both TAG and MEG also contained quercetin and catechin which were higher in the TAG compared to the MEG. The DPPH scavenging activities of the TAG and MEG, measured in IC50 values, were 15.40 ± 0.21 µg/ml and 12.25 ± 0.04 µg/ml, respectively. The IC50 values of the alpha-glucosidase inhibition of TAG and MEG were 35.84 ± 1.75 µg/ml and 83.14 ± 1.26 µg/ml, respectively. The best hypoglycemic activity was observed in the TAG group. The group given TAG and high glucose had lower blood glucose (127 mg/dl) compared to the group only given high glucose (178 mg/dl). These results indicated that TAG had a better potential for antidiabetic activities compared to MEG, and it can be proposed for further investigations as a potential antidiabetic agent.

***Keywords*:** Alpha-glucosidase inhibitor; Antioxidant; Diabetes; Gambier; Glucose

INTRODUCTION

Diabetes mellitus is a global disease, with the number of prevalences increasing every year.[1-4] Apart from being a health burden, diabetes also poses a significant economic burden on the healthcare systems of some countries, such as USA, China, and Germany.[5-7] Another critical point is that Indonesia ranks fifth worldwide for the highest number of diabetes patients, with about 19 million in 2021 and estimated to increase to 28.6 million by 2045.[8] Managing diabetes mellitus is undoubtedly one of the health priorities worldwide. A potential solution to address this disease is to explore and evaluate various substances that have the potential to act as anti-diabetic agents.

Gambier is a dry extract derived from the leaves and twigs of *Uncaria gambir*. It belongs to the Rubiaceae family. The plant

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originates from Southeast Asia, particularly Indonesia and Malaysia.[9] Gambier is used to 'menginang' in some areas of Indonesia. The term 'menginang' (sometimes referred to as 'menyirih') is the process of mixing various ingredients, including gambier, wrapped using betel leaves, which is then chewed by the local community as a tradition. The local community produces gambier with a traditionally unique method. The method is similar to the extraction principle using water solvent but differs regarding traditional equipment utilization and heating process. The use of water as a solvent may be more convenient and acceptable for further application based on safety reasons. Water solvents also had an excellent ability to produce pharmacological functions from a particular plant.[10-14] It is also considered the greenest solvent in chemistry from an experimental and an industrial perspective.[15]

The hypothesis of the antidiabetic potency of gambier is based on previous studies. *Uncaria tomentosa*, a species native to the Amazon forest, has the same genus as *U. gambir* and could prevent diabetes mellitus. It reduces the blood glucose level, delays diabetes incidence, and protects beta cell mass loss.[16] Some flavonoids were tested to inhibit the intestinal glucose transporter GLUT2. The tests revealed that quercetin could inhibit glucose absorption in the intestines via the transporter GLUT2.[17] Quercetin could also inhibit the alpha-glucosidase enzyme.[18] Another flavonoid, Catechins, also has some beneficial effects in managing diabetes. Catechins could improve insulin resistance, alleviate oxidative stress, regulate mitochondrial function, alleviate endoplasmic reticulum stress, produce anti-inflammatory effects, reduce blood sugar sources, and regulate intestinal function.[19-24] Thus, gambier is strongly expected to have antidiabetic potency, as it was observed to contain both catechin and quercetin.

A study reported antioxidant activity and alpha-glucosidase inhibition of gambier.[25] However, the study was conducted using the ethanol extract of commercial gambier from a local market in Indonesia. The extract was produced from a re-extraction of traditional gambier extract, which may cause the loss of some active compounds.

This study will be the first to evaluate the antidiabetic potency of traditional gambier extract. This study compared the antidiabetic potency of the two types of gambier extract, namely traditional aqueous gambier (TAG) made using the traditional extraction method and maceration ethanol gambier (MEG) made using the maceration extraction method. Furthermore, the in vivo study of these extracts has yet to be previously reported with regard to assessing the antidiabetic potency of gambier. Thus, this study aimed to analyze the phytochemical compounds, antioxidant activity, alpha-glucosidase inhibition, and in vivo hypoglycemic activity of two gambier extracts.

METHODS

Plant materials

Leaves and twigs of *Uncaria gambir* were harvested in September in Pesisir Selatan District, West Sumatera, Indonesia. The validation of the *U. gambir* was done by identifying the plant in the herbarium of Andalas University (UNAND), Padang, West Sumatera, Indonesia.

Animals

Six weeks old, Sprague Dawley male rats were purchased from Indoanilab, a private company in Bogor, Indonesia. All animals received standard commercial rat food and water *ad libitum*. The Animals were acclimatized for two weeks before experiments. Clinically healthy animals with a body weight of 200-230 grams were used for the study. Ethical clearance was obtained from The Veterinary Teaching Hospital, Faculty of Veterinary Medicine, Bogor Agricultural University (No. 29-2016 ACUC RSHP FKH-IPB).

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Extraction

Gambier extract was made using two different methods: traditional extraction yielding traditional aqueous gambier (TAG) and maceration extraction yielding maceration ethanol gambier (MEG). In the traditional extraction, 36.5 kg of fresh leaves and twigs were boiled and then pressed using a jack press to get the liquid extract. Liquid extract was filtered and then deposited in a wooden container called *paraku* for 24 hours. In *paraku*, the extract was allowed to cool into the form of a paste. The extract was then drained and pressed again with stone ballast to allow the paste to be denser and immediately printable. The extract was then blocked and sun-dried. In the maceration extraction, 14 kg of fresh leaves and twigs were ground, producing a coarse, smaller sample. The sample was extracted using the standard procedure of maceration in ethanol 70% for three days at room temperature. The resulting filtrate was then filtered and evaporated to produce the solid extract.

Phytochemical profile

Phytochemical tests were carried out using qualitative and quantitative methods. Qualitative methods to check alkaloids, flavonoids, saponins, quinones, tannins, triterpenoids, and steroids following the standard procedure.[26] Quercetin was determined using High-Performance Liquid Chromatography (HPLC-UV/Vis Hitachi), according to a previous study.[27] The quantitative analysis of catechin was carried out by spectrophotometry at a wavelength of 279 nm according to the Indonesian National Standard.

DPPH (2,2-Diphenyl-1-picrylhydrazyl) assay

The assay of DPPH was conducted according to a modified method from the previous study.[28] A series of sample solutions of different concentrations were prepared at 100 µL by serial dilution method. The concentrations were 100, 50, 25, 12.5, 6.25, 3.125 µg/ml. Next, 100 µL DPPH (125 µM in ethanol) was added to each sample solution (S1). The control sample only contained 100 µL of the sample solution and 100 µL of ethanol (S0). A blank solution consisting of 100 µL ethanol was added to the DPPH of 100 µL (B1). The blank control contained ethanol only (B0). The final volume of each solution was 200 µL. These solutions were incubated at 37^{o}C in a dark condition for 30 minutes. Absorbance was measured using an ELISA reader with a wavelength of 517 nm. The scavenging capacity (SC) was calculated as follows: SC% = [(B-S)/B] x 100% where B was the absorbance of black corrected (B1-B0), and S was the absorbance of the sample corrected (S1-S0). All treatments were done in triplicate.

Alpha-glucosidase inhibition assay

The inhibitory activity of the alpha-glucosidase enzyme was determined based on the method in the previous study.[29] Briefly, the reagent mixture contained 50 µL of Phosphate buffer, 25 µL of p-nitrophenyl α-D glucopyranoside 0.5 mM, ten µL of the test sample in DMSO with a concentration range of 7.8125 µg/ml - 500 µg/ml. 25 µL enzyme solution was added to the solution (S1). Control samples contained 10 µL of the sample solution, 25 µL of p-nitrophenyl α-D-glucopyranoside and 75 µL of phosphate buffer (S0). The blank solution contained 25 µL of enzyme solution, 25 µL of p-nitrophenyl α-D-glucopyranoside, 10 µL of DMSO, and 50 µL of phosphate buffer (B1). The blank control contained 25 µL of p-nitrophenyl α-D-glucopyranoside, 10 µL of DMSO, and 75 µL of phosphate buffer (B0). The mixed solution to be incubated was 100 µL. The reaction mixture was then incubated at 37°C for 30 minutes. The reaction was stopped by the addition of 100 µL of Na2CO3 0.2 M. Substrate enzymatic hydrolysis was monitored through the amount of p-nitrophenol released in the reaction mixture at 410 nm using an ELISA reader. All treatments were triplicated. The inhibitory activity (IA) was calculated as IA% = [(B-S)/B] x 100%, where B was the corrected blank absorbance (B1-B0), and S

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was the corrected sample absorbance (S1-S0).

Hypoglycemic activity test

The hypoglycemic activity of gambier was examined using an Oral Glucose Tolerant Test (OGTT) according to a modified method from the previous study.[30] The test was performed on five rats from each group. There were nine groups as follows: G1 (negative control group), G2 (positive control group), G3 (commercial drug group treated with Glucobay© at a dose of 4.5 mg/kg BW), G4 to G6 (TAG groups treated with TAG at doses of 100 mg/kg BW, 200 mg/kg BW, and 300 mg/kg BW, respectively), and G7 to G9 (MEG groups treated with MEG at doses of 100 mg/kg BW, 200 mg/kg BW, and 300 mg/kg BW, respectively). Rats fasted overnight before treatment. They were then given gambier extracts, except positive and negative control groups that were given distilled water and the commercial drug group that was given Glucobay. A glucose load was then orally administered via a gavage (90% glucose solution, 1 ml), except for the negative control group that was given distilled water as a placebo. The blood glucose levels were then measured every 30 minutes for two hours. Blood samples were taken from rat tails cleaned with alcohol (70%). The blood glucose was measured using an Accu-Check® Active glucometer (Roche, Germany). The area under the glucose curve (AUC) during the OGTT was determined using the trapezoidal method.

Statistical analysis

Antioxidant activity, alpha-glucosidase inhibition and glucose AUC results were presented as mean ± SD. IC50 values from log regression were used to present antioxidant activity and alpha-glucosidase inhibition. We used the Mann-Whitney test to compare quantitative phytochemical content, DPPH scavenging activity and alpha-glucosidase inhibition of two gambier extracts. Glucose AUC was analyzed using ANOVA followed by Duncan's multiple range tests ($p<0.05$ or $p<0.01$).

RESULTS AND DISCUSSION

Natural products have been targeted for many years to cope with various diseases, including diabetes, for their medicinal value. This study evaluated the antidiabetic potency of two types of extract of *Uncaria gambir*. They are traditional aqueous gambier (TAG), which uses water as the solvent, and maceration ethanol gambier (MEG), which uses ethanol as the solvent. Both aqueous and ethanolic solvents were less toxic than other organic solvents. Thus, further application of the extracts could be more acceptable.[31]

The extraction yield of *Uncaria gambier* leaves and twigs is shown in Table 1. This study showed that 36.5 kg of leaves and twigs of *U. gambir* produced 3.50 kg of TAG (9.59%). Meanwhile, 14 kg of *U. gambir* produced 1.92 kg of MEG (13.71%). The higher yield of MEG compared to TAG suggests that the type of solvent could influence the yield of each extract. The MEG obtained using the ethanol solvent (containing 70% ethanol as an organic solvent and 30% water) may facilitate the extraction of both water-soluble chemicals and an organic solvent.[32] Also, the organic compounds are generally non-polar, and most of them are insoluble in water as water is a polar solvent. Most carbohydrates and pigments as organic compounds elute with ethanol.[33] It is possible that these factors contributed to the higher yield of MEG compared to TAG.

In this study, both TAG and MEG were evaluated for their phytochemical compounds as shown in Table 1. It can be used for estimating a plant's pharmacological function. A qualitative phytochemical analysis was conducted on both TAG and MEG, revealing the presence of flavonoids, tannins, and triterpenoids in both. However, only TAG contained saponins, and MEG contained steroids. In the quantitative analysis, TAG had higher levels of both quercetin and catechin compared to MEG. Specifically, TAG

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contained 2.65 mg/g of quercetin, while MEG contained 1.69 mg/g. Additionally, TAG had 80.56%wt of catechin, while MEG had 71.73%wt. These findings suggest that TAG and MEG differ qualitatively and quantitatively in terms of phytochemical compounds. The extraction temperature, extraction time, and type of solvents may influence these variations, which could affect the antidiabetic potency of TAG and MEG. It is important to determine the amount of catechin present in the gambier, as it is used as a marker in trade and establishes the quality of the gambier.[34] The quantification of quercetin may also provide valuable information for evaluating the antidiabetic potency of gambier, as previous studies have reported its effectiveness.[35,36] However, the contribution of other compounds should also be considered.

Table 1. The profile of gambier extracts

Profile		TAG	MEG
Qualitative Phytochemical			
Alkaloids	Wagner	Negative	Negative
	Mayer	Negative	Negative
	Dragendorf	Negative	Negative
Flavonoids		Positive	Positive
Tannins		Positive	Positive
Saponins		Positive	Negative
Quinones		Negative	Negative
Triterpenoids		Positive	Positive
Steroids		Negative	Positive
Quercetin		Positive	Positive
Quantitative Phytochemical			
Catechin (wt%)		80.56 ± 0.57^{a}	71.73 ± 1.29^{b}

Statistically significant differences are indicated by a, b ($p < 0.05$).
Abbreviations: Traditional Aqueous Gambier (TAG); Maceration Ethanol Gambier (MEG).

This study evaluated the antioxidant activity of two types of gambier extract using the DPPH method. The results of the DPPH are expressed in IC50 values and presented in Table 2. The DPPH IC50 values of the TAG and MEG were 15.40 µg/ml and 12.25 µg/ml, respectively. The IC50 value of MEG was lower than that of TAG. It indicated that TAG has slightly higher antioxidant activity than the MEG. However, both of them were categorized as very strong antioxidants. Antioxidant activity is classified as very strong (IC50 <50 µg/ml), strong (IC50 50-100 µg/ml), moderate (IC50 100-150 µg/ml), and weak (IC50 150-200 µg/ml. The information on the antioxidant activity of gambier is essential, with increasing evidence showing that oxidative stress contributes to the development and complications of diabetes.[37,38] Thus, the antioxidant is expected to inhibit these two aspects of diabetes. Additionally, several studies reported that various plants that have antioxidant properties showed antidiabetic activities.[39-41]

Two types of gambier extracts, TAG and MEG, were studied for the inhibitory activity of the alpha-glucosidase enzyme (Table 2). It was surprising to find that TAG showed more significant inhibition of the enzyme, with roughly twice the potency of MEG. The IC50 values for TAG and MEG were 35.84 µg/ml and 83.14 µg/ml, respectively. Recent research has identified phytochemical compounds such as quercetin and catechin with alpha-glucosidase inhibition activity.[42-45] These compounds were found to be more abundant in TAG than MEG. Additionally, saponins were also reported to have alpha-glucosidase inhibition activities, but they were not detected in MEG.[46,47]

The alpha-glucosidase inhibition of gambier was found to be dose-dependent. It was elevated as the concentration of gambier extracts increased. However, when the gambier extract concentration gradually increased, the inhibition activity slowed. It could be a consequence of the enzyme molecules being occupied, becoming a limiting factor. The inhibition became plateau regardless of the increased extract concentration, suggesting that all enzyme molecules are occupied, and gambier extracts as an inhibitor were in excess.[48]

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Table 2. Alpha-glucosidase inhibition and antioxidant activity of gambier extracts

Assay	Extract (µg/ml)	TAG		MEG	
		Percent activity*	IC_{50} (µg/ml)#	Percent activity*	IC_{50} (µg/ml)#
DPPH scavenging activity	100	92.48 ± 0.13	15.40 ± 0.21[a] (R^2 = 0.96)	90.15 ± 0.13	12.25 ± 0.04[b] (R^2 = 0.91)
	50	91.56 ± 0.13		90.24 ± 0.26	
	25	65.68 ± 0.26		83.61 ± 3.13	
	12.5	37.38 ± 3.28		48.16 ± 0.13	
	6.25	20.04 ± 2.89		26.89 ± 0.52	
	3.125	8.44 ± 4.59		15.38 ± 1.43	
Alpha glucosidase inhibition activity	250	96.15 ± 0.19	35.84 ± 1.75[a] (R^2 = 0.94)	77.29 ± 0.13	83.14 ± 1.26[b] (R^2 = 0.98)
	125	90.32 ± 0.23		57.91 ± 0.76	
	62.5	71.68 ± 0.70		41.19 ± 0.08	
	31.25	43.12 ± 1.80		23.69 ± 2.86	
	15.625	23.71 ± 1.84		12.50 ± 1.77	
	7.8125	14.64 ± 1.52		7.95 ± 0.55	

Notes: *Percentage of DPPH scavenging or alpha-glucosidase inhibition activity. #Concentrations of extract that scavenged or inhibited 50% system, equipped with R-value from log regression. Statistically significant differences between the means of IC50 are indicated by a, b ($p < 0.05$).
Abbreviations: Traditional Aqueous Gambier (TAG); Maceration Ethanol Gambier (MEG).

The hypoglycemic activity of gambier extracts was analyzed using the Oral Glucose Tolerant Test (OGTT). OGTT is widely utilized to investigate and evaluate the hypoglycemic potential of various plants.[49-53] The test could be the initial approach in considering the properness of a plant for further study and development as an antidiabetic agent. The anti-diabetic properties of plants, especially alpha-glucosidase inhibitors, are expected to reduce glucose absorption in the intestine.[54-57] As a result, during the OGTT test, the blood glucose levels of rats given the antidiabetic candidate were lower than the control group.

The results of the OGTT test are displayed in Figure 1 and Table 3. Blood glucose levels rose above the normal range 30 minutes after administering glucose, particularly in the G2 group. The G2 group had blood glucose levels that nearly reached 180 mg/dl. However, all treated gambier groups (G4 to G9) showed lower blood glucose levels compared to G2. Table 3 shows the AUC glucose during the OGTT, which confirms that the gambier groups (G4 to G9) are significantly different from the untreated group (G2). The AUC glucose demonstrated that TAG groups (G4 to G6) at doses of 100 mg/kg BW, 200 mg/kg BW, and 300 mg/kg BW had lower AUC glucose, which correlated with blood glucose levels over two hours compared to MEG groups (G7 to G9) using the same extract doses. Among the TAG groups, 200 mg/kg BW (G5) produced the best hypoglycemic activity. This test proved that TAG had better hypoglycemic activity than MEG.

The exact mechanism of TAG lowers blood glucose levels still needs to be fully understood. The hypoglycemic effects of gambier can be attributed to its various phytochemical components. Some of these components, such as catechin, quercetin, and saponin, are found in gambier. Among these components, catechin and quercetin are more prevalent in TAG, while saponin is only present in TAG, not MEG. According to a study, saponins have been known to enhance insulin sensitivity both in vitro and in vivo.[23,58-60] While MEG has been found to have hypoglycemic properties, it has some limitations. For instance, in a study involving rats, those given MEG had higher blood glucose levels than those given TAG. Additionally, the MEG could not return blood glucose levels to normal range at the 120-minute mark. It may also be due to the presence of antagonistic substances, thereby inhibiting gambier's hypoglycemic activity.

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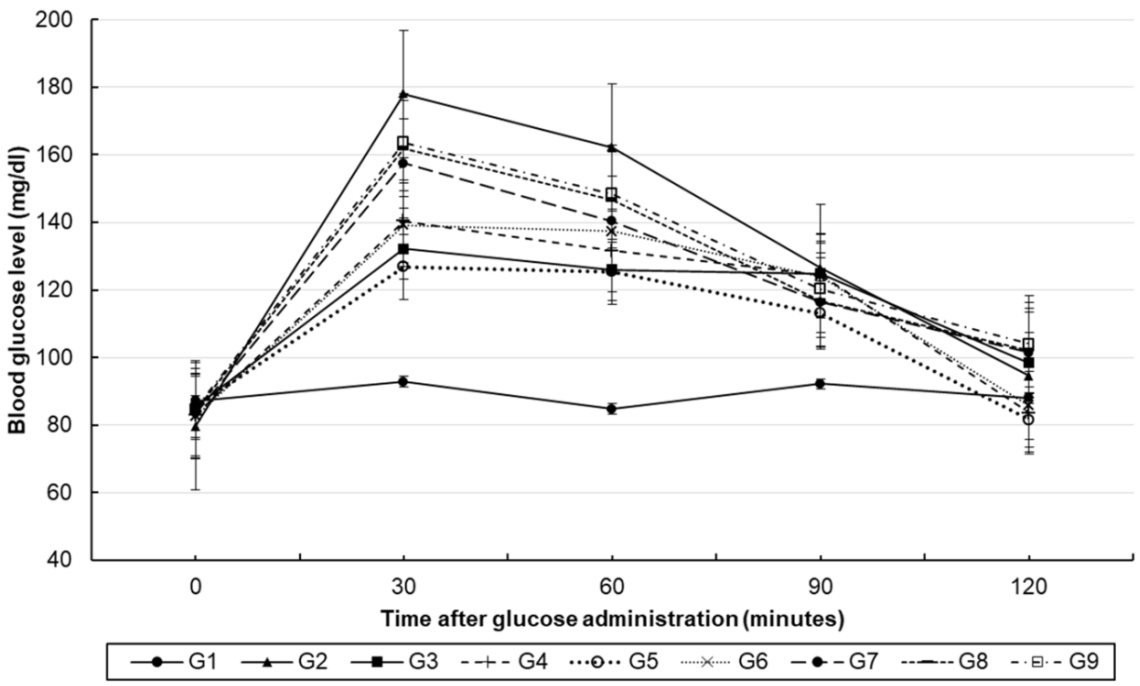

Figure 1. Hypoglycemic effect of gambier extracts. Values are expressed as means of blood glucose levels (n = 5 per group). G1 and G2: negative control and positive control group, respectively; G3: glucobay followed by 90% glucose 1 ml; G4, G5, G6: TAG at 100, 200, 300 mg/kg, respectively, followed by glucose 90% 1 ml; MEG at 100, 200, 300 mg/kg, respectively, followed by 90% glucose 1 ml. **Abbreviations:** Traditional Aqueous Gambier (TAG); Maceration Ethanol Gambier (MEG).

Table 3. The area under the 2hr glucose curve (AUC) for each group during OGTT

Groups	AUC-Glucose
G1 — Negative control	178.70 ± 7.398[a]
G2 — Positive control	276.85 ± 26.484[d]
G3 — Glucobay	237.45 ± 15.923[bc]
G4 — TAG 100	239.85 ± 12.260[bc]
G5 — TAG 200	224.35 ± 15.417[b]
G6 — TAG 300	242.40 ± 6.035[bc]
G7 — MEG 100	253.30 ± 6.542[cd]
G8 — MEG 200	259.20 ± 13.654[cd]
G9 — MEG 300	263.30 ± 11.226[cd]

The same letter in the same column means not significantly different ($p < 0.05$).
Abbreviations: Traditional Aqueous Gambier (TAG); Maceration Ethanol Gambier (MEG).

Another previous study had studied the antidiabetic potential of gambier through DPPH scavenging activity and alpha-glucosidase inhibition evaluation tests. However, the study was conducted using re-extracted commercial gambier from a local market in Indonesia, which was different to aqueous and ethanol extractions from fresh leaves and twigs of *U. gambir*, refers to gambier.[25] The re-extraction process is a method reported to increase catechin content in gambier, as catechin is a primary active compound. In comparison, this study revealed that gambier in the form of crude extracts (TAG and MEG) had IC50 values of both DPPH scavenging activity and alpha-glucosidase inhibition, which were similar to those of the re-extraction process. Further study is required to determine whether the phytochemical contribution of gambier is individual or synergistic. So, this extract or more purified derivatives could be applied as an antidiabetic agent.

CONCLUSION

Two types of gambier extracts (traditional aqueous gambier and maceration ethanol gambier) were examined in this study. Both extracts showed intense DPPH scavenging activity and inhibited the alpha-glucosidase enzyme. They also reduced rat blood glucose levels. However, traditional aqueous gambier showed better antidiabetic potency. Further studies on the animal model of diabetes are being carried

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out to precisely understand the antidiabetic mechanism of TAG and determine its maximum potency in treating diabetes.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them. All authors contributed equally to this work.

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