

α -Glucosidase inhibitor and antioxidant activity of procyanidin, an isolated compound from *Quercus gilva* Blume leaves

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ABSTRACT

Potential candidates for antioxidants and antidiabetics from nature are needed because they are safer and have few side effects. This report performed the extraction and isolation of biologically active compounds from *Quercus gilva* Blume leaves. In our previous study, several active compounds, including tiliroside, catechin, and epicatechin, had been isolated from *Q. gilva* leaves. This study obtained the active compound from *Q. gilva* leaves through bioassay-guided isolation by silica gel column chromatography using organic solvents from low-to-high polarity. The compound capability in scavenging free radicals was evaluated using the 1,1-diphenyl-2-picrylhydrazyl radical scavenging activity (DPPH) assay, reducing power assay, β -carotene assay, and hydrogen peroxide (H₂O₂) assay. The *in vitro* test of the antidiabetic assay was performed against the α -glucosidase enzyme. It showed that one compound, identified as procyanidin B3, was isolated. The isolated compound has antioxidant activity IC₅₀ of 7.86 ± 0.41 μ g/ml by the DPPH test and IC₅₀ of 34.51 ± 1.34 μ g/ml by the H₂O₂ assay. Moreover, the α -glucosidase inhibitory activity (IC₅₀) of the isolated compound was 40.05 ± 0.51 μ g/ml. This study showed that the isolated compound from *Q. gilva* showed the potential for natural antidiabetic medicine and antioxidants from nature.

INTRODUCTION

Reactive oxygen species are reactive atoms that have unpaired electrons. They can cause oxidative stress in DNA, lipids, proteins, or carbohydrates, eventually leading to neurodegenerative disease and cancer (Halliwell, 2012). The source of free radicals may come from external factors, such as junk food, alcohol, drugs, tobacco, environmental pollution, and heavy metals. However, free radicals can also be produced in the human body from endogenous reactions, such as phagocytosis, mitochondria by producing adenosine triphosphate, and β -oxidation of fatty acids

(Jakubczyk *et al.*, 2020; Liguori *et al.*, 2018; Namkoong *et al.*, 2018; Petruk *et al.*, 2018). Therefore, an antioxidant that can slow or inhibit cellular damage in the human body is urgently needed (Lobo *et al.*, 2010). Antioxidants may vary in the mechanism of actions and composition, which can scavenge free radicals, chelate metals, and inhibit enzymes (Gioti *et al.*, 2009; González-Palma *et al.*, 2016).

Plants are potential sources of antioxidants. Phenolic compounds, vitamins, and carotenoids have been reported as the primary contributors to antioxidant activities (Indrianingsih *et al.*, 2015b; Olugbami *et al.*, 2015; Rodríguez-García *et al.*, 2019). The utilization of plants includes different parts of them, such as flowers, leaves, bark, fruits, and roots. Several customers and manufacturers use plant extracts for medicinal use and cosmetic products (Sitarek *et al.*, 2020). Antioxidants from plants are preferred over synthetic antioxidants because of their safety and nutritional benefits (Deng *et al.*, 2011).

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Diabetes mellitus (DM) is a disease diagnosed with hyperglycemia. It is caused by either insulin resistance or an insulin production problem, and the symptoms include weight loss, thirst, and frequent urination (Klein *et al.*, 2007). DM complications could damage the kidneys, eyes, nerves, and heart (Sukardiman and Ervina, 2020). According to the WHO, DM patients are estimated to reach approximately 342 million by 2030 and will be a burden for developing countries (Sukardiman and Ervina, 2020). One treatment to overcome DM, primarily type 2, is consuming an α -glucosidase inhibitor. It can postpone glucose absorption and prevent increasing blood glucose levels (Sy *et al.*, 2005). Plants are a potential alternative to treat DM. Besides managing stable blood glucose levels, it can also prevent complications, an advantage over synthetic drugs (Sukardiman and Ervina, 2020). Approximately 1,200 plants were found to have an ability to lower blood glucose levels in ethnopharmacological surveys (Pandey *et al.*, 2011).

Quercus gilva Blume is an evergreen tree grown in Japan and South Korea (Kim and You, 2012; Noshiro and Sasaki, 2011). In Japan, *Q. gilva* was used as a raw material for agriculture tools, such as spades, axe handles, and hoes. The previous study has reported the bioactivity of phenolic compounds from the bark of *Q. gilva*, such as anti-inflammatory, antiurolithiasis, and antioxidative agents (Youn *et al.*, 2017). Several studies also identified terpenes from the fruit of *Q. gilva* and antioxidative agents from the branches of *Q. gilva* (Itokawa *et al.*, 1978; Moon *et al.*, 2009). The bioactive compounds from *Quercus* species leaves were phenolic compounds, vitamins, aliphatic alcohols, fatty acids, and sterol (Lämke and Unsicker, 2018; Vinha *et al.*, 2016). Several phenolic constituents in the *Quercus* species leaves are tannins, flavonoids (epicatechin, quercetin, rutin, kaempferol, and naringin), and phenolic acids (ellagic acid, gallic acid, gentisic acid, *p*-coumaric acid, vanillic acid, caffeic acid, and ferulic acid) (Brossa *et al.*, 2009; Cantos-Villar *et al.*, 2003; Jong *et al.*, 2012). Our previous study isolated three compounds, namely, catechin, epicatechin, and tiliroside, from *Q. gilva* leaves (Indrianingsih *et al.*, 2015). However, the isolation of polyphenol and study of its bioactivity on the *Q. gilva* leaves have not yet been done. Polyphenols such as procyanidins were often obtained as a mixture constituent, such as oligomeric and stereochemical mixtures. It was hard to isolate it as a pure compound (Oizumi *et al.*, 2010). The synthesis of procyanidin itself also had several problems, such as the needed large amount of nucleophile at low temperature and the formation of side products in oligomeric form (Kozikowski *et al.*, 2001).

In the present study, we isolated the polyphenol compound from methanolic extract of *Q. gilva* leaves and studied its bioactivity, such as antioxidant and antidiabetic activity.

MATERIALS AND METHODS

Plant materials, reagents, and general instrumentation

Quercus gilva leaves were harvested from Ehime University Garden, Matsuyama, Japan. Samples had been saved in the Faculty of Agriculture, Ehime University, Japan. The α -glucosidase enzyme, 1,1-diphenyl-2-picrylhydrazyl (DPPH), β -carotene, *p*-nitrophenyl α -D-glucopyranoside (*p*-NPG), potassium ferricyanide [$K_3Fe(CN)_6$], hydrogen peroxide (H_2O_2), ferric chloride ($FeCl_3$), trichloroacetic acid, n-hexane, chloroform, toluene, methanol, acetone ethanol, and ethyl acetate were obtained

from Wako, Ltd. (Japan). Gallic acid, quercetin, and Tween 40 were obtained from Sigma-Aldrich, Ltd. (Japan). Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-AL 500 spectrometer (Tokyo, Japan) using tetramethylsilane as the internal standard. Gas chromatography-mass spectrometry and fast atom bombardment-mass spectroscopy (FAB-MS) were performed using equipment from Shimadzu, Japan.

Compound isolation from *Q. gilva*

Leaves powder of *Q. gilva* (1.1 kg) was macerated with 8.8 l of methanol at room temperature. After 2 days of immersion, the filtrate was evaporated, separated, and isolated using bioassay-guided isolation. The solvent for silica column chromatography was started from n-hexane (100%), followed by n-hexane:ethyl acetate (50:50) and ethyl acetate:methanol (50:50), and finally methanol (100%). Five fractions F1–F5 were obtained, and further repeated silica column chromatography of F5 resulted in F51 to F53. Compound **1** was isolated as a light brown powder (20 mg) from silica column chromatography of F53.

Compound **1** (light brown powder): Catechin (4 α →8)-Catechin (Procyanidin B3). UV, λ_{max} 280.5 nm; Electrospray ionization–mass spectrometry (ESI-MS, positive ion mode) m/z 579 [M + H]⁺. ¹³C-NMR (125 MHz, CD₃OD) δ 157.9 (C-5u), 157.2 (C-5t), 156.7 (C-7u), 156.4 (C-7t), 146.9 (C-3u'), 146.7 (C-3't), 146.6 (C-4'u), 146.4 (C-4't), 133.1 (C-1'u, C-1't), 120.6 (C-6'u), 120.2 (C-6't), 116.8 (C-2'u), 116.4 (C-2't), 116.3 (C-5'u), 116.1 (C-5't), 108.0 (C-8t), 98.4 (C-10u; C-10t), 96.9 (C-6t), 96.8 (C-6u), 96.7 (C-8u), 83.2 (C-3u), 74.5 (C-2u), 69.7 (C-2t), 68.2 (C-3t), 39.3 (C-4t), 29.6 (C-4u).

HRFAB-MS: [M + H]⁺: m/z 579 for C₃₀H₂₆O₁₂.

DPPH assay

The antioxidant activity of the isolated compound was performed by the DPPH assay (Indrianingsih *et al.*, 2021). The sample was diluted in methanol in several concentrations, reacted with DPPH (1.01 mM) at room temperature for 30 minutes in dark conditions. The absorbance of the final solution was measured using a UV spectrophotometer at 517 nm. The radical scavenging activity of compound **1** was calculated using

$$\text{DPPH scavenging activity (\%)} = \left(\frac{A_0 - A_1}{A_0} \times 100 \right), \quad (1)$$

where A_0 is the absorbance of the control and A_1 is the absorbance of the sample. The measurement was conducted in triplicate. Quercetin was used as the positive standard in the DPPH assay.

H₂O₂ assay

The capability of compound **1** in the H₂O₂ radical scavenging assay was evaluated according to the literature (Indrianingsih *et al.*, 2015) with slight adjustments. H₂O₂ was diluted in phosphate buffer solution (PBS) (pH 7.4) to obtain the concentration of 40 mmol/l. Compound **1** (4 ml in Aquades) was reacted for 10 minutes with 0.6 ml of H₂O₂. The absorbance of the final solution was measured at 230 nm using a UV spectrophotometer.

Reducing power assay

According to the literature, the reducing power assay was conducted (Indrianingsih *et al.*, 2015). Compound **1** (20 g/ml) in PBS (2.5 ml) was reacted with $K_3Fe(CN)_6$ (2.5 ml), left to stand for 20 minutes at 50°C, and added with trichloroacetic acid (2.5 ml). After centrifugation for approximately 8 minutes, the upper layer (2.5 ml) was reacted with Aquades and $FeCl_3$ (0.5 ml). The final solution was evaluated at 700 nm using a spectrophotometer.

β -Carotene bleaching assay

According to a previous study, the capability of compound **1** in preventing β -carotene bleaching was performed (Indrianingsih *et al.*, 2015). β -carotene (0.2 mg/ml) in $CHCl_3$ was reacted with linoleic acid (20 mg) and Tween 40 (200 mg). After evaporation, distilled water (50 ml) was added, and 4.8 ml of the solution was reacted with 0.2 ml of compound **1** solution in methanol. This solution was incubated at 50°C. The absorbance of the solution was evaluated at 20 minutes intervals at 470 nm.

α -Glucosidase inhibitory assay

The α -glucosidase assay was conducted according to the literature (Indrianingsih *et al.*, 2015). Several concentrations of compound **1** in dimethyl sulfoxide (10 μ l) were mixed with PBS (pH 7, 490 μ l) and 250 μ l of *p*-NPG (3 mmol/l). After being reacted for 5 minutes at 37°C, 250 μ l of the α -glucosidase enzyme (0.065 IU/ml) was added and left to stand for 15 minutes. One milliliter of Na_2CO_3 (0.2 mol/l) was added to stop the reaction, and the absorbance of the final solution was evaluated at 400 nm.

RESULTS AND DISCUSSION

Isolation and structure identification

The chemical structure of compound **1** is illustrated in Figure 1. The ESI-MS of compound **1** recorded in positive ion mode exhibited a protonated ion $[M + H]^+$ at m/z 579, indicating molecular formulas of $C_{30}H_{26}O_{12}$. The 1H -NMR (Table 1) and ^{13}C -NMR spectral data of compound **1** were compared with the literature (Kiss *et al.*, 2008; Köhler *et al.*, 2008; Wang *et al.*, 2015), and structures were identified as procyanidin B3.

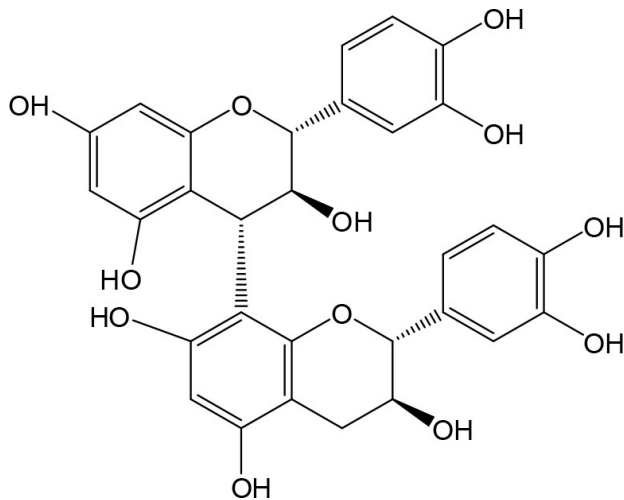


Figure 1. Compound **1** (procyanidin B3).

Several studies reported the bioactivity of procyanidins, such as antiproliferation (Kresty *et al.*, 2011), antioxidant (Fu *et al.*, 2013; Määttä-Riihinen *et al.*, 2005), antimicrobial (Zang *et al.*, 2013), and enzyme inhibitor (Wang *et al.*, 2013) activities. In this study, the isolated procyanidin consisted of two catechin units; meanwhile, there are also existing procyanidins with five to six catechin or epicatechin units or larger polymeric procyanidins (Wang *et al.*, 2015). However, the large polymeric procyanidins were little understood.

Antioxidant activity of compound **1**

The antioxidant activities of compound **1** were evaluated using various assays: H_2O_2 radical scavenging activity, DPPH free radical scavenging activity, β -carotene-linoleate model assay, and reducing power assay. Table 2 shows the result of the DPPH assay and H_2O_2 assay.

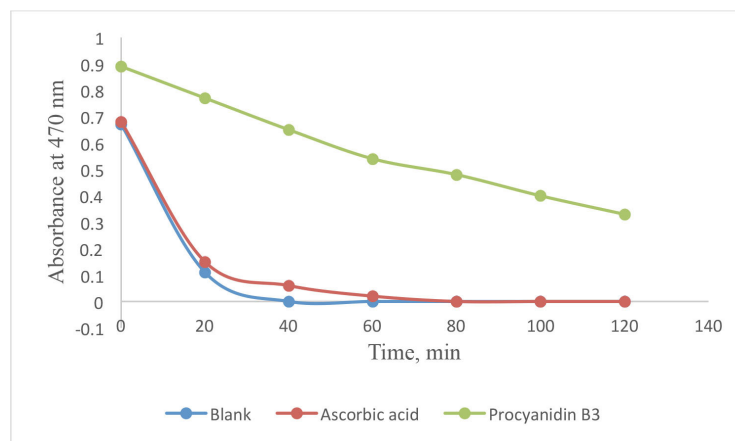
Compound **1** showed the scavenging capacity against DPPH radicals (IC_{50}) of 7.86 ± 0.38 μ g/ml. Quercetin as control exhibited an IC_{50} of 8.48 ± 0.39 μ g/ml. Based on this result, compound **1** has a higher antioxidant activity than quercetin. The good antioxidant activity of procyanidin B3 is probably due to

Table 1. 1H -NMR (500 MHz, CD_3OD) spectroscopic data for compound **1**.

Ring	Carbon	1H -NMR, δ (ppm), J (Hz)
C	2	4.24, d, [9.7]
	3	4.40, m
	4	4.41, d, [7.4]
	5	5.91, d, [2.3]
A	6	5.91, d, [2.3]
	7	
	8	5.80, d, [2.3]
	4a	
B	8a	
	1	
	2	6.78, d, [1.4]
	3	
F	4	
	5	6.67, d, [8.3]
	6	6.47, dd, [2.0; 8.2]
	2	4.72, d, [7.6]
D	3	3.83, ddd, [4.7; 7.1; 7.8]
	4	4 α : 2.75, dd, [5.5; 16.2]
		4 β : 2.49, dd, [8.0; 16.2]
	5	
E	6	6.09, s
	7	
	8	
	4a	
E	8a	
	1	
	2	6.66, d, [1.7]
	3	
	4	
	5	6.71, d, [8.4]
	6	6.25, dd, [1.9; 8.2]

Table 2. The result of the DPPH and H₂O₂ assay of compound 1.

Compound	Antioxidant activity using DPPH assay (IC ₅₀ , µg/ml)	Antioxidant activity using H ₂ O ₂ assay (IC ₅₀ , µg/ml)
1 (procyanidin B3)	7.86 ± 0.41	34.51 ± 1.34
Quercetin	8.48 ± 0.39	—
Gallic acid	—	52.40 ± 0.42

**Figure 2.** The result of the β -carotene bleaching assay of procyanidin B3 at 40 μ g/ml.

the phenolic group of compound 1. A mechanism for the reaction was possible because the DPPH radical-driven catechin oxidation product attacks the A-ring unit, forms hydrophilic dimers, and oxidizes to oligomers (Osman, 2011). The DPPH assay was used for a simple, rapid, and efficient method (Kedar and Singh, 2011). Several studies showed that tocopherol, ascorbic acid, and phenolic compound could reduce DPPH radical form to its stable form (Arya *et al.*, 2011; Liu *et al.*, 2009).

Compound 1 also had scavenging abilities against hydroxide peroxide as shown in Table 2 (IC₅₀) of 34.51 ± 1.34 μ g/ml. The IC₅₀ of gallic acid as control was 52.40 ± 0.42 μ g/ml. The higher capability of compound 1 compared to gallic acid to scavenge free radicals showed that it had better potential as an antioxidant, in concurrence with the result from the DPPH assay. The ability evaluation of the isolated compound to scavenge H₂O₂ needs to be conducted since H₂O₂ could be toxic to the human body if it changed to the hydroxide radicals in cells (Kumar *et al.*, 2012).

The β -carotene-linoleate bleaching assay was conducted to evaluate the isolated compounds' ability to inhibit the bleaching caused by the peroxy radical. The free radicals were formed when oxidized linoleic acid attacked the β -carotene molecules; thus, the β -carotene would undergo decolorization. This system consisted of an aqueous emulsion of linoleic acid and β -carotene that is similar to the food system that usually consists of water and lipid with some emulsifier. Figure 2 presents the ability of compound 1 (procyanidin B3) to prevent the decolorization of β -carotene.

The results showed that compound 1 efficiently prevented the oxidation of β -carotene in the system higher than that of ascorbic acid in the 120 minutes of the time range. Compound 1 retained antioxidant activity of 0.54% while ascorbic acid had 0.02% of activity after 60 minutes of assay; meanwhile, after 120 minutes, compound 1 still retained antioxidant activity

of 0.33%, while ascorbic acid had 0% of activity. A study revealed that flavanols, anthocyanins, and phenolic acid were active in the β -carotene bleaching test (Singhal *et al.*, 2014).

Figure 3 shows the result of the reducing power test of compound 1. This study used ascorbic acid and gallic acid equivalents to express the reducing power capability. It was presented that compound 1 had good reducing power activity of 87.80 mg/g [ascorbic acid equivalent (AAE)] and 50.49 mg/g [gallic acid equivalent (GAE)], in concurrence with H₂O₂ and DPPH radicals scavenging assays. The literature revealed that the antioxidant activity was related to the structure of a constituent, especially the active functional group (NH₂ or OH). The position of the active group also had an important role, as the ortho position was more active than the para and meta position (Bendary *et al.*, 2013).

α -Glucosidase inhibitor activity

Table 3 shows the IC₅₀ values of α -glucosidase inhibitory activities of compound 1. Compound 1 had α -glucosidase inhibitory activity 58.81% ± 0.61% at a concentration of 50 μ g/ml and IC₅₀ of 40.05 ± 0.51 μ g/ml. Meanwhile, the IC₅₀ of quercetin was 4.20 ± 0.01 μ g/ml. A previous study reported that phenolic constituents had a strong inhibitory effect on α -glucosidase compared to acarbose (Zechel and Withers, 2000).

α -Glucosidase inhibitors play an essential role for DM patients with type 2 since they could inhibit the enzyme in the intestine and delay glucose absorption. Natural, safe, and effective α -glucosidase inhibitors from plants, microbes, and fungi were sought to develop functional food for DM patients (Katalinic *et al.*, 2010). A study revealed that polyphenol could inhibit α -glucosidase and α -amylase since they also had good properties of antioxidant activities (Perron and Brumaghim, 2009). This study indicated that the isolated compound from *Q. gilva* leaves,

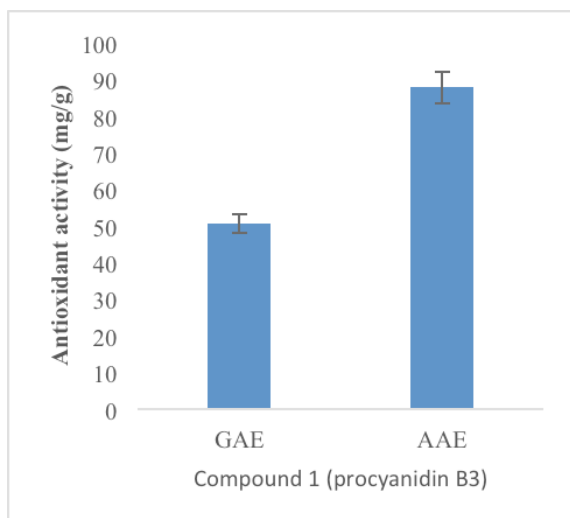


Figure 3. Antioxidant activities of procyanidin B3 using the reducing power assay. AAE: ascorbic acid equivalent; GAE: gallic acid equivalent.

Table 3. α -Glucosidase inhibitory activities of procyanidin B3 from *Q. gilva*.

Compound	α -Glucosidase inhibitory activity (IC_{50} , μ g/ml)	α -Glucosidase inhibitory activity at 50 μ g/ml (%)
1 (procyanidin B3)	40.05 \pm 0.51	58.81 \pm 0.61
Quercetin	4.20 \pm 0.01	—

procyanidin B3, has potential as the natural agent for type 2 DM patients since it is from nature. There is hope that pharmaceutical drugs for DM patients from nature have lower side effects than synthetic drugs (Eurich *et al.*, 2007; Mohammed *et al.*, 2013).

CONCLUSION

In the present study, we have isolated one constituent (procyanidin B3) from the methanol extract of *Q. gilva* leaves. It showed satisfactory antioxidant activities using several assays such as the DPPH assay, H_2O_2 assay, β -carotene bleaching assay, and reducing power assay. The α -glucosidase inhibitory activity against the *Saccharomyces cerevisiae* α -glucosidase enzyme also showed promising results. This result will be helpful as important information for preparing pharmaceutical drugs sourced from nature.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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