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Research article

Antioxidant activity and antidiabetic activities of Northern Thai indigenous edible plant extracts and their phytochemical constituents

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HIGHLIGHTS

- Some selected edible plants in this study provided the potential uses for the prevention of diabetes and its complications.
- The highest content of phenolic and flavonoid were found in *C. mimosoides* Lam. and *G. hirsutum* (Roxb.) Voigt, respectively.
- Among the selected edible plants in this study, *S. terebinthifolius* Raddi provided the highest activity for antioxidants.
- The antiglycation effects of *G. hirsutum* and *P. odoratum* Lour. were stronger than aminoguanidine in the BSA-glucose model.
- Among the selected edible plants in this study, the highest inhibitory effect of α-amylase was found in *B. alba* L.
- Among the selected plants in this study, *S. terebinthifolius* Raddi provided the highest inhibitory activity of α-glucosidase.

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ABSTRACT

Diabetes mellitus is the most common non-infective disease characterized by hyperglycemia (high level of blood glucose). Formation of advanced glycation end products (AGEs) in long termed-hyperglycemia and oxidative stress are the key factors to accelerate diabetic complications. To screen potential candidates for treating diabetes, total phenolic content, total flavonoid content, antioxidant activity from crude extracts of some Thai edible plants were primarily assessed, and the inhibiting potential of diabetes and its complications provided from some of these plants were evaluated in terms of their inhibitory activities of α-amylase, α-glycosidase, and AGEs formation. The highest amounts of phenolic and flavonoid compounds were found in the ethanolic extract of *Caesalpinia mimosoides* (S20, 12.63 ± 1.70 mg GAE/g DW) and *Glochidion hirsutum* (S8, 3.02 ± 0.25 mg CE/g DW), respectively. The highest antioxidant activity was found in *Schinus terebinthifolius* Raddi (S26, 217.94 ± 32.30 μg AAE/g DW) whereas the highest inhibitory activities of α-amylase and α-glycosidase were obtained from *Basella alba* L. (S11, IC_{50} = 0.21 ± 0.01 mg/ml) and *S. terebinthifolius* (S26, IC_{50} = 0.05 ± 0.02 mg/ml) respectively. The inhibitory effects of AGEs formation were studied *in vitro* using two model systems: BSA-glucose and BSA-methylglycoxal (MGO). The extracts of *Glochidion hirsutum* (Roxb.) Voigt (S8, IC_{50} = 0.20 ± 0.01 mg/ml) and *Polygonum odoratum* Lour. (S13, IC_{50} = 0.03 ± 0.01 mg/ml) exhibited the inhibitory activity of AGEs formation derived from glucose (BSA-glucose system) stronger than aminoguanidine (AG) (0.26 ± 0.00 mg/ml), which is a common AGEs formation inhibitory drug. By BSA-MGO assay, the inhibition of some selected extracts in this study (*G. hirsutum*, *G. sphaerogynum*, and *S. terebinthifolius* with IC_{50} = 0.11 ± 0.01, 0.11 ± 0.01, and 0.10 ± 0.00 mg/ml, respectively) were slightly less efficient than AG (the IC_{50} = 0.06 ± 0.00 mg/ml). These results indicated that some selected Thai edible plants in this present study provided potential applications towards the prevention of diabetes and their complications via the inhibitory of α-amylase, α-glycosidase, AGEs formation, and oxidative stress. This fundamental information would be important for alternative drug discovery and nutritional recommendations for diabetic patients.

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1. Introduction

Diabetes mellitus is characterized by abnormally high levels of glucose in the bloodstream called hyperglycemia. The long-term of this effect can cause several serious complications in diabetic patient such as blood vessel damages, heart attack, stroke, and problems with the kidneys, eyes, and feet (Méndez et al., 2010; Thilagam et al., 2013). Chronic hyperglycemia is known to be a major cause of elevation of advanced glycation end products (AGEs), which implicate importantly in the pathogenesis of the diabetic complications (Brownlee, 2001; Ahmed, 2005). The AGEs are formed by the glycation reaction between protein or lipids and sugar in bloodstream and undergoes a series of rearrangements to form AGEs. In addition, various free radicals could be generated during the glycation reactions and enhance oxidative stress, which has an important role in cell or tissue damages as well as in the development of type 2 diabetes mellitus (T2DM) (Asmat et al., 2016). The reduction of blood sugar level, AGEs formation, and oxidative stress are therefore, the critical strategies for prevention of diabetes and their complications.

The inhibitor drugs used currently to reduce hyperglycemia in diabetic patients are acarbose, miglitol and voglibose. However, they are often reported to have diverse side effects such as diarrhea, abdomen distention, meteorism and other intestinal disturbances, with corresponding intestinal pain and flatulence (Yilmazer-Musa et al., 2012; Lebovitz, 1997). Hence, there are several research have been conducted to fine dietary plants that can effectively treat diabetes due to their safety and nutrition (McMacken and Shah, 2017).

Several chemical constituents found in plant, generally called phytochemicals, such as polyphenols, terpenes, and carotenoids have been reported to have the reduction potential of blood sugar level and other factors causing diabetes (Ali Asgar, 2013; Lin et al., 2016; Omar et al., 2016).

Phenolic compounds contain a wide range of molecules that can be classified as simple flavonoids, phenolic acids, complicated flavonoids, and colored anthocyanins. These compounds have one or more aromatic rings linked with hydroxyl substituents. Gallic acid, ferulic acid, caffeic acid, coumaric acid, protocatechuic acid, resveratrol, quercetin and rosmarinic acid are examples of common phenolic compound found in plants (Lin et al., 2016).

In plant food, many phenolic compounds have recently attracted a lot of attention due to their ability to influence starch digestibility and have strong antioxidant properties (Ali Asgar, 2013). These compounds have been also reported to promote health benefits by reducing the risk of diabetes and its complications such as catechins, procyanidins, caffeic acid, chlorogenic acid, *p*-coumaric acid, berberine, quercetin, *o*-coumaric acid, ferulic acid, protocatechuic acid, quercetin, and gallic acid (Aryaeian et al., 2017; Chen et al., 2019; Omar et al., 2016; Choi et al., 2011; Ormazabal et al., 2018; Yang and Kang, 2018; Abdel-Moneim et al., 2017). Furthermore, many phenolic compounds in plant food were also found to have antioxidant activity and the ability to resist the reaction of protein glycation (Ishioka et al., 2015; Odjakova et al., 2012). This can be seen when the antioxidant activities of gallic acid, *p*-coumaric acid, and rutin were tested by 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) free radical and the ferric reducing antioxidant power (FRAP) assays as shown in a research work of Ouffai et al. (2021). These compounds could also show strong inhibitory effect on α-amylase and α-glucosidase (Ouffai et al., 2021).

Different classes of phenolic compounds have diverse biological properties, however, the information about their mechanisms to prevent diseases is still limited (Lin et al., 2016; Redan et al., 2016). So, identifying phenolic constituents could help to get a better sense of the quality and quantity in the studied plants. Furthermore, evaluating the relationship between various polyphenols and bioavailability is necessary to understand their differential health effects.

In addition, several α-amylase and α-glucosidase inhibitors have been found in plants that have practical clinical significance (Thilagam et al., 2013). Screening of the inhibition of α-amylase and α-glucosidase activities are commonly used as key methods for the study of inhibitor efficiency to reduce postprandial hyperglycemia by delaying the digestion and absorption of carbohydrates into the bloodstream (Kumar et al., 2011).

Edible plants are important protective food which are rich of nutrients, vitamins, and dietary fiber. They are also the source of various bioactive pharmaceutical compounds providing several health benefits such as antioxidant, anticancer, antihypertensive, and antidiabetic properties. Many of these bioactive compounds presented in vegetables are terpenoids, carotenoids, phenolics, phytosterols, and glucosinolates (Ağagündüz et al., 2022).

Among 5800 edible plant species in Thailand, over 250 species have been practically used as vegetables in many Thai cuisines (Ponglux et al., 1987; Prachasaisoradech, 1999). Several species of these vegetables have been reported for their anti-diabetic potential (Suttisansanee et al., 2021; Chokthaweepanich and Kaewkumsai, 2019; Platel and Srinivasan, 1997). Due to the high diversity of plant species and diverse food cultures in the Northern part of Thailand, the majority of vegetables in Thailand were found in the northern region (more than 139 species (Deewiset and Khumklang, 1998)). Many indigenous edible plants found in the northern part of Thailand exhibit the anti-diabetes properties such as *Houttuynia cordata* Thunb (Kumar et al., 2014), *Gymnema inodorum* (Lour.) Decne (Srinuanchai et al., 2021), *Aegle marmelos* (L.) Corrêa (Sharma et al., 2007), *B. alba* L. (Bamidele et al., 2014; Ahmed, 2022), *Glinus oppositifolius* (L.) Aug.DC (Behera et al., 2010), *Amaranthus lividus* Linn. (Sangameswaran and Jayakar, 2008), *Dregea volubilis* Benth (Thuy et al., 2021; Natarajan and Dhas, 2013; Natarajan et al., 2020), *S. terebinthifolius* Raddi (da Rocha et al., 2019; Iwanaga et al., 2019), *Tiliacora triandra* (Colebr.) Diels (Katisart and Rattana, 2017; Makinde et al., 2020). However, the information on the anti-diabetic mechanisms, the inhibition of enzymes involved in carbohydrate digestion, and the inhibition of protein glycation are still very limited for these edible plants. Upon our survey, the anti-diabetes properties of some Thai northern indigenous vegetables have also not yet been investigated.

This research mainly focuses on the inhibitory effects of plant extracts from some selected indigenous edible plants found in Northern Thailand on the carbohydrate hydrolyzing enzymes (α-amylase and α-glucosidase activities), AGEs formation and free radicals. The determination of some chemical composition on these plants such as total flavonoid content (TFC), total phenolic content (TPC), and some phytochemical compounds commonly found in food plants were also performed. The information obtained in this research study can be the fundamental information on the nutrition counseling for diabetes prevention and alternative medicine. In addition, it would be useful for further in-depth research for anti-diabetic drug development.

2. Materials and methods

2.1. Chemicals

All chemicals used in this study are analytical grades and used without further purification. The Milli-Q water was used. Ethanol (95%, RCI Labscan, Bangkok, Thailand) was used as a solvent extraction. The Folin-Ciocalteu reagent (2 N, Merck, Germany), gallic acid (≥98%, Sigma-Aldrich, USA) and anhydrous sodium carbonate (99.5%, Lobachemie, India) were used for the determination of the TPC. L-Ascorbic acid was used as a standard reagent and 2,2-diphenyl-1-picrylhydrazyl reagent (DPPH) (Sigma-Aldrich, USA) were employed for the determination of the antioxidant activity. Sodium hydroxide (97%, RCI Labscan, Thailand), Sodium nitrite (Sigma-Aldrich, USA), Aluminium chloride hexahydrate (QRec, New Zealand) and (+) catechin hydrate (Sigma-Aldrich, USA) were purchased for the determination of TFC.

α-Glucosidase enzyme produced from *Saccharomyces cerevisiae* (EC 3.2.1.20), 4-nitrophenyl α-D-glucopyranoside (*p*NPG), and acarbose (≥95%) were used as a positive control standard (which is a reliable antidiabetic treatment), were bought from Sigma-Aldrich Corporation.

Sodium phosphate buffer (PBS, 20 mM) was prepared from di-sodium hydrogen phosphate dihydrate (RCI Labscan, Bangkok, Thailand) and sodium dihydrogen orthophosphate (Ajax Finechem, Auckland, New Zealand). Dimethyl sulfoxide (DMSO) was obtained from Fisher, UK. α-Amylase from *Aspergillus oryzae* (EC: 3.2.1.1, Sigma-Aldrich, USA) was dissolved in 20 mM PBS buffer with 6 mM sodium chloride (PBS/NaCl). 1% starch was prepared by dissolving starch powder in DI water and heating with gentle stirring. Hydrochloric acid (37%, Merck, Germany) was diluted to 1.0 M. Iodine reagent was obtained from 5.0 mM of iodine mixed with 5.0 mM of potassium iodide (Sigma-Aldrich, USA). DMSO solution (20%) was prepared in the PBS/NaCl for crude re-dissolution.

Aqueous formic acid (0.2% v/v, Sigma-Aldrich, USA) and acetonitrile (Sigma-Aldrich, USA) was used as a mobile phase for the analysis of phytochemical constituents using a triple quadrupole liquid chromatography-mass spectrometry. The standard compound of caffeic acid, chlorogenic acid, *p*-coumaric acid, *o*-coumaric acid, catechin, ferulic acid, protocatechuic acid and quercetin were purchased from Sigma-Aldrich, USA and gallic acid from Fluka, Spain.

2.2. Northern Thai indigenous edible plants

Leaves of the indigenous edible plants were collected from the local markets in Northern Thailand (Chiang Mai, Chiang Rai, Phrae, Phayao, Lamphun and Nan provinces) during the year 2018. Those leaves of the edible plants are often utilized in Thai cuisine from the north. The list of the indigenous edible plants along with their scientific names, family names, medicinal properties, and traditional uses were shown in Table 1. The finding shows that some of them have anti-diabetic capabilities as well.

2.3. Sample preparation

The sample indigenous plants were washed and chopped into small pieces. Then, they were dried at 50 °C for 3–5 h in a hot air oven (UN55, Memmert, Germany) and pulverized into fine powder. The obtained powder (1.00 g dry weight) was soaked in 95% ethanol (150 ml) with continuous shaking at 80 rpm, at 37 °C for 72 h (Maxtury-18, DAIHAN Scientific, KOREA). The mixture was then filtered into a round bottom flask. The residual indigenous leaves were re-extracted twice with ethanol. The pooled filtrate solution was dried by using a rotary evaporator at 75 rpm, 60 °C (IKA® RV 10, IKA, Germany). The extract yields were calculated using the following equation: Yield (g/100 g) = (W1x100)/W2, where W1 is the weight of the solvent-free extract residue and W2 is the weight of the dried edible plants. The crude extracts were stored at −20 °C till further use. The dried crude extract was re-dissolved in 95% ethanol (2.0 mg/ml) for the analysis of TPC, TFC, and antioxidant activity. The crude extract was redissolved in dimethyl sulfoxide (20% DMSO/20 mM phosphate buffer pH 6.8) and diluted to different concentrations (0.2, 0.5, 1.0, 2.0 and 10.0 mg/ml) for α-glucosidase inhibitory and α-amylase inhibitory assays.

2.4. Total antioxidant capacity

Total antioxidant capacity was performed following the method of de Oliveira et al. (2009) with minor modification. Antioxidant capacity was determined by using DPPH free radical scavenging activity. The DPPH solution (1.0 ml, 0.3 mM) was added into the extracted samples (100 μl) and shaken. The solution was adjusted to 4.0 ml with ethanol. The mixtures were kept in a dark area at room temperature for 30 min. Then, the absorbance was measured at 515 nm by using a visible spectrophotometer (USB4000, Ocean Optics, US). The antioxidant activity was calculated by comparing the absorbance of the sample solution with the calibration curve of L-ascorbic acid standard. The results were presented as mg L-ascorbic acid equivalent per gram extract (mg AAE/g extract).

2.5. Total flavonoid content (TFC) assay

Total flavonoid content was performed following the method of Khorasani Esmaeili et al. (2015) with minor modification. The TFC was performed by adding 50 μl of the extracted samples into a test tube containing 0.55 M aluminum trichloride (100 μl), 3 M sodium nitrite (50 μl) and 2.5 M sodium hydroxide (250 μl). Then, the mixture was incubated for 30 min. The solution was adjusted to 1.0 ml with ethanol. After that, the absorbance at 510 nm was determined by a visible spectrophotometer (USB4000, Ocean Optics, US). The TFC was evaluated by using the calibration curve of catechin standard. The results are presented as catechin equivalent (CE) in mg per gram dry weight (mg CE/g DW).

2.6. Total phenolic content (TPC) assay

The TPC was determined by using Folin-Ciocalteu's method (de Oliveira et al., 2009). Briefly, the extracted sample (50 μl) was added into the 250 μl of 10% Folin-Ciocalteu' reagent in test tubes. After that, 500 μl of sodium carbonate solution (Na_2CO_3, 7% w/v) followed by 2.0 ml Milli-Q water was added. The mixture solution was then allowed to stand at room temperature for 30 min before absorbance monitoring at 765 nm by a visible spectrophotometer (USB4000, Ocean Optics, US). The TPC was calculated by using a calibration curve of gallic acid standard. The results were presented as gallic acid equivalents (GAE) in mg per gram dry weight (mg GAE/g DW).

2.7. Antidiabetic activities

2.7.1. α-Amylase inhibition assay

α-Amylase inhibitory assay was performed following the method of Akoro et al. (2017) with minor modification. Briefly, the plant extract was diluted with 20% DMSO/PBS/NaCl to prepare in the range of 0.5–2.0 mg/ml α-Amylase (1 U/ml, 250 μl) was added into the diluted extracted solution (250 μl). PBS/Na buffer (250 μl) was added, and the mixture was left in a water bath at 37 °C for 10 min. The mixture was added with 1% soluble starch and incubated at 37 °C for 10 min. The reaction was then terminated by adding 250 μl of 1.0 M hydrochloric acid. After the hydrolysis reaction termination, the remaining starch was determined by adding 10 μl of iodine solution (5 mM I_2 and 5 mM KI). The mixture was diluted with DI water (2.0 ml) and the maximum absorption was measured at 620 nm by a visible spectrophotometer (USB4000, Ocean Optics, US). Blank sample used to eliminate the absorbance produced by plant extract was prepared as above without adding the α-amylase enzyme. Acarbose was used as a positive control at a concentration range of 0.50–10 mg/ml. The calibration of starch was constructed in the range of 0.0–0.1 %w/v for comparative evaluation of the remaining starch in the reaction. The different amounts of starch between enzymatic reaction and a blank sample were the actual value of starch. Then, the α-amylase inhibitory activity was calculated as percentage inhibition as shown in Eq. (A). Finally, the IC_{50} value was determined graphically.

$$\%\text{Inhibition} = \frac{(\text{Absorbance of control} - \text{Absorbance of extract})}{\text{Absorbance of control}} \times 100 \quad \text{(A)}$$

where the absorbance of control means the absorbance value obtained from the solution containing all the reagents without the crude extract and acarbose standard.

2.7.2. α-Glucosidase inhibition assay

α-Glucosidase inhibition assay was performed according to the standard method with minor modification (Shai et al., 2011). The mixture solution containing 112 μl of 20 mM phosphate buffer (pH 6.8), 50 μl of

Table 1. Information of Thai indigenous edible plants collected from Northern Thailand used in this study.

Local Name (Sample code)	Scientific names (Family names)	Medicinal properties	Traditional uses
Kan Aor (S1)	*Oenanthe javanica* (Blume) DC. (Apiaceae)	Hepatoprotective, anti-inflammatory, immune enhancement, hypoglycemic (Lu and Li, 2019)	Food and medicinal (Lu and Li, 2019)
Khao Tong (S2)	*Houttuynia cordata* Thunb. (Saururaceae)	anti-mutagenic, anti-cancer, anti-obesity, anti-viral, anti-bacterial, anti-inflammatory, anti-microbial, anti-allergic, antioxidant and anti-diabetic (Kumar et al., 2014)	Vegetable and aromatic medicinal herb (Kumar et al., 2014)
Chiang Da (S3)	*Gymnema inodorum* (Lour.) Decne. (Asclepiadaceae)	Anti-diabetic, gout, rheumatoid arthritis (Ounjaijean et al., 2021) and anti-inflammatory (Dunkhunthod et al., 2021)	Vegetable and herb tea products (Dunkhunthod et al., 2021)
Bon Tao (S4)	*Hapaline benthamiana* Schott (Araceae)	Antioxidant (Kantadoung et al., 2017)	Food supplement, religious ceremonies, and ornamental plant (Kantadoung et al., 2017)
Bai Ma Pin (S5)	*Aegle marmelos* (L.) Corrêa (Rutaceae)	Antidiarrheal, anti-microbial, anti-inflammatory, antipyretic, and anti-diabetic (Pathirana et al., 2020)	Fruits and vegetables (Pathirana et al., 2020)
Bai Mamao (S6)	*Antidesma ghaesembilla* (Phyllanthaceae)	Antibacterial (Sakunpak and Panichayupakaranant, 2012) Treat anemia and promote blood circulation (Sithisarn et al., 2015)	Medicinal purposes and food product (Sithisarn et al., 2015)
Paem (S7)	*Eleutherococcus trifoliatus* (L.) S. Y. Hu (Araliaceae)	Anti-tumor, rheumatism, anti-inflammatory, arthritis and hypertension (Huang et al., 2021)	Folk medicine, and herbal tea (Huang et al., 2021)
Phak Khi Mot (S8)	*Glochidion hirsutum* (Roxb.) Voigt (Phyllanthaceae)	Leaf: toothaches, carbuncles, urticaria, eczema (Thang et al., 2017)	Folk medicine (Thang et al., 2017)
Phak Khi Kuang (S9)	*Glinus oppositifolius* (L.) Aug.DC. (Molluginaceae)	analgesic, antidiabetic, anti-hyperlipidemic, antihelminthic, antidiarrhoeal, diuretic, antimalarial, antiviral, antimicrobial and antioxidant properties (Martin-Puzon and Rivera, 2015)	Traditional medicine (Martin-Puzon and Rivera, 2015)
Phak Chum Pa (S10)	*Sphenoclea zeylanica* Gaertn. (Sphenocleaceae)	Treat gastrointestinal disorders (Neamsuvan and Ruangrit, 2017)	Folk medicine (Neamsuvan and Ruangrit, 2017)
Phak Pang (S11)	*Basella alba* L. (Basellaceae)	Hypoglycemic potential, and antidiabetic action (Ahmed, 2022).	Vegetable (Ahmed, 2022).
Phak Phet (S12)	*Acmella oleracea* (L.) R. K. Jansen (Asteraceae)	Anti-inflammatory (Stein et al., 2021)	Food flavoring and folk medicine (Stein et al., 2021)
Phak Phai (S13)	*Polygonum odoratum* Lour. (Polygonaceae)	Antioxidant activities (Ahongshangbam et al., 2014)	Herb, aromatic plants (Ahongshangbam et al., 2014)
Phak Man Pla (S14)	*Glochidion sphaerogynum* (Müll.Arg.) Kurz (Euphorbiaceae)	Anti-cancer (breast adenocarcinoma, cell lung cancer and central nervous system tumors) (Puapairoj et al., 2005)	Food and medicinal purposes (Puapairoj et al., 2005)
Phak Yira (S15)	*Ocimum gratissimum* L. (Lamiaceae)	Anti-inflammatory, anti-cancer, treating diarrhea, anti-diabetic (Ugbogu et al., 2021)	Medicinal purposes (Ugbogu et al., 2021)
Phak Siao (S16)	*Bauhinia purpurea* L. (Fabaceae)	Antipsychotic, analgesic activities, antiulcer activity (Zakaria et al., 2011)	Folk medicine (Zakaria et al., 2011)
Phak Hom/Khom Mueang (S17)	*Amaranthus lividus* Linn. (Amaranthaceae)	Antioxidant, antipyretic (Kumar et al., 2010), and anti-diabetic (Sangameswaran and Jayakar, 2008)	Folk medicine and juice (Kumar et al., 2010)
Phak Hak (S18)	*Erythropalum scandens* Blume (Olacaceae)	Antioxidant activity (Somdee et al., 2016)	Edible wild vegetable (Somdee et al., 2016)
Phak Hudt (S19)	*Ficus geniculata* Kurz (Moraceae)	Treat diabetes (Khan et al., 2011)	Traditional medical practices (Khan et al., 2011)
Phi Puya (S20)	*Caesalpinia mimosoides* Lam. (Fabaceae)	Antimicrobial, antioxidant (Bhat et al., 2016) and anticholinesterase (Tangsaengvit et al., 2013)	Folk medicine (Tangsaengvit et al., 2013)
Phaya Yo (S21)	*Clinacanthus nutans* (Burm. f.) Lindau (Acanthaceae)	Antivenom, analgesic, anti-inflammatory, immunomodulating, neuromodulating, anti-diabetic, antioxidant, anti-cancer (Khoo et al., 2018)	Traditional herb and vegetable (Khoo et al., 2018)
Phia Phan (S22)	*Clausena excavata* Burm.f. (Rutaceae)	Wound healing, antioxidant (Albaayit et al., 2015), anti-cancer, antibacterial, antifungal, and immunomodulatory (Arbab et al., 2011)	Folk medicine (Arbab et al., 2011)

(*continued on next page*)

Table 1 (*continued*)

Local Name (Sample code)	Scientific names (Family names)	Medicinal properties	Traditional uses
Yot Nang Laew (S23)	*Aspidistra sutepensis* K. Larsen (Asparagaceae)	-	Relieves back and waist pains (Phonsena and De Wilde, 2010)
Yanang (S24)	*Tiliacora triandra* (Colebr.) Diels (Menispermaceae)	Anti-diabetes (Makinde et al., 2020) and anti-malarial activity (Saiin and Markmee, 2003)	Food (Makinde et al., 2020)
Luk Chi Kuk (S25)	*Amomum* sp. (Zingiberaceae)	Antiulcerogenic effects, hepatoprotective activity, and fungi toxicant (Prakash et al., 2012)	Food and medicine (Prakash et al., 2012)
Sa Riam Malay (S26)	*Schinus terebinthifolius* Raddi (Anacardiaceae)	Microbiological quality, antioxidant activity, activity of α-glucosidase inhibitory and anti-glycation (da Rocha et al., 2019)	Traditional medicine (da Rocha et al., 2019)
Hom Yae (S27)	*Coriandrum* sp. (Umbelliferae)	Analgesic, antibacterial, anti-cancer, anti-convulsant, anti-fungal, anti-inflammatory and antioxidant (Laribi et al., 2015)	Herb, ingredient and flavoring in food (Laribi et al., 2015)
Huan Moo (S28)	*Dregea volubilis* Benth. (Apocynaceae)	Anti-diabetic, antioxidant, anti-diabetes, antibacterial (Amalraj et al., 2021)	Ingredient in medicine (Amalraj et al., 2021)

extracted solution at different concentrations and 20 μl of α-glucosidase (1 U/ml) was incubated at 37 °C for 10 min. After that, the 20 μl of 2.5 mM *p*NPG solution dissolved in 20% DMSO was added. The mixture was then incubated sequentially at 37 °C for 10 min. The reaction was stopped by adding 80 μl of sodium carbonate (0.2 M in 25 ml of distilled water) and the absorbance was measured at 405 nm using a visible spectrophotometer (USB4000, Ocean Optics, US). The α-glucosidase inhibitory activity was calculated as percentage inhibition using the formula shown in equation A. Finally, the IC_{50} value was determined graphically and illustrated as mg crude extract/ml.

2.8. Advanced glycation end products (AGEs) inhibition assay

The AGEs assay based on BSA-glucose and BSA-MGO models were slightly modified from Lunceford and Gugliucci (2005) and Szawara-Nowak et al. (2014). Briefly, BSA protein (0.8 mg/ml) in a phosphate buffer (PBS) pH 7.4 (0.1 mol/L, containing 0.02% sodium azide) was incubated in the dark with either glucose (200 mM) or MGO (15 mM) in the absence or presence of plant ethanolic extract samples at different concentration (1.0 mg/ml, 0.75 mg/ml, 0.5 mg/ml, 0.25 mg/ml, 0.125 mg/ml, and 0.05 mg/ml). After seven days of the incubation, fluorescence intensity (FI) of the sample was measured using excitation wavelength of 340 nm and emission wavelength of 420 nm with a fluorescent spectrometer. Aminoguanidine (AG) was used as positive control. Percent inhibition was calculated as follows (Eq. (B)):

$$\%inhibition = \frac{(Fc - Fcb) - (Fs - Fsb)}{(Fc - Fcb)} \times 100 \quad \text{(B)}$$

where Fc and Fcb represent the fluorescence intensity of the control and control blank, respectively. Fs and Fsb represent the fluorescence intensity of the sample and the sample blank, respectively.

2.9. Determination of phenolic compounds

The crude extract (1.00 mg) was redissolved in HPLC grade methanol (1.0 ml). The mixture was then sonicated (WUC-D03H, Daihan, Korea) at a 50% frequency (or 50% power level), and room temperature until a homogeneous solution was obtained. The solution was filtered with a nylon filter (0.22 μm, 13 mm, Agilent) before the quantitative analysis of some chemical compounds. The analysis was performed by the UHPLC model Shimadzu Nexera X2 LC-30AD coupled to a Shimadzu LCMS 8060 triple quadrupole mass spectrometer equipped with electrospray ionization (Shimadzu, Kyoto, Japan), according to the methodology described by Shanmugam et al. (2018). The chromatographic separation was performed on Shim-pack GISS C18, 3.0 μm particle size and 100 × 2.1 mm i.d. column (Shimadzu, Kyoto Japan). Aqueous formic acid (0.2% v/v) solution (A) and acetonitrile (B) were used as the mobile phase solutions, with a flow rate of 0.2 ml/min under gradient elution at temperature of 40 °C. The gradient profile was as follows: 0–1 min, 10% B; 1–6 min, 15% B; 6–8 min, 20% B; 8–8.5 min, 20% B; 8.5–12 min, 95% B; 12–13 min, 95% B; 13–15 min, 10% B. The injection volume was 2 μl. The LC-MS data were acquired using the Shimadzu lab solutions software.

Electrospray ionization (ESI) was used as an ion source. Mass spectrometry conditions were as follows: the ESI interface volt: 4.00 kV; DUIS corona needle volt:4.50 kV; the ESI interface temperature: 300 °C; desolvation line (DL) temperature: 250 °C; heat block: 400 °C; heating flow: 10.00 l/min; drying gas flow: 10.00 L/min; nebulizing gas flow: 3.00 l/min; collision induced dissociation (CID) Gas: 70 kPa; conversion dynode: -10.00 kV; dwell time: 25 ms. Acquisition mode was multiple reaction monitoring (MRM, also known as selective reaction monitoring – SRM). Electrospray ionization source was operated in a negative mode for all studied compounds.

The mixed standard of caffeic acid, gallic acid, chlorogenic acid, *p*-coumaric acid, *o*-coumaric acid, catechin, ferulic acid, protocatechuic acid and quercetin in the range of 0.05–10 ppm were prepared in methanol as external standards for the identification and determination of the studied compounds by the UHPLC-MS/MS method. The linearity of each standard compound's calibration curves were determined. Individual filtered extract solutions were injected into the UHPLC-MS/MS for analysis. The concentrations of the studied compounds were calculated as mg/g dried crude samples.

2.10. Statistical analysis

The Pearson's correlation (also known as Pearson's R) was used for the correlation analysis of all edible plant results (TPC, TFC, antioxidant activity, α-amylase inhibitory activity, α-glucosidase inhibitory activity, and phytochemical constituent) by mean of the online MetaboAnalyst® 5.0 program. Its value can range from -1 for a perfect negative linear relationship to +1 for a perfect positive linear relationship. A value of 0 (zero) indicates no relationship between two variables. A one-way ANOVA with post-hoc analysis ($p < 0.05$) was also used to select edible plants with strong antioxidant content that differ significantly from others for future anti-glycation inhibition study. Then, a correlation analysis was investigated utilizing all the results obtained from the selected edible plants, including anti-glycation inhibitory action.

3. Results and discussion

3.1. Extraction yield

The dried indigenous edible plants were extracted with ethanol solvent. The average percentage yields of crude extracts obtained from the

extraction was 4.56 ± 2.07%. These extraction yields obtained in this study do not deviate from the report of Khorasani Esmaeili et al. (2015).

3.2. Total phenolic and total flavonoid content

Phenolic compounds or polyphenols belong to the families of phenolic acids, flavonoids, and others. They have an aromatic ring with at least one hydroxyl group, making them good electron donors since their hydroxyl groups can contribute directly to antioxidant activity. Phenolic compounds play a critical role in antioxidant activity by inactivating lipid free radical chains and avoiding the hydroperoxide conversions into reactive oxyradicals causing diabetic complications (de Oliveira et al., 2009). An important therapeutic strategy for treating non-insulin-dependent diabetes is to decrease the postprandial hyperglycemia by delaying the absorption of glucose through the inhibition of the enzymes such as α-amylase, and α-glucosidase (Rhabasa-Lhoret and Chiasson, 2004). Flavonoids are the most widely dispersed secondary metabolites of phenolic compounds in plant. They reduce the pathogenesis of diabetes and its consequences by regulating glucose metabolism, hepatic enzyme activity, and lipid profile (Al-Ishaq et al., 2019), however the mechanisms of action and adverse effects are unclear. According to Funke and Melzig (2005), compounds that can form quinones or lactones, as well as chemicals with a 4-oxo-pyrane structure, induce an inhibiting effect on the activity of α-amylase. Additionally, the molecule's free hydroxyl groups were found to have an impact on a more strong inhibitory effect on α-amylase. Therefore, determining the total phenolic and flavonoid content in plants is critical as a preliminary step in determining antidiabetic potential.

The TPCs of the crude extracts were determined by the Folin-Ciocalteu method and expressed as mg gallic acid equivalent (GAE) per g dried weight of sample. The TPCs in various plant extracts presenting from 0.25 ± 0.03 mg GAE/g to 12.63 ± 1.70 mg GAE/g were shown in Table 2. The highest amount of TPC was found in *C. mimosoides* (S20, 12.63 ± 1.70 mg GAE/g) followed by *G. hirsutum* (S8, 11.57 ± 1.16 mg GAE/g), *S. terebinthifolius* (S26, 10.84 ± 1.86 mg GAE/g), *G. sphaerogynum* (S14, 4.83 ± 0.51 mg GAE/g), and *P. odoratum* (S13, 3.89 ± 0.45 mg GAE/g), respectively.

Because *C. mimosoides* shows the highest amount of the TPC. Therefore, the TPC in crude extract of *C. mimosoides* (444.90 ± 59.90 mg GAE/g crude extract) was compared to that published by Rangsinth et al. (460.25 ± 3.08 mg GAE/g crude extract, Rangsinth et al., 2019). It could be observed that both values are not significantly different ($p < 0.05$). A high content of phenolics (659.21 mg of gallic acid equivalents/g of sample, Folin-Ciocalteau method) and total flavonoids (140.69 mg of rutin equivalents/g of sample, aluminum chloride method) also were observed in *S. terebinthifolius* (de Lima Glória et al., 2017). In addition, the TPC published as mg GAE per g dried weight sample of *G. sphaerogynum* (0.709 mg GAE/g, Bagoudou et al., 2021), and *P. odoratum* (13.03 ± 0.61 mg GAE/g, Ahongshangbam et al., 2014) were discovered. However, no information on *G. hirsutum* was discovered.

The TFCs of the extracts were presented as catechin equivalent (CE) in mg per g of dried weight of sample (mg CE/g DW) (Table 2). The TFCs were presented in the range of 0.40 ± 0.00 mg CE/g to 3.02 ± 0.25 mg CE/g. The top five species with the highest TFC are *G. hirsutum* (S8, 3.02 ± 0.25 mg CE/g), *P. odoratum* (S13, 2.93 ± 0.02 mg CE/g), *A. ghaesembilla* (S6, 2.82 ± 0.23 mg CE/g), *Amomum sp.* (S25, 2.38 ± 0.13

Table 2. Results of the total phenolic and flavonoid contents, the antioxidant activity, α-amylase inhibition, and α-glucosidase inhibition activities of the indigenous edible plants (S1–S28).

Sample Code	TPC content (mg GAE/g DW)	TFC content (mg CE/g DW)	Antioxidant activity (μg AAE/g DW)	α-Amylase inhibition (IC_{50} mg/ml)	α-Glucosidase inhibition (IC_{50} mg/ml)
S1	0.80 ± 0.10	0.81 ± 0.07	3.36 ± 0.34	1.01 ± 0.02	3.01 ± 0.35
S2	1.53 ± 0.18	2.15 ± 0.11	5.23 ± 0.45	1.79 ± 0.08	2.43 ± 0.30
S3	1.92 ± 0.21	2.13 ± 0.24	2.76 ± 0.40	1.41 ± 0.02	2.28 ± 0.23
S4	0.25 ± 0.03	0.40 ± 0.00	1.14 ± 0.04	2.73 ± 0.12	8.72 ± 0.95
S5	2.45 ± 0.29	1.18 ± 0.17	3.84 ± 0.36	1.21 ± 0.01	18.25 ± 1.39
S6	3.40 ± 0.39	2.82 ± 0.23	10.01 ± 0.72	1.63 ± 0.44	4.67 ± 0.44
S7	0.65 ± 0.06	0.60 ± 0.06	0.93 ± 0.09	2.89 ± 0.21	4.64 ± 0.53
S8	11.57 ± 1.16	**3.02 ± 0.25**	181.74 ± 17.28	1.01 ± 0.02	0.59 ± 0.08
S9	0.44 ± 0.05	0.81 ± 0.10	1.30 ± 0.17	2.31 ± 0.05	9.14 ± 1.04
S10	0.80 ± 0.10	0.99 ± 0.11	0.92 ± 0.07	0.85 ± 0.02	5.80 ± 0.53
S11	0.94 ± 0.09	0.75 ± 0.08	1.12 ± 0.06	**0.21 ± 0.00**	2.05 ± 0.22
S12	0.42 ± 0.05	1.11 ± 0.01	1.84 ± 0.03	1.47 ± 0.01	6.53 ± 0.76
S13	3.89 ± 0.45	2.93 ± 0.02	30.52 ± 2.68	1.93 ± 0.01	0.66 ± 0.08
S14	4.83 ± 0.51	1.93 ± 0.02	42.19 ± 1.64	2.21 ± 0.07	2.84 ± 0.00
S15	1.24 ± 0.10	0.77 ± 0.00	3.24 ± 0.11	1.73 ± 0.19	7.93 ± 0.74
S16	0.29 ± 0.01	0.74 ± 0.01	0.35 ± 0.00	1.48 ± 0.00	1.81 ± 0.21
S17	0.40 ± 0.05	0.92 ± 0.02	2.61 ± 0.22	0.49 ± 0.05	3.74 ± 0.03
S18	0.38 ± 0.03	0.68 ± 0.01	2.72 ± 0.00	2.28 ± 0.01	2.97 ± 0.03
S19	0.46 ± 0.01	1.12 ± 0.04	0.94 ± 0.05	1.47 ± 0.02	6.12 ± 0.70
S20	**12.63 ± 1.70**	1.20 ± 0.11	5.16 ± 0.66	1.15 ± 0.06	0.18 ± 0.03
S21	0.59 ± 0.05	1.07 ± 0.02	0.96 ± 0.08	1.98 ± 0.05	7.52 ± 0.49
S22	1.90 ± 0.18	1.67 ± 0.14	1.67 ± 0.19	3.03 ± 0.06	1.25 ± 0.27
S23	0.63 ± 0.07	1.04 ± 0.04	2.24 ± 0.00	0.50 ± 0.02	6.02 ± 0.08
S24	0.59 ± 0.07	0.47 ± 0.02	1.54 ± 0.10	1.39 ± 0.02	3.09 ± 0.38
S25	0.43 ± 0.06	2.38 ± 0.13	3.80 ± 0.56	0.92 ± 0.02	1.12 ± 0.15
S26	10.84 ± 1.86	1.64 ± 0.04	**217.94 ± 32.30**	1.29 ± 0.02	**0.05 ± 0.01**
S27	0.76 ± 0.10	1.07 ± 0.10	0.00 ± 0.00	0.34 ± 0.01	2.70 ± 0.30
S28	2.98 ± 0.36	1.80 ± 0.09	10.34 ± 0.17	0.90 ± 0.01	1.69 ± 0.14

TPC: Total phenolic content; TFC: Total flavonoid content; the IC_{50} for α-glucosidase and α-amylase inhibition activities of acarbose were 1.59 ± 0.08 mg/ml and 0.29 ± 0.02 mg/ml, respectively.

mg CE/g), and *H. cordata* (S2, 2.15 ± 0.11 mg CE/g), respectively. The literature discovered that several standard compounds such as rutin, quercetin, and catechin, could be used to calculate TFC. The published result of TFC of *P. odoratum* (4.92 ± 0.62 mg QE/g of dry weight (Ahongshangbam et al., 2014)), *A. ghaesembilla* (95.72 mg QE/g of extract, (Sayeed, 2011)), and *H. cordata* (0.751 ± 12.4 mg rutin/g of dried weight sample (Cai et al., 2012)) were discovered. On the other hand, the TFC of *G. hirsutum* and *Amomum* sp. were not discovered. The phenolic and flavonoid contents differed slightly from those found in the literature. This could be due to the presence of different amounts of chemical constituent, or the duration, geographical variation, methods of extraction (Aryal et al., 2019). The extracts of *G. hirsutum* and *P. odoratum* are among the top 5 samples with high the TPC and TFC. The results show significant differences ($p < 0.05$) between the TPC and TFC of all plant extracts, except for sample numbers S1, S6, S7, S10, S11, S13, S22, S24, and S27. Total phenolic content measure both polyphenols and flavonoids. As such, the total flavonoid content should be lower than that of total phenolic content. However, the lower amount of phenolic was observed when compared to that of total flavonoids in this study. The similar result could be previously observed and explained by Anh et al. (2021). The first reason to explain this phenomenon is that the higher ratios of total flavonoid and phenolic content is actually present in some studied plants. In addition, there is a limitation of Folin-Ciocalteu reagent usually used for the determination of total phenolic content in term of its specificity because it can react not only the phenolic compounds but also any other reducing molecules in tested samples. While $AlCl_3$ reagent will specifically react with functional groups in the flavonoid molecules such as keto, hydroxyl, and ortho-dihydroxyl groups (Anh et al., 2021).

3.3. Antioxidant capacity

Oxidative stress plays a crucial role in the progression of diabetes and its complications. Many medicinal plants possess potent antioxidant activities, have been reported to have the correlation with their hypoglycemic activities and are considered to be used for the therapeutic treatment of diabetic complications (Rajendiran et al., 2018). Many published studies have suggested that the antioxidant activity of plant extracts is related to their antidiabetic activities and antiglycation activity. As demonstrated by Anh's research, the extracts from *Miliusa velutna* flowers showed a positive correlation between their antioxidant activity and their capacities to inhibit the carbohydrate digestive enzymes (α-amylase and α-glucosidase) (Anh et al., 2021). In addition, some edible and medicinal plants have high antioxidant activity, exhibited strong antiglycation activity (Kaewnarin et al., 2014). The DPPH method was used for these studies because the DPPH free radical is stable and unaffected by certain side reactions of polyphenols, its direct measurement of inhibition, and simplicity and quick analysis (de Oliveira et al., 2009; Kaewnarin et al., 2014). The results of total antioxidant capacity (Table 2) were shown as μg L-ascorbic acid equivalent per gram dried weight of sample (μg AAE/g DW). The indigenous edible plants with significantly higher amounts of total antioxidant capacity than the others were *S. terebinthifolius* (S26, 217.94 ± 32.30 μg AAE/g), *G. hirsutum* (S8, 181.74 ± 17.28 μg AAE/g), *G. sphaerogynum* (S14, 42.19 ± 1.64 μg AAE/g), and *P. odoratum* (S13, 30.52 ± 2.68 μg AAE/g). In addition, *D. volubilis* (S28, 10.34 ± 0.17 μg AAE/g), and *A. ghaesembilla* (S6, 10.01 ± 0.72 μg AAE/g) presented a moderate antioxidant capacity.

The statical analysis demonstrates a moderate correlation between antioxidant activity and TPC ($r = 0.57$, $p < 0.05$) for all extracts, which is higher than the correlation between antioxidant activity and TFC ($r = 0.42$, $p < 0.05$). Plants with high levels of TPC and TFC tend to have high antioxidant capacity. Over 80 percent of the antioxidant activity from plant extracts have been proved to be contributed from their phenolic compounds (Ouffai et al., 2021; Indrianingsih et al., 2015).

The antioxidant activity of *C. mimosoides*, which has the highest TPC and thus is expected to have high antioxidant, was 5.16 ± 0.66 g AAE/g. The antioxidant activities reported as the IC_{50} measuring by the DPPH assay of *C. mimosoides* and *S. terebinthifolius*, which has the highest antioxidant activity, were compared. It was discovered that *C. mimosoides* shows a higher IC_{50} (8.20 ± 0.29 μg/ml, Rangsinth et al., 2019) than *S. terebinthifolius* (3.7 ± 1.6 μg/mL, Rocha et al., 2018). This could be because individual phenolic compounds have different levels of antioxidant activity depending on their structure and chemical function.

3.4. α-Amylase and α-glucosidase inhibition assays

The most common carbohydrate in the diet is starch which consists of amylose (linear polymer of α-D-glucose units linked by α-1,4 glycosidic linkages) and amylose (branched polymer of α-D-glucose units linked by α-1,4 and α-1,6 glycosidic linkages). Pancreatic α-amylases and intestinal α-glucosidases are important enzymes in the carbohydrate digestion pathways, leading to the release of monomeric glucose molecules that are absorbed into the bloodstream (Ali Asgar, 2013). The inhibition of these enzyme's activities can delay the carbohydrate digestion thus leading to the effective retardation of the monosaccharide absorption and blood glucose elevation. Carbohydrate digestive enzyme inhibitors, therefore, play a potential roles as chemotherapeutic agents for type II diabetes mellitus (Indrianingsih et al., 2015). Though acarbose, miglitol and voglibose, which are commonly used to reduce blood glucose levels, they are reported to cause side effects such as diarrhea, abdomen distention, meteorism and other intestinal disturbances, with corresponding intestinal pain and flatulence (Yilmazer-Musa et al., 2012; Lebovitz, 1997).

The half-maximal inhibitory concentration (IC_{50}) for α-glucosidase and α-amylase inhibition activities of the indigenous vegetable extracts were shown in Table 2, respectively. The IC_{50} values for both inhibition activities were found in a range of 0.05 ± 0.02 to 18.25 ± 1.39 mg crude extract/ml and 0.21 ± 0.01 to 3.03 ± 0.06 mg crude extract/ml, respectively. While the IC_{50} for α-glucosidase inhibition activity and α-amylase inhibition activity of acarbose were 1.59 ± 0.08 mg/ml and 0.29 ± 0.02 mg/ml, respectively. The lowest IC_{50} value for α-glucosidase inhibition was found in *S. terebinthifolius* (S26, 0.05 ± 0.02 mg/ml), followed by *C. mimosoides* (S20, 0.18 ± 0.03 mg/ml), *G. hirsutum* (S8, 0.59 ± 0.08 mg/ml) and *P. odoratum* (S13, 0.66 ± 0.08 mg/ml), which significantly showed a higher level of inhibition than the acarbose standard ($p < 0.05$). According to the literature, the extract of *S. terebinthifolius* has a low IC_{50} value of 16.13 ± 0.49 g/ml for α-glucosidase inhibition (da Rocha et al., 2019), while information for *C. mimosoides* was not found. The statistical analysis showed a significant negative correlation between α-glucosidase inhibition and TPC ($r = 0.35$), TFC ($r = 0.51$), and antioxidant activity ($r = 0.32$) for all the extracts. According to the results, the edible plants with the highest α-glucosidase inhibitory activity are among the Top 5 with the highest TFC. The results indicate that TPC and TFC positively correlate to antioxidant capacity, α-glucosidase inhibition activity, which was also discovered in a previous study (Ramkumar et al., 2010).

The lowest IC_{50} value for α-amylase inhibition was found in the extract of *B. alba* (S11, 0.21 ± 0.01 mg/ml) followed by *Coriandrum* spp. (S27, 0.34 ± 0.01 mg/ml), *A. lividus* (S17, 0.49 ± 0.05 mg/ml) and *A. sutepensis* (S23, 0.50 ± 0.02 mg/ml). Only *B. alba* significantly showed a higher level of inhibition than the acarbose standard ($p < 0.05$). According to Tiwari's research, *B. alba* exhibits no inhibition for α-glucosidase and α-amylase (Tiwari et al., 2013). However, Ahmed recently proposed that *B. alba* has hypoglycemic effects. Its solutions (2% and 4% powder) are more effective to bind with glucose than 2% wheat bran solution. Its solution also delays the diffusion of glucose through the dialysis membrane. It also demonstrated that glucose diffusion was entirely slowed until 120 min in a starch digestibility assay, like acarbose, which had no glucose diffusion until 240 min. This may be due to the *B. alba* contains a high concentration of polysaccharides, which have been reported to have potent antidiabetic effects (Ahmed, 2022).

The statistical analysis showed a week negative correlation between α-amylase inhibition and TFC ($r = 0.28$), but no correlation between α-amylase inhibition and antioxidant activity and TPC,

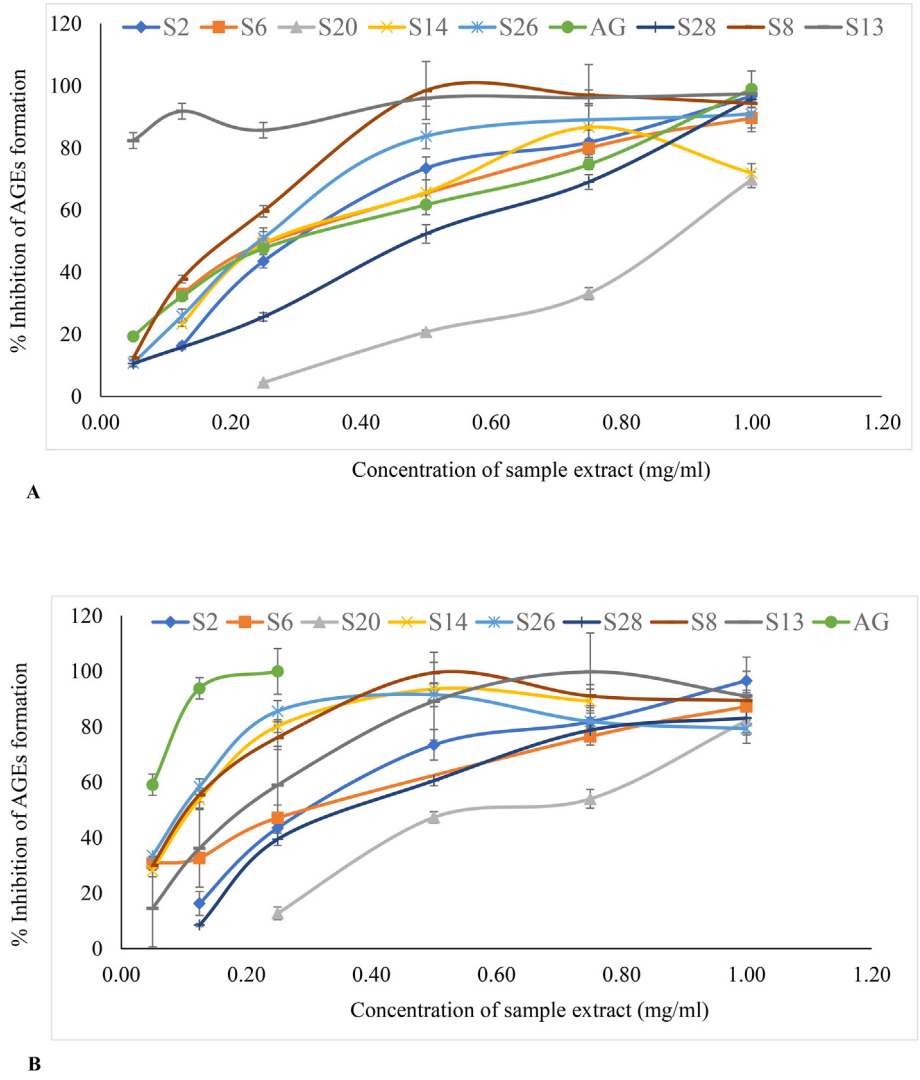

Figure 1. Anti-AGEs formation activity of the selected plant extracts at different concentrations in BSA-glucose model (A), and in BSA-MGO model (B). Aminoguanidine (AG) was used as a positive control.

respectively. The results also found that a group of edible plant extracts in the top 5 samples with low IC_{50} for the inhibitory activities of α-glucosidase and α-amylase is different. Additionally, a week correlation (r = 0.26) was observed between α-glucosidase and α-amylase inhibitory activities. The amounts of phenolic compounds in plant extracts have been founded to be linked with their inhibitory capacity of the carbohydrate-hydrolyzing enzymes in many studies. However, the level of phenolic contents of plant extracts is not always correlated with their inhibitory efficiency for α-amylase and α-glucosidase. It is possible that other factors such as the specific type of phenolic compounds and the interaction among them may be also important for the inhibitory activity (Xiong et al., 2020)

The extracts of *S. terebinthifolius* (S26), *C. mimosoides* (S20), *G. hirsutum* (S8), and *P. odoratum* (S13) exhibited comparable activities against α-glucosidase to acarbose, whereas *B. alba* (S11) extracts obtained similar activity against α-amylase to acarbose. Therefore, these plants can be recommended as potential natural sources for further investigation of antidiabetic medication research.

3.5. Advanced glycation end products (AGEs) inhibition assay

Advanced glycation end products (AGEs) are the result of protein glycation occurring by Maillard reaction in which the amine group of proteins or lipid molecules reacts with carbonyl group of reducing sugar and rearranged into stable Amadori products (Ahmed, 2005). During protein glycation, methylglyoxal (MGO), an intermediate of AGEs, is produced (Lv et al., 2011; Son and Shim, 2015). It is a highly reactive dicarbonyl compound and serves as a major precursor in the formation of AGEs (Allaman et al., 2015).

Several drugs such as aminoguanidine, metformin, carnosine and tenilsetam have been found to inhibit AGEs formation and proved to be effective against diabetic complications (Rahbar and Figarola, 2003; Yoon and Shim, 2015). However, some serious side effects such as anemia, atrial fibrillation, congestive heart failure, myocardial infarction, and gastrointestinal disturbance have been reported (Freedman et al., 1999). Therefore, much effort has been invested in a search of dietary plants effectively prevent and ameliorate AGEs-mediated diabetic complications (Wu et al., 2011).

To evaluate the inhibitory effects of the edible plant extracts on AGEs formation in the present study, two fluorescence-based model systems were adapted from Lunceford and Gugliucci (2005) and Szawara-Nowak et al. (2014). BSA-glucose and BSA-methylglyoxal (MGO) systems were used to monitor AGEs levels induced by glucose and MGO respectively. Due to there are several reported that anti-glycation activity tends to be correlated with antioxidant activity (Ramkissoon et al., 2013), the edible plants with significantly higher antioxidant activity ($p < 0.05$) than the others (S2, S6, S8, S13, S14, S20, S26, and S28), were selected for the investigation of AGEs formation inhibition.

In this work, the statistical analysis demonstrated a strong correlation between antioxidant activity and anti-glycation inhibitory as measured by the BSA-glucose assay ($r = 0.61$) in the selected edible plant extract, which had significantly higher antioxidant significantly than the others. However, antioxidant activity and anti-glycation inhibition as measured by the BSA-MGO assay had a moderate correlation ($r = 0.33$).

The experimental results obtained from both model systems (BSA-glucose and BSA-MGO) indicated that all selected plant extract exhibited a potential inhibitory effect of AGEs formation (Figure 1). All plant extracts provided stronger inhibition of fluorescent AGEs formation when higher concentrations were added. Sample number S8 provided the highest inhibition of AGEs formation at 0.5 mg/ml for both model systems: BSA-glucose and BSA-MGO (98.5% and 89.4%, respectively).

The comparison of the inhibitory effects of all sample plant extracts were done by using the IC_{50} values against AGEs formation for both model systems as shown in Figure 2. In BSA-glucose model system (Figure 2A), *G. hirsutum* (S8) and *P. odoratum* (S13) (the $IC_{50} = 0.20 \pm 0.01$ mg/ml and 0.03 ± 0.00 mg/ml, respectively) provided the inhibitory effects higher than Aminoguanidine (AG) (The $IC_{50} = 0.26 \pm 0.01$ mg/ml) which is a common AGEs formation inhibitor drug (Rahbar and Figarola, 2003; Yoon and Shim, 2015). The IC_{50} for AGEs inhibitory of *A. ghaesembilla* (S6, 0.24 ± 0.01 mg/ml), *G. sphaerogynum* (S14, 0.26 ± 0.01 mg/ml) and *S. terebinthifolius* (S26, 0.24 ± 0.02 mg/ml) were found to be very close to that of AG indicating their similar AGEs inhibitory efficiency compared to AG.

BSA-MGO assay was also performed to evaluate the middle stage of protein glycation in which a major α-dicarbonyl compound, MGO is formed through degradation and oxidation of glucose. MGO is more reactive in linking with an amino group of protein and leads to AGEs formation (Wang et al., 2011). By the comparison of the IC_{50} against AGEs formation in the BSA-MGO system (Figure 2B), the result showed that the inhibition of all extracts in this study were less efficient than AG (The $IC_{50} = 0.06 \pm 0.00$ mg/ml) in this stage. However, the IC_{50} of sample number S6, S8, S13, S14, and S26 obtained by the BSA-MGO assay (0.25 ± 0.02, 0.11 ± 0.01, 0.20 ± 0.01, 0.11 ± 0.01, and 0.10 ± 0.00 mg/ml, respectively) were still less than that of AG tested by BSA-glucose assay (0.26 ± 0.00 mg/ml). This suggested that the AGEs inhibitions of these plant extracts by interfering with MGO were greater efficient than by interfering glycation of glucose. It may be related to the fact that the formation of AGEs by MGO was faster than glucose (Lo et al., 1994; Ahmed, 2005).

Due to these results demonstrated that the selected plant extracts in this study have anti-AGEs formation activity greater or close to AG which is known to be used as a drug for diabetic complication treatment, they might be used as candidates for the treatment of several diabetic complications.

3.6. Analysis of phenolic compounds

Polyphenols, also known as phenolic chemicals, are secondary metabolites produced by plants via the pentose phosphate, shikimate, and phenylpropanoid pathways. Polyphenols contain a wide range of molecules that can be classified as simple flavonoids, phenolic acids, complicated flavonoids, and colored anthocyanins. Common phenolic compounds in plants were gallic acid, caffeic acid, ferulic acid, protocatechuic acid, coumaric acid, ellagic acid, resveratrol, quercetin, and rosmarinic acid (Lin et al., 2016). Phenolic compounds have been shown to improve starch digestibility and have strong antioxidant effects (Ali Asgar, 2013), reducing the risk of metabolic syndrome and type 2 diabetes complications (Lin et al., 2016).

Polyphenols are conjugated to glucuronide, sulphate, and methyl groups, in the gastrointestinal mucosa and inner tissues. It is broken down into a variety of low molecular weight phenolic acids by bacteria in the colon. However, the biological characteristics of conjugated derivatives and microbial metabolites have rarely been investigated, there

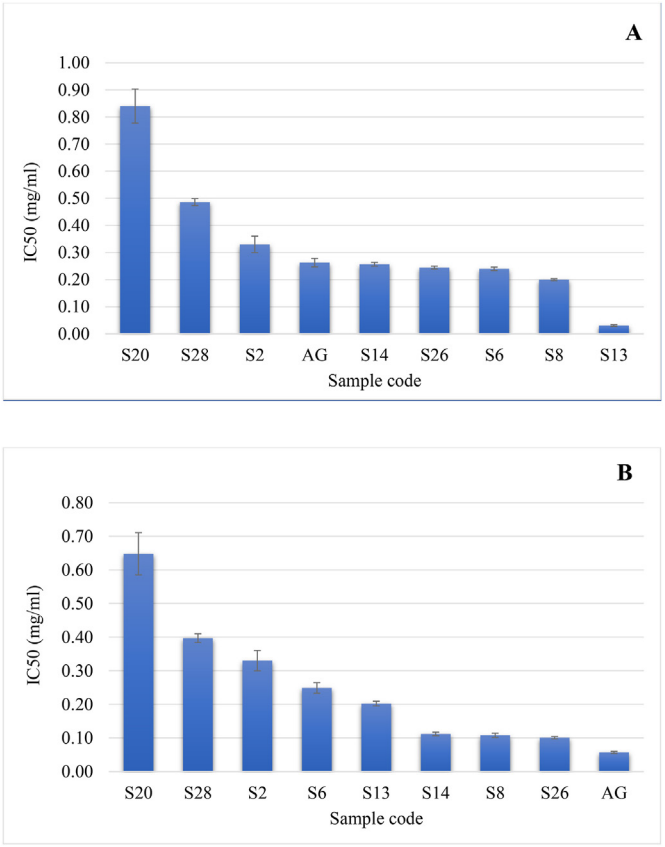

Figure 2. Comparison of the concentrations of crude plant extract at 50% inhibition (IC_{50}) of fluorescent advanced glycation end products (AGEs) formation in BSA-glucose model (A), and in BSA-MGO model (B). Aminoguanidine (AG) was used as a positive control.

is still a need for more research (Scalbert et al., 2002). As previously introduced, phenolic compounds have various biological properties depending on the category of chemicals. Additionally, there is little knowledge about their mechanism (Lin et al., 2016; Redan et al., 2016). Analyzing phenolic components and investigating the correlation of their bioactivities may therefore result in improving information of the studying edible plants.

The compound of caffeic acid, gallic acid, chlorogenic acid, *p*-coumaric acid, *o*-coumaric acid, catechin, ferulic acid, protocatechuic acid, quercetin, which are among the most phenolic chemicals in plants (Lin et al., 2016; Yu et al., 2021), were investigated. Phytochemical constituents were determined by a UHPLC-QqQ-LC-MS/MS. The correlation coefficients (r^2) on the calibration curve of all external standards were acceptable at 0.995. The precursor and target products and some confirmation product with associated collision energies and the retention time of the phenolic compounds were presented in Table 3. Almost all studied compounds were ionized by using negative mode because the MS results of the compounds show that the negative ionization has more intensity values, and the signal-to-noise ratio was higher in negative ionization mode compared to positive mode. The content of the studied chemical compounds, expressed as μg/g dried crude samples, were presented in Table 4. The highest concentration of each studied compound detected in crude extracts was indicated in bold. The highest amounts of ferulic acid (472.10 ± 16.52 μg/g crude) and *p*-coumaric acid (3309.80 ± 165.49 μg/g crude) were found in the *G. inodorum* (S3), chlorogenic acid (7058.10 ± 317.61 μg/g crude) was found in the *F. geniculata* (S19). Q (4665.20 ± 233.26 μg/g crude) was found in the *D. volubilis* (S28). While *o*-coumalic acid was not found in any of the studied edible plants. It was found that all the investigated polyphenol compounds are present in the crude extract of *P. odoratum* (S13).

Table 3. The precursor, target products, and some confirmation products with associated collision energies and their retention time of the phenolic compounds.

Compounds	Molecular formula	IM*	Precursor (m/z)	Products (m/z)								RT* (min)
				QT* (m/z)	Q1 Pre-Bias (eV)	CE (eV)	Q3 Pre-Bias (eV)	CT* (m/z)	Q1 Pre-Bias (eV)	CE (eV)	Q3 Pre-Bias (eV)	
Caffeic acid	$C_9H_8O_4$	ESI-	178.8	135.20	19	18	12	-	-	-	-	6.638
Gallic acid	$C_7H_6O_5$	ESI-	169.1	125.20	12	17	12	-	-	-	-	2.221
Chlorogenic acid	$C_{16}H_{18}O_9$	ESI-	352.95	191.05	17	20	11	-	-	-	-	3.277
p-coumaric acid	$C_9H_8O_3$	ESI-	162.85	119.00	17	15	17	-	-	-	-	9.353
o-Coumaric acid	$C_9H_8O_3$	ESI-	163.0	119.00	18	15	23	-	-	-	-	11.553
Catechin	$C_{15}H_{14}O_6$	ESI-	289.25	245.20	15	15	15	205.20	11	17	13	5.173
Ferulic acid	$C_{10}H_{10}O_4$	ESI-	193.0	134.10	10	15	13	178.05	21	15	16	10.317
Quercetin	$C_{15}H_{10}O_7$	ESI-	300.75	151.20	15	22	13	179.00	15	20	17	12.102

* Remark: RT: retention time; IM: ionization mode; QT: quantification transition mass (target mass); CT: confirmation transition mass.

Table 4. Phytochemical compound contents found in the crude extracts of the studied indigenous edible plants.

Sample Code	Phytochemical compound contents (μg/g dried crude extract)							
	CA (ug/g)	CGA	GA ug/g	PCA	C	PTC	Q	FA
S1	845.30 ± 38.04	191.90 ± 8.64	8.90 ± 0.40	102.10 ± 4.59	ND	188.70 ± 8.49	1140.00 ± 39.90	116.30 ± 4.59
S2	572.40 ± 24.61	2723.60 ± 62.64	17.40 ± 0.75	101.20 ± 4.35	ND	229.40 ± 9.18	563.70 ± 19.73	111.60 ± 4.41
S3	17.20 ± 1.03	95.20 ± 5.71	1.00 ± 0.06	**3309.80 ± 165.49**	**117.90 ± 6.58**	64.90 ± 2.92	ND	**472.10 ± 16.52**
S4	20.90 ± 1.25	137.80 ± 8.27	ND	8.70 ± 0.52	ND	53.10 ± 2.39	ND	26.70 ± 1.05
S5	43.10 ± 2.59	125.70 ± 7.54	0.70 ± 0.04	165.70 ± 9.94	97.30 ± 5.84	69.90 ± 3.15	ND	48.70 ± 1.92
S6	**1323.60 ± 46.33**	89.60 ± 3.14	9.60 ± 0.34	1560.20 ± 54.61	ND	193.30 ± 7.73	253.20 ± 8.86	127.30 ± 5.03
S7	472.50 ± 28.35	304.70 ± 18.28	11.80 ± 0.71	70.50 ± 4.23	ND	59.20 ± 2.66	ND	43.50 ± 1.72
S8	41.40 ± 2.48	88.60 ± 5.32	10757.10 ± 225.90	233.90 ± 14.03	ND	115.40 ± 5.19	ND	28.90 ± 1.14
S9	13.80 ± 0.83	88.30 ± 5.30	10.50 ± 0.63	18.40 ± 1.10	64.10 ± 3.85	ND	ND	17.70 ± 0.70
S10	168.10 ± 10.09	109.40 ± 6.56	10.30 ± 0.62	69.60 ± 4.18	ND	48.80 ± 2.20	ND	25.90 ± 1.02
S11	20.90 ± 1.25	115.20 ± 6.91	ND	16.20 ± 0.97	ND	44.30 ± 1.99	ND	54.90 ± 2.17
S12	61.20 ± 3.67	105.50 ± 6.33	5.10 ± 0.31	67.10 ± 4.03	39.40 ± 2.36	50.00 ± 2.25	ND	185.50 ± 7.33
S13	164.90 ± 9.89	183.10 ± 10.99	1241.50 ± 74.49	300.80 ± 12.03	44.20 ± 2.19	274.80 ± 9.62	2221.10 ± 51.09	144.20 ± 5.70
S14	436.20 ± 18.89	304.40 ± 13.18	6641.90 ± 86.34	190.60 ± 8.25	ND	351.70 ± 12.31	16.60 ± 0.58	35.60 ± 1.41
S15	1285.20 ± 64.26	100.70 ± 5.04	48.40 ± 2.42	116.50 ± 5.83	ND	164.20 ± 7.39	ND	119.90 ± 4.74
S16	55.50 ± 3.33	122.40 ± 7.34	38.50 ± 2.31	7.10 ± 0.43	ND	50.70 ± 2.28	ND	30.70 ± 1.21
S17	17.10 ± 10.03	112.20 ± 6.73	ND	15.10 ± 0.91	ND	25.50 ± 1.15	ND	21.00 ± 0.83
S18	ND	102.80 ± 6.17	ND	3.10 ± 0.19	ND	39.40 ± 1.77	ND	17.60 ± 0.70
S19	266.90 ± 16.01	**7058.10 ± 317.61**	28.00 ± 1.68	39.50 ± 2.37	ND	785.20 ± 18.45	ND	22.90 ± 0.90
S20	1286.50 ± 37.31	1250.10 ± 36.25	**91374.80 ± 4568.74**	251.40 ± 7.29	ND	**1197.40 ± 33.53**	666.30 ± 23.32	ND
S21	34.30 ± 2.06	109.40 ± 6.56	8.40 ± 0.50	45.60 ± 2.74	ND	41.90 ± 1.89	ND	32.90 ± 1.30
S22	ND	ND	ND	236.20 ± 14.17	ND	52.20 ± 2.35	ND	ND
S23	46.10 ± 2.77	107.40 ± 6.44	3.20 ± 0.19	452.20 ± 19.04	ND	43.50 ± 1.96	ND	303.00 ± 11.97
S24	17.30 ± 1.04	127.50 ± 7.65	0.60 ± 0.04	23.70 ± 1.42	ND	45.40 ± 2.04	ND	25.30 ± 1.00
S25	ND	ND	ND	22.30 ± 1.34	ND	0.00 ± 0.00	ND	22.40 ± 0.88
S26	60.60 ± 3.64	125.10 ± 7.51	20587.30 ± 555.86	85.10 ± 5.11	ND	580.70 ± 16.48	32.90 ± 1.15	ND
S27	223.60 ± 8.94	112.80 ± 4.51	13.00 ± 0.52	252.80 ± 5.84	ND	202.10 ± 9.09	31.30 ± 1.10	156.00 ± 6.16
S28	129.00 ± 5.16	105.00 ± 4.20	44.00 ± 1.76	192.90 ± 7.72	ND	604.30 ± 24.17	**4665.20 ± 233.26**	333.80 ± 13.35

CA: caffeic acid; GA: gallic acid; CGA: chlorogenic acid; PCA: *p*-coumaric acid; OCA: *o*-coumaric acid; C: catechin; FA: ferulic acid; PTC: protocatechuic acid; Q: quercetin; ND: not detectable.

The highest gallic acid substance was found in the *C. mimosoides* (S20, 91374.80 ± 4568.74 μg/g extract). Furthermore, the contents of gallic acid found in *S. terebinthifolius* (S26), *G. hirsutum* (S8), *G. sphaerogynum* (S14), and *P. odoratum* (S13) were higher significantly than those found in the other studied edible plants. These findings result in the TPC levels found in those samples are significantly higher than those found in the other samples (Table 2) because gallic acid was used as a reference standard solution for TPC analysis. It also was found that there was a very strong correlation ($r = 0.91$) between the content of gallic acid and the TPC. However, the finding demonstrates that antioxidant activity and gallic acid content have a weak association ($r = 0.21$). This observation could be used to explain why *C. mimosoides* (S20) exhibits a moderate antioxidant activity despite having the highest TPC.

The content of protocatechuic acid is also strongly correlated with TPC, with coefficient of 0.72. The IC_{50} for α-glucosidase inhibitory activity is correlated significantly with the content of quercetin ($r = 0.24$), gallic acid ($r = 0.28$), protocatechuic acid ($r = 0.30$). The IC_{50} for α-amylase inhibitory activity is correlated significantly with ferulic acid content ($r = 0.26$). According to the results, the capacity of polyphenols to inhibit digestive enzymes is dependent on their structure and interaction, which may be important factors for inhibitory activity (Xiong et al., 2020). The IC_{50} for anti-glycation inhibitory activity (BSA-MGO

assay) is correlated significantly with catechin content ($r = 0.45$). This result was supported by the previous study that flavonoids developed a morn significant inhibitory effect on methylglyoxal medicated protein modification (Wu and Yen, 2005). Another phenolic compound produced by plants should be studied further to learn more about its diabetes-inhibitory activities.

4. Conclusion

Local indigenous edible plants from Northern Thailand were collected and performed ethanolic extraction. *In vitro* anti-diabetic abilities by means of α-glucosidase inhibition and α-amylase inhibition activities including inhibition of advanced glycation end-product formation of the crude extract were investigated. The plant extracts were also studied for total phenolic content, total flavonoid content, antioxidant activity and some diabetic preventive phytochemical constituents. The obtained IC_{50} values for α-glucosidase inhibition and α-amylase inhibition activities were compared to those obtained from the standard anti-diabetic drug (Acarbose).

The extracts of *S. terebinthifolius* (S26), *C. mimosoides* (S20), *G. hirsutum* (S8), and *P. odoratum* (S13) had comparable α-glucosidase inhibitory activities to acarbose, while the extracts of *B. alba* (S11) had comparable α-amylase inhibitory activity to acarbose. The inhibitory effects of *G. hirsutum* (S8) and *P. odoratum* (S13) were stronger than the aminoguanidine (AG) drug in the BSA-glucose model system. The extracts of *A. ghaesembilla* (S6), *G. sphaerogynum* (S14), *S. terebinthifolius* (S26) show the same AGE inhibitory efficacy as AG. Those extracts were effective in the anti-glycation base BSA-MGO assay, although their IC_{50} was still lower than that of AG. Therefore, these plants can be recommended as potential natural sources for further investigation of antidiabetic medication research. Human dose-selecting studies and well-controlled long-term human studies would help to optimize the beneficial effects of those extracts. For a better understanding of the effect on anti-diabetics, more research on phytochemical constituents is needed. The preliminary findings could lead to more in-depth research in animals and humans, as well as community dissemination. The beneficial uses of indigenous edible plants are also an important alternative natural nutrition for treating and delaying diabetes. The information obtained in this study can serve as a guideline in pharmaceutical research to conduct more studies on these plants from other point of view. Also, it would be beneficial for nutritional counseling and diabetes management.

Declarations

Author contribution statement

Plaipol Dedvisitsakul, Kanchana Watla-iad: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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