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SHORT COMMUNICATION

Alpha-amylase and Alpha-glucosidase Inhibitory Activities of Philippine Indigenous Medicinal Plants

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Abstract

In the Philippines, medicinal plants still provide the first line of therapeutic remedies and their reported efficacy in traditional treatments provides an opportunity for drug discovery and development. The study aimed to evaluate *in vitro* commonly used Philippine medicinal plants for their alpha-amylase and alpha-glucosidase inhibitory activities as potential sources of antidiabetic agents. The study emphasised the inhibitory activities of 54 medicinal plants against α-amylase and α-glucosidase enzymes. The findings revealed 7 medicinal plants with the highest alpha-glucosidase inhibitory activity of ≥ 50% and 3 with alpha-amylase inhibitory activity of ≥ 20%. Ethyl acetate extract of *Cycas* sp. exhibited the highest α-glucosidase inhibitory activity with 83.87% ± 1.52 followed by the aqueous extract of *cf. Calyptranthera* sp. With 82.07% ± 0.14 with Acarbose as the reference standard (99.71% ± 0.63) at 10µg/mL (w/v) concentration. For the alpha-amylase inhibitory assay, the highest bioactivity was observed in ethyl acetate extract of *Curcuma longa* L. (39.44% ± 1.56) with Acarbose as the reference standard (51.59% ± 0.98) at 10µg/mL (w/v) concentration. These findings suggest the potential of the above-mentioned plants as sources of alpha-amylase and alpha-glucosidase inhibitors that may be used as antidiabetic agents.

Keywords: Alpha-amylase, Alpha-glucosidase, Diabetes, Medicinal Plants

1. Introduction

Medicinal plants play an important role in the treatment of Diabetes Mellitus (DM), particularly in developing and least-developed countries, where accessibility to modern treatments is limited. DM is a common chronic metabolic disease that affects millions of individuals worldwide. Clinically, it is mainly characterised by insulin deficiency (Type 1) and insulin inefficiency (Type 2) or both that lead to hyperglycemia. The most prevalent form of diabetes affecting 90-95% of diabetics worldwide is Type 2 diabetes, which is associated with elevated Postprandial Hyperglycemia (PPHG)[1,2]. Global statistics revealed that the number of people getting affected every year is increasing. A study by Saeedi *et al.*, presented that there is likely a 10.2% (578 million) increase in diabetic patients by 2030 from 9.3% (463 million people) in 2019[3]. Generally, DM treatment is achieved by conventional drugs which act mainly by stimulating insulin absorption and its release from the pancreas or by inhibiting carbohydrate-degrading enzymes[4].

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The incessant development in natural product research catalysed extensive studies of numerous plant species for their pharmacological roles[5]. In the Philippines alone, there is remarkably rich flora with approximately 10,000 different species[6] and over the years, medicinal plants have been used for the discovery of novel treatments either in the form of pure compounds or crude extracts[7]. A review on natural products also presented an overwhelming number of databases and collection of information on natural products which establishes the importance of natural products in disease treatment[8]. More than 50% of the drugs developed between 1981 and 2014 were from natural products[9]. The Department of Health of the Philippines has approved 10 plant species for medicinal use[10] and another 69 plant species were promoted for pharmacological studies. With the increasing demand for naturally-derived drugs, the present study was designed to evaluate the anti-diabetic potential of selected Philippine medicinal plants scientifically.

2. Materials and Methods

2.1 Plant Materials

A total of 54 plant species of different parts (B-Bark, L-Leaves, F-Fruit, AP-Aerial Part, Co-Core, Bu-Bulb, R-Roots, T-Tuber) were collected from various parts of Eastern Visayas, Philippines (Table 1). 21 plant species were included in the report on a publication made by Patel *et. al.* on antidiabetic medicinal plants[11]. Some of the plant materials were recommended by the local communities during the collection. The identity of plant materials was confirmed and authenticated by a taxonomic botanist at the Visayas State University. The voucher specimen of the bioactive plant species was deposited at the Tuklas Lunas Development Center in the same university. Accepted scientific names were verified in "The Plant List" (http://www.theplantlist.org/).

Table 1. Plant species used in the study

Species	Local Name
Acacia arabica (Lam.) Willd.	Acacia
Allium sativum L.	Ahos
Aloe vera (L.) Burm.f.	Sabila
Annona muricata L.	Guyabano
Annona squamosa L.	Atis
Averrhoa bilimbi L.	Kamias
Basella rubra L.	Alugbati
Capsicum frutescens L.	Siling Kulikot
Catharanthus roseus (L.) G.Don	Rosy Periwinkle
Curcuma longa L.	Duwaw
Euphorbia hirta L.	Gatas-Gatas
Mucuna pruriens (L.) DC.	Nipai
Ocimum basilicum L.	Solasi
Orthosiphon aristatus (Blume) Miq.	Balbas Pusa
Pandanus amaryllifolius Roxb.	Pandan
Peperomia pellucida (L.) Kunth	Sinaw-Sinaw
Piper betle L.	Buyo
Pithecellobium dulce (Roxb.) Benth.	Kamatsile
Psidium guajava L.	Bayabas
Smallanthus sonchifolius (Poepp.) H.Rob.	Yacon
Stevia rebaudiana (Bertoni) Bertoni	Stevia
Achyranthes aspera L.	Lopo-loo/ Saramo
Alstonia scholaris (L.) R. Br.	Dita
Alternanthera sessilis (L.) Br. Ex DC	Bunga-Punga
Apium graveolens L.	Kintsay
Artemisia vulgaris L.	Hilbas
Bidens pilosa L.	Pisau-Pisau
Bixa orellana L.	Achuete
Caesalpinia sappan L.	Sibukaw
Cassia fistula L.	Lombayong
Ceiba pentandra (L.) Gaertn.	Kapok
"To be characterised" *cf. Calyptranthera* sp.	Red Magsumpay
Chamaecostus cuspidatus (Nees and Mart.) C.Specht and D.W.Stev.	Insulin Plant
Crescentia cujete L.	Kalabas
"To be characterised" *Cycas* sp.	Pitogo
Hibiscus rosa sinensis L.	Gumamela
Ixora coccinea L.	Santan
Jatropha curcas L.	Tuba-Tuba
Lantana camara L.	Lantana
Ludwigia octovalvis (Jacq.) P.H.Raven	Tayilakton
Mimosa pudica L.	Makahiya
"To be characterised" *Pandanus* sp. (1)	Bariw
"To be characterised" *Pandanus* sp. (2)	Bariw

Table 1. Continued...

Phyllanthus amarus Schumach. and Thonn.	Malakinum-Kirum
Portulaca oleracea L.	Ulasiman
Premna serratifolia L.	Abgaw
Rubus rosifolius Sm.	Daguinot
Solanum torvum Sw.	Taogotan
Swietenia mahagoni (L.) Jacq.	Mahogany
Talinum fruticosum (L.) Juss.	Alugbating Kahoy
"To be characterised"	Magsumpay
Tectona grandis L.f.	Dalandon
Tinospora crispa (L.) Hook. f. and Thomson	Panyawan
"To be characterised"	Ginlakdan

2.2 Plant Preparation and Extraction

The protocol was adapted from the Institute of Chemistry of the University of Philippines, Diliman. Samples were cleansed and oven-dried for 3-5 days at 40°C. Dried samples were pulverised and soaked with 100% methanol and filtrates were collected 3 days after. Soaking was done six times with a ratio of 1kg sample to 10L solvent. Then, 10g of methanol extract was dissolved in 250mL distilled water (Aq). It was then transferred to a separatory funnel and 250mL of hexane (Hx) was added while shaking 3 times and allowed to stand for 3-5 min. The hexane layer was then collected and another 250mL of hexane was added to the same aqueous layer. The procedure was repeated six times. After the 6th batch of the hexane layer, 250mL of ethyl acetate (Ea) was added to the same aqueous layer. The procedure was also repeated six times. Organic layers were concentrated using a rotary evaporator while the aqueous layer was lyophilised. Concentrated and lyophilised extracts were reconstituted with Dimethylsulfoxide (DMSO). 1µg/mL and 10µg/mL (w/v) concentrations were used to screen the extracts.

2.3 Alpha-glucosidase Inhibition Assay

The inhibition assay protocol was adapted from the Institute of Chemistry of the University of the Philippines, Diliman. To the reaction mixture, 10µL extract added with 190µL potassium phosphate buffer (pH 6.8) was mixed with 50µL of 120 mU/mL enzyme solution and incubated at 37°C for 10 minutes. After incubation, 50µL of 1.86mM pNPG substrate was added and absorbance was measured at 405nm every 30 seconds for 30 minutes. Absorbance was plotted against time and the slope was taken for each line. Two trials with two replicates each were used for screening. The inhibition percentage of the α-glucosidase was assessed using the formula:

$$\text{Inhibition (\%)} = [((V_{control}\text{-}Vs_{ample}))/((V_{control}))] \times 100$$

where;

$V_{control}$ = Reaction Velocity of Negative Control

V_{sample} = Reaction Velocity of Samples

2.4 Alpha-amylase Inhibition Assay

The α-amylase inhibitory activity for each extract was determined based on the method described by Ali, H. *et al*[12]. 200µL of each plant extract and 200µL of enzyme solution were mixed in a tube and incubated at 25°C for 5 minutes. After incubation, a 400µL starch solution was added and the tube was again incubated at 25°C for 3 minutes. Then, 400µL of the colour reagent was added. The closed tubes were placed into an 85°C water bath. After 15 minutes, the reaction mixture was removed from the water bath, cooled and diluted with 3,600µL sterilised deionised water. The absorbance value of the reaction mixture was determined at 540nm in a spectrophotometer. The activity of each plant extract was compared to positive control acarbose at the same concentration.

Individual blanks were prepared to correct the background absorbance. In this case, the colour reagent solution was added before the addition of the starch solution. The other procedures were carried out as above. Controls were also conducted in an identical fashion replacing the plant extracts with either DMSO. Three trials with three replicates each were used for screening.

The following formula assessed the inhibition percentage of the α-amylase:

$$\text{Inhibition (\%)} = [((\Delta A_{control}\text{-}\Delta_{Asample}))/\Delta A_{control}] \times 100$$

where;

$\Delta A_{control}$ = Absorbance of Control – Absorbance of Blank

ΔA_{sample} = Absorbance of Sample - Absorbance of Blank

2.5 Data Analysis

Two trials with two replicates each were used for alpha-glucosidase inhibition assay while three trials with three replicates each were used for alpha-amylase inhibition assay. Data are presented as mean ± SD.

3. Results

A total of 54 plant species were screened and evaluated for their anti-diabetic potential through alpha-amylase and alpha-glucosidase inhibition assay. Tables 2 and 3 show the list of plant extracts exhibiting appreciable inhibitory activity against alpha-glucosidase and alpha-amylase, respectively, with acarbose as the reference standard. The 1µg/mL and 10µg/mL (w/v) concentrations of aqueous, hexane and ethyl acetate crude extracts were used in the screening. Table 1 presents plant extracts with ≥15% inhibitory activity against alpha-glucosidase enzyme. The positive control acarbose inhibited 99.71% ± 0.63 of the alpha-glucosidase enzyme activity at 10µg/mL (w/v). Extracts from *Cycas* sp. (83.87% ± 1.52 - Ethyl acetate), *cf. Calyptranthera* sp. (82.07% ± 0.14 - Aqueous), *Mimosa pudica* L. (73.48% ± 1.08 - Aqueous), *C. longa* L. (67.83% ± 1.31 – Ethyl acetate), *P. guajava* L. (61.06% ± 1.89 - Aqueous), *B. rubra* L. (56.78% ± 1.36 – Ethyl acetate), and *S. mahagoni* (L.) Jacq. (55.28% ± 1.05 - aqueous) are the most active inhibiting ≥ 50% of the alpha-glucosidase enzyme activity at 10µg/mL (w/v) crude extract.

Table 2. Alpha-glucosidase inhibitory activity of plant extracts

Species	Plant Part	Extract Type	Percent Inhibition	
			1µg/mL	10µg/mL
Acarbose (+ Control)			**97.73 ± 1.07**	**99.71 ± 0.63**
"To be characterised" *Cycas* sp.	F	Ea	26.67 ± 2.56	83.87 ± 1.52
"To be characterised" *cf. Calyptranthera* sp.	B	Aq	14.65 ± 2.55	82.07 ± 0.14
Mimosa pudica L.	R	Aq	8.73 ± 2.72	73.48 ± 1.08
Curcuma longa L.	T	Ea	12.48 ± 0.64	67.83 ± 1.31
Psidium guajava L.	L	Aq	-32.67 ± 5.8	61.06 ± 1.89
Basella rubra L.	L	Ea	33.87 ± 2.90	56.78 ± 1.36
Swietenia mahagoni (L.) Jacq.	B	Aq	16.87 ± 3.31	55.28 ± 1.05
To be characterised "*cf. Calyptranthera* sp."	B	Ea	2.61 ± 6.70	42.14 ± 1.64
To be characterised as "Ginlakdan"	L	Hx	28.42 ± 0.90	41.29 ± 13.92
Alstonia scholaris (L.) R. Br.	B	Ea	28.69 ± 1.52	41.19 ± 6.96
Psidium guajava L.	L	Hx	35.89 ± 5.3	40.34 ± 1.38
Pandanus amaryllifolius Roxb.	R	Aq	13.81 ± 3.30	39.54 ± 0.19
Jatropha curcas L.	L	Hx	20.02 ± 1.38	38.56 ± 4.68
Jatropha curcas L.	L	Ea	18.27 ± 2.15	36.4 ± 1.34
Alternanthera sessilis (L.) Br. Ex DC	L	Hx	12.46 ± 3.43	35.35 ± 6.68
Catharanthus roseus (L.) G. Don	L	Ea	6.39 ± 2.22	34.54 ± 3.25
Euphorbia hirta L.	AP	Ea	10.9 ± 4.87	34.03 ± 0.79
Capsicum frutescens L.	F	Ea	15.53 ± 0.18	33.83 ± 0.41
Allium sativum L.	Bu	Ea	27.41 ± 0.32	31.74 ± 0.48
cf. Calyptranthera sp.	Co	Ea	4.19 ± 3.90	30.86 ± 3.18
Premna serratifolia L.	L	Ea	-5.64 ± 4.63	29.2 ± 2.02
To be characterised "*Cycas* sp."	F	Hx	20.25 ± 5.34	29.09 ± 2.80
Swietenia mahagoni (L.) Jacq.	B	Hx	-2.86 ± 0.33	25.5 ± 5.45
Averrhoa bilimbi L.	F	Hx	16.01 ± 0.55	25.16 ± 2.65

Table 2. Continued...

Apium graveolens L.	L	Aq	8.64 ± 2.29	24.31 ± 6.99
Piper betle L.	L	Aq	-26.3 ± 2.10	22.9 ± 3.07
Crescentia cujete L.	L	Ea	12 ± 0.35	22.53 ± 1.02
Apium graveolens L.	L	Ea	7.04 ± 0.95	22.43 ± 1.87
Curcuma longa L.	T	Hx	-13.90 ± 5.77	22.20 ± 0.53
Swietenia mahagoni (L.) Jacq.	B	Ea	6.12 ± 2.50	21.68 ± 0.99
Pandanus amaryllifolius Roxb.	R	Ea	25.68 ± 0.34	21.3 ± 0.08
Cassia fistula L.	L	Hx	12.88 ± 1.81	21.05 ± 9.42
cf. Calyptranthera sp.	R	Ea	17.7 ± 3.20	20.62 ± 9.17
cf. Calyptranthera sp.	Co	Hx	5.27 ± 1.14	18.64 ± 10.5
Peperomia pellucida (L.) Kunth	AP	Ea	10.78 ± 2.79	17.23 ± 1.44
Averrhoa bilimbi L.	F	Ea	7.03 ± 2.27	15.86 ± 1.16
To be characterised as "*Pandanus* sp. (2)"	F	Ea	-0.73 ± 0.99	15.40 ± 0.27
Premna serratifolia L.	L	Hx	-1.35 ± 0.96	15.21 ± 3.16
Alternanthera sessilis (L.) Br. Ex DC	L	Ea	6.13 ± 0.47	15.16 ± 1.67

Table 3. Alpha-amylase inhibitory activity of plant extracts

Species	Plant Part	Extract Type	Percent Inhibition	
			1µg/mL	10µg/mL
Acarbose (+ Control)			**13.53 ± 1.33**	**51.59 ± 0.98**
Curcuma longa L.	T	Ea	8.34 ± 1.17	39.44 ± 1.56
Swietenia mahagoni (L.) Jacq.	B	Hx	1.97 ± 0.57	26.39 ± 0.28
Euphorbia hirta L.	AP	Ea	11.35 ± 0.19	20.43 ± 0.82
Psidium guajava L.	L	Aq	2.56 ± 0.35	15.59 ± 0.57
Psidium guajava L.	L	Hx	5.57 ± 0.10	15.44 ± 1.03
Euphorbia hirta L.	AP	Hx	5.39 ± 0.09	14.50 ± 1.22
Basella rubra L.	L	Hx	1.93 ± 0.48	12.27 ± 0.97
Pandanus sp. (2)	F	Hx	4 ± 0.50	12.16 ± 0.82
Curcuma longa L.	T	Hx	4.93 ± 0.42	11.76 ± 0.25
Allium sativum L.	Bu	Hx	5.77 ± 0.33	11.55 ± 0.41
Jatropha curcas L.	L	Ea	5.2 ± 0.32	11.51 ± 1.03
Alstonia scholaris (L.) R. Br.	B	Hx	5.23 ± 0.58	11.32 ± 0.15
Allium sativum L.	Bu	Ea	8.77 ± 0.07	11.02 ± 0.81
Stevia rebaudiana (Bertoni) Bertoni	L	Hx	4.61 ± 0.61	10.84 ± 0.47
Basella rubra L.	L	Ea	5.32 ± 0.27	0.27

Similarly, plant extracts were also tested for alpha-amylase inhibitory activity. Table 2 presents plant extracts with ≥ 10% inhibitory activity against alpha-amylase enzyme. The positive control acarbose inhibited 51.59% ± 0.98 of the enzyme activity at 10µg/mL (w/v). Extracts from *C. longa* L. (39.44 ± 1.56 – Ethyl acetate), *S. mahagoni* (L.) Jacq. (26.39 ± 0.28 – Hexane), and *E. hirta* L. (20.43 ± 0.82 – Ethyl acetate) were the most active inhibiting ≥ 20% of the alpha-amylase enzyme activity in 10µg/mL (w/v) crude extract.

4. Discussion

The initiative for scientific-based studies on medicinal plants for the treatment of diabetes has been prominent in recent years. Enzyme-based studies for the investigation of the medicinal value of plant species have mostly been the primary step in drug discovery and development from natural products[13]. Providing dynamic applications is essential considering that a single enzyme can represent several biochemical processes. Understanding the mechanism of a single enzyme to various biochemical processes can be used to aptly address diseases and develop specialised treatments[14].

Alpha-amylases and alpha-glucosidases are among the key enzymes in the metabolism of carbohydrates. Alpha-amylases are protein enzymes in the digestive system that catalyses the initial step in the hydrolysis of starch to a mixture of smaller oligosaccharides, which are then further broken down by alpha-glucosidases into glucose for absorption into the bloodstream[15]. These are normal biochemical processes. However, for diabetic patients, the rapid metabolism of carbohydrates may lead to elevated Postprandial Hyperglycemia (PPHG), which could be fatal if not addressed appropriately. One of the therapeutic approaches to decrease PPHG is by retarding the activity of these carbohydrate-hydrolysing enzymes, which is also considered one of the major strategies in the treatment development for diabetes.

The present study showed active plant species, i.e., *Cycas* sp. and *cf. Calyptranthera* sp., exhibiting bioactivity of more than ≥ 80% against the alpha-glucosidase enzyme. *Cycas* sp. locally known as Pitogo belongs to the Cycadaceae family. There are about 10 species of the genus *Cycas* in the Philippines of which some were considered endemic[16]. Considering that it is widely used nowadays as an ornamental plant in the country, little is known about the medicinal value of this plant species. However, there are reports on the anti-diabetic potential of other *Cycas* species. Laishram *et al.*, reported that ethyl acetate fruit extract of *Cycas pectinata* Buch.-Ham exhibited alpha-glucosidase inhibitory activity with an IC_{50} value of (42.82 ± 0.039µg/ml)[17]. Leaf extract of *C. riuminiana* also showed antidiabetic potential by lowering the blood glucose level in alloxan-induced diabetic ICR mice[18]. Folklorically, powdered roasted whole seeds of pitogo are mixed with coconut oil and applied to wounds, boils and itchy skin lesions—likewise, *cf. Calyptranthera*, locally known as Red Magsumpay, also exhibited the highest bioactivity of more than ≥ 80%. This plant species is common among traditional healers in Eastern Samar, Philippines, and is used for treating various diseases. To the best of our knowledge, there is no published report elucidating the bioactivity of this plant against diabetes and other diseases.

In addition, *C. longa* L. exhibited the highest bioactivity of more than 30% against alpha-amylase enzyme. This is locally known as Duwaw or Turmeric in this region and is used for various ailments. This plant species is one of the well-studied medicinal plants and has been used for thousands of years as complementary and alternative medicine[19]. Reported bioactivity of turmeric includes the yellow phenolic diarylheptanoid curcumin, the major pigment in the turmeric rhizome, which shows potent anti-oxidative and anti-inflammatory effects, cytotoxicity against tumour cells and antitumor-promoting activity[20,21].

The enzyme inhibitory activities of these medicinal plants are possibly constituted by the presence of secondary metabolites, which have been widely studied for their pharmacological roles in the treatment of diabetes[22]. The activity exhibited by the most active plant species may also indicate specific binding between the compounds in the extracts and the receptor site of the enzyme since a significant decrease in enzyme activity was observed. This biochemical interaction was also observed in several molecular docking studies, which show the binding affinity of plant-derived compounds to that of the α-glucosidase enzyme[23,24].

5. Conclusion

The *in vitro* evaluation employed in this study validates the traditional use of some medicinal plants as complementary and alternative medicine for the treatment of Diabetes mellitus. Although *in vitro* studies cannot replace animal experimental models for drug discovery and development, the result of this study can be used to select the best candidate for further studies. The findings of this study will also provide scientific information to individuals in selecting effective

complementary medicines as potential anti-diabetic agents.

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