Review Article

α-Glucosidase Inhibitory Activity of Selected Malaysian Plants

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ABSTRACT

Diabetes is a common metabolic disease indicated by unusually high plasma glucose level that can lead to major complications such as diabetic neuropathy, retinopathy, and cardiovascular diseases. One of the effective therapeutic managements of the disease is to reduce postprandial hyperglycemia through inhibition of α-glucosidase, a carbohydrate-hydrolyzing enzyme to retard overall glucose absorption. In recent years, a plenty of research works have been conducted looking for novel and effective α-glucosidase inhibitors (AGIs) from natural sources as alternatives for the synthetic AGI due to their unpleasant side effects. Plants and herbs are rich with secondary metabolites that have massive pharmaceutical potential. Besides, studies showed that phytochemicals such as flavonoids, alkaloids, terpenoids, anthocyanins, glycosides, and phenolic compounds possess significant inhibitory activity against α-glucosidase enzyme. Malaysia is a tropical country that is rich with medicinal herbs. In this review, we focus on eight Malaysian plants with the potential as AGI to develop a potential functional food or lead compounds against diabetes.

KEYWORDS: Diabetes, Malaysian plants, α-glucosidase inhibitor

INTRODUCTION

Diabetes mellitus (DM) is a chronic, life-long condition that results in deficiency of overall insulin secretion or a reduced sensitivity of insulin-producing organs. Currently, DM is becoming one of the most expensive and worrisome chronic illnesses that keep escalating in numbers all over the world, particularly in low- and middle-income countries. Type 2 diabetes is increasing worldwide in epidemic proportions. Its associated morbidity and mortality is imposing a major burden on the healthcare system. The latest update from the World Health Organization shows that about 422 million people are having the disease, which is approximately a quadruple since 1980. In 2015, there were 3.3 million of diabetes cases in Malaysia. α-Glucosidase inhibitor (AGI) is one of the antidiabetic drugs that are widely used and works efficiently in delaying the carbohydrates absorption from the small intestine to result in a reduced postprandial blood glucose and insulin levels. Examples of AGI in the current market include acarbose, miglitol, and voglibose. Due to the side effects of these synthetic AGIs (flatulence, bloating, stomach pain, and diarrhea), there is a demand of exploring novel AGI from natural sources as alternatives. A review by Kumar et al. revealed that AGI activity is possessed by plants’ secondary metabolites such as flavonoids, alkaloids, terpenoids, anthocyanins, glycosides, curcuminoids, and phenolic compounds. Besides, studies also showed a strong correlation between total phenolic content (TPC) and AGI activity. A potent natural AGI kotalanol was isolated from the antidiabetic traditional Ayurvedic medicine (Salacia reticulata) and appeared to be more potent than acarbose.

Malaysia has a diverse range of herbal medicines that provide essential therapeutic benefits for locals. A plenty of works have been carried out on tropical plant extracts

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How to cite this article: Mohd Bukhari DA, Siddiqui MJ, Shamsudin SH, Rahman MM, So’ad SZ. α-Glucosidase inhibitory activity of selected Malaysian plants. J Pharm Bioall Sci 2017;9:164-70.
to prove its potential as antihyperglycemic agents, particularly as AGI.\textsuperscript{[10]} Furthermore, Agamuthu reported that about 1.2 million ton of agricultural waste including fruit peels and seeds was disposed into landfills every year. Therefore, the recycling of these wastes will be desirable to reduce the environmental impact following their disposal.\textsuperscript{[11]}

This review will be focusing on the potential of eight Malaysia plants (\textit{Garcinia mangostana}, \textit{Nephelium lappaceum} \textit{L.}, \textit{Barringtonia racemosa}, \textit{Phyllanthus acidus}, \textit{Cynometra cauliflora}, \textit{Myristica fragrans}, \textit{Cosmos caulatus}, and \textit{Orthosiphon stamineus}) possessing AGI activity. Three main aspects will be covered in this review; extraction and isolation methods of bioactive compounds, AGI assay protocols, and the potency of plant extract as AGI.

\textbf{\textit{Garcinia mangostana} (Guttiferae)}

\textit{G. mangostana} (mangosteen) is naturally growing in Southeast Asian nations – Malaysia, Indonesia, Sri Lanka, Philippines, Myanmar, and Thailand. In Malaysia, it is locally known as manggis, mesetor, semetah, or sementah. On average, the tree can slowly grow to a range of 6–25 m in height. The fruits are of round-shaped in dark-purple to red-purple with rind’s thickness of 6–10 mm and white juicy flesh.\textsuperscript{[12]} The fruit is traditionally used to heal various illnesses including infections, wounds, diarrhea, and gastrointestinal disorder.\textsuperscript{[13]}

A study by Ryu \textit{et al.} was conducted to evaluate the potential of AGI activity of \textit{G. mangostana} extract and its isolated compounds.\textsuperscript{[14]} The study disclosed that the xanthone backbone is a potent molecular basis for AGI mechanism. Seedcases (10 g) of the plant collected in Vietnam were extracted with 200 ml of solvent by shaking at 30°C for 3 days before being evaporated under reduced pressure. Ethanolic extract showed the highest extraction yield (14.2%) of AGI, followed by 50% ethanol (13.7%), water (10.6%), and chloroform (4.9%). Extracts obtained were later subjected to isolation using silica gel column with hexane and acetone as eluent.

The \textit{in vitro} assay was performed according to Kim \textit{et al.} method.\textsuperscript{[15]} All the assessed compounds showed remarkable \(\alpha\)-glucosidase inhibition (\(IC_{50}\) 1.5–58.8 \(\mu\)M, more potent than the conventional AGI deoxynojirimycin \(IC_{50}\) 68.8 \(\mu\)M). In addition, \textit{in vivo} test of ethanolic xanthone extract was carried out in hyperglycemic rats. The ethanol extract (100 mg/kg BW) showed a significant hypoglycemic impact after 30 min of oral maltose administration, and it was sustained up to 2 h which was similar to the reaction set out by the reference drug, acarbose.\textsuperscript{[16]}

\textbf{\textit{Nephelium lappaceum} L. (Sapindaceae)}

\textit{N. lappaceum} \textit{L.} (rambutan) is one of the valued plant species in Southeast Asia, widely cultivated in Malaysia, Indonesia, Thailand, and Philippines. Rambutan trees grow in warm, wet, and lowland areas into distinct feature of red or yellow hairy skin.\textsuperscript{[17]} Different part of the plant is well known at its respective medicinal benefits. Malay population uses decoction of rambutan roots to relieve fever. The fruit is traditionally used as anthelmintic to eradicate intestinal worms, whereas the leaves are believed to cure headaches.\textsuperscript{[18]}

It was reported that the major component in \textit{N. lappaceum} rind extracts is geraniin, an ellagitannin with an approximate dry weight of 3.79% (37.9 mg/g of the crude extract).\textsuperscript{[19,20]} Palanisamy \textit{et al.} had extracted the \textit{N. lappaceum} rind with water and ethanol, and it was found that the ethanolic extracts procured a higher yield as opposed to the aqueous extract (ethanol 17.8%, aqueous 13.2%). In addition, incorporation of milling process in the extraction has significantly increased the yield by approximately 77% and 87% in the aqueous and ethanol extracts, respectively (ethanol 33.2%, aqueous 23.4%). However, both rind extracts exhibited significant AGI activity when compared with acarbose. In addition, promising AGI activity of geraniin had been observed in an \textit{in vitro} study with \(IC_{50}\) 0.92 µg/ml, lower than acarbose (\(IC_{50}\) 25 µg/ml), the positive control.\textsuperscript{[20]}

Other than fruit peels, rambutan seeds also contain a variety of phenolic compounds such as ellagic acid, corilagin, and geraniin.\textsuperscript{[20]} In one of the studies by Soeng \textit{et al.},\textsuperscript{[21]} rambutan seeds extract and fractions have shown to possess a significant inhibitory impact on \(\alpha\)-glucosidase enzyme \textit{in vitro} compared to drug acarbose. The extraction of rambutan seeds was performed using the maceration method and then fractioned using four partitioning solvents (hexane, ethyl acetate, butanol, and water).\textsuperscript{[22]}

A modified Farnsworth method was implemented as the phytochemical assay to test the rambutan seeds extract and fraction. The assay showed that the 70% ethanolic extract contained a moderate content of terpenoids, whereas other fractions (hexane, ethyl acetate, butanol, and water) contained a much lower content. Phenol is found in all extracts and fractions, except in the water fraction. The most potent \(\alpha\)-glucosidase activity was demonstrated by the seeds ethanolic extract at the dose of 50 µg/ml.\textsuperscript{[21]}

\textbf{\textit{Barringtonia racemosa} (Lecythidaceae)}

\textit{B. racemosa} is an unexceptional mangrove tree species that grow in Bangladesh, Sri Lanka, India, Singapore,
et al. evaluated the AGI activity leaves has significant hepatoprotective racemosa g < 0.03). µ 26.96 µ 200 g of P. acidus fruits was washed with distilled water and later ground to obtain a fine puree (40 mesh or 400 µm of particle size). The puree was subjected into two groups – first group was soaked in distilled water (500 ml) for 15 min at room temperature and the second group was left undiluted. Both puree groups were then filtered using a clean muslin cloth and centrifuged for 15 min. Extraction was done in triplicate and the extract juices were stored at −10°C in the dark until further analysis.[39]

The AGI activity of P. acidus juice extracts was evaluated according to the method by Ooi et al.[39] P. acidus extract demonstrated the highest AGI percentage with 95.37% ± 0.15%. However, the value was not significantly different from other tested juices of B. racemosa, Cynometra cauliflora, M. fragrans, G. mangostana, Bouea macrophylla, Syzygium samarangense, and Citrus microcarpa. Previously, a very low AGI activity was discovered from P. acidus extract.[40,41] On that account, the potent activity might be due to the presence of inhibitors in the juice compared to the extracts.

The separation of compounds in fruit extracts was carried out by UPLC that eventually identified gallic acid as the major compound in the extract that is responsible on the activity. Apart from that, several other flavonol and flavanone compounds were identified in the extracts chromatogram; myricetin, glycosidic querctein, kaempferol, and glycosidic dihydroquerctein.[28] In one of the studies, Jain and Singhai suggest that the aqueous extract of P. acidus leaves has significant hepatoprotective activity on acetaminophen- and thioacetamide-induced hepatotoxicity, which might be associated with its high phenolic and flavonoid content and antioxidant properties.[42]

**Cynometra cauliflora (Fabaceae)**

*C. cauliflora* (namnam) is typically found in eastern and northern parts of Peninsular Malaysia, Southeast Asia, and India.[43] Namnam leaves are traditionally used for treating diabetes and hyperlipidemia,[44,45] whereas fruits are used as cure for appetite loss. On the other hand, seed oil of plants is good for skin diseases.[46]

Ado et al. had extracted the plant material by maceration technique in 100% methanol for 48 h at room temperature. After 48 h, the extract was decanted and fresh solvent was added to the plant residue for another cycle. This process was repeated several times. The extracts obtained were then concentrated under reduced

Malaysia, Madagascar, Thailand, Laos, Southern China, and Northern Australia.[25] It is locally known as putat and fish poison tree or powder puff tree. Nearly all parts of this plant possess bioactivity against various illnesses, including seeds (colic, ophthalmic disorders, and antitumor), stem bark (mitogenic activity), bark and leaves (rat-snake bites, rat poisoning, and gastric ulcer), and roots (antibacterial).[24,26]

Gowri et al. investigated the inhibitory activity of plant seeds extract against yeast and intestinal α-glucosidase enzyme. The coarsely powdered dried seeds (Kerala, India) were extracted using percolation method with hexane, ethanol, and methanol at ambient temperature for 4 days, followed by activity screening against the enzyme. Methanol extract showed the most potent inhibitory activity against α-glucosidase enzyme. Hence, the isolation was done on the methanol extract, which was subjected to vacuum liquid chromatography over a column of silica gel.[27]

Bartogenic acid was isolated as the prime compound of the methanol extract. Despite that, the enzyme inhibition showed by isolated bartogenic acid alone was significantly less than the methanol extract (P < 0.03). The experimental outcomes showed that methanol extract had the most potent AGI activity (IC50 26.96 µg/ml), followed by the hexane (IC50 131.68 µg/ml) and ethanol extracts (IC50 163.67 µg/ml). As for the activity of isolated bartogenic acid alone, it was found to be less than all crude extracts; IC50 198.09 µg/ml.

Another study by Sulaiman and Ooi had determined that the juices from B. racemosa flesh possessed significant AGI activity with the inhibition percentage of approximately 94%. This result was correspondent to its high TPC (>600 µg gallic acid equivalent/g sample). Other than that, the same study also revealed the highest antioxidant activity by the plant fruit juice through ferric reducing antioxidant power and α,α-diphenyl-β-picrylhydrazyl assays. From the ultra-performance liquid chromatography (UPLC) chromatogram, ellagic acid, myricetin, and glycosidic querctein were identified to be present in the fruit extract and the result was validated by comparing the peaks’ retention times and ultraviolet spectra against the standards. Ellagic acid was discovered to be the major compound of the juice extract.[28]

**Phyllanthus acidus (Phyllanthaceae)**

*P. acidus* (gooseberry) is widely distributed across Asia (India, Malaysia, Indonesia, Vietnam and Laos), parts of Central America, the Caribbean, and parts of South America.[29,30] The plant has been used traditionally at treating pain, rheumatism, bronchitis, asthma, diabetes, gonorrhea, hypertension, etc.[31-33] Many studies were conducted at determining the potential of each part of this plant, especially leaves, fruits, and roots.[34-38]
pressure and the dried extract was stored at −20°C until further study.\textsuperscript{[47]}

The inhibitory activity against α-glucosidase enzyme was evaluated using modified method of Kim et al.\textsuperscript{[15]} The results showed that ethyl acetate and n-butanol extracts displayed the most potent inhibition compared to hexane, dichloromethane, and aqueous fractions, with IC\textsubscript{50} values of 0.03 ± 0.004 and 0.044 ± 0.072 mg/ml, respectively. In addition, Pearson’s correlation test showed a moderate correlation between TPC and AGI activity with an $R^2 = 0.417$. This demonstrated the presence of nonphenolic compounds that were responsible for the enzyme inhibition. Besides that, it was presumed that the inhibitory activity was due to specific individual phenolic compound, rather than the overall phenolic content.

**Myristica fragrans** L. (Myristicaceae)

*M. fragrans* (nutmeg) is indigenous to Australia, Asia, and the tropical regions of Southeast Asia. Nutmeg is an expensive herb, often used as spice in cooking. The fruit consists of flesh, nutmeg, nut seed, and mace. Mace is normally used as flavoring agent and also traditionally consumed as the treatment for flatulence, vomiting, bladder and urinary tract inflammation, expectorant, and rheumatism.\textsuperscript{[48]}

The powdered *M. fragrans* fruits were extracted by Soxhlet extraction using methanol. The extract obtained was later filtered, concentrated under vacuum, and stored at −4°C until further use. A range of plant extract (yield 23.61%) concentration was prepared by diluting the extract in dimethyl sulfoxide.\textsuperscript{[49]}

In *vitro* screening of AGI activity of the fruits extract was carried out using the procedure by Iauk et al.\textsuperscript{[50]} Promising inhibitory activity was shown by nutmeg extract due to its comparable IC\textsubscript{50} value (75.7 ± 2.3 μg/ml) to that of the positive control acarbose (35.5 ± 1.2 μg/ml). Other *in vitro* rat intestinal AGI activity by Patil et al.\textsuperscript{[49]} demonstrated that *M. fragrans* was responsible at inducing the insulin secretion in a dose-dependent manner. It was reported that nutmeg extract inhibited α-glucosidase enzyme at IC\textsubscript{50} 0.85 mg/ml, whereas acarbose recorded an IC\textsubscript{50} 0.031 mg/ml.

**Cosmos caudatus** (Asteraceae)

*C. caudatus* is locally known as Ulam Raja or “King’s Salad” in Malaysia. It is originally grown in Latin America and later distributed extensively to Southeast Asia, especially Malaysia, Indonesia, and Thailand. Conventionally, the plant leaves are consumed as a booster for blood circulation, strengthening the bones, cooling effect for body, antiaging agent, and also beneficial in treating infectious diseases.\textsuperscript{[51]}

Javadi et al.\textsuperscript{[52]} had reported the inhibitory activity of *C. caudatus* leaves extract against α-glucosidase enzyme. A total of 108 samples of *C. caudatus* leaves were prepared, which was comprised of 18 replicates for each of the six different ethanol concentrations. Each sample that weighed 5.5 g was subjected to sonication for 30 min by immersion in ethanol at various concentrations (0%, 20%, 40%, 60%, 80%, and 100%). In addition, it was determined that hexane extract of the plant showed remarkable activity at inhibiting the α-glucosidase enzyme by Loh and Hadira.\textsuperscript{[53]}

In addition, a metabolomics study to analyze the correlation between the activity and the potential responsible metabolites was also carried out by Javadi et al.\textsuperscript{[53]} The result showed that four compounds were active at inhibiting the enzyme. The compounds identity was confirmed using GC-MS NIST08 database library and literature data. They are phenolic and organic acids; α-tocopherol, catechin, α-linolenic acid (9Z,12Z, 15Z)-octadeca-9,12, 15-trienoic acid, and α-D-glucopyranoside.

Other than that, *C. caudatus* has also been studied in an *in vivo* study, conducted by Perumal et al.\textsuperscript{[54]} In that particular study, rats treated with *C. caudatus* extract demonstrated a significant decline in plasma blood glucose after 1 month of *C. caudatus* extract supplementation as opposed to that of control group.

**Orthosiphon stamineus** (Lamiaceae)

*O. stamineus* is one of various plants widely found in tropical countries, especially in Southeast Asian region – Malaysia, Thailand, and Indonesia. In Malaysia, it is locally known as Misai Kucing or Cat’s Whiskers.\textsuperscript{[55]} It is extensively used to treat many diseases including urinary tract disease, DM, hypertension, rheumatism, tonsillitis, and menstrual disorders.\textsuperscript{[56]}

Previously, a study to determine the potential of *O. stamineus* leaves at inhibiting α-glucosidase enzyme was conducted.\textsuperscript{[57]} Before extraction, the dried leaves were made into powder by a milling machine. Maceration method was performed with 50% (v/v) ethanol used as solvent. The extracts obtained were filtered and concentrated using a rotary evaporator and later was subjected to freeze-drying process. 10.3% of dry powder was attained. After that, the 50% ethanolic extract of *O. stamineus* was fractionated into ethyl acetate, butanol, and water extracts. The ethyl acetate fraction with antihyperglycemic activity was separated via silica-gel column chromatography to give two
subfractions: ESF-1 (nonactive) and ESF-2 (active). The ESF-2 was fraction was then subjected to silica gel chromatography for bioactive compound isolation. Isolated compound was subjected NMR study.[58]

**In vitro** α-glucosidase inhibition study was done using modified method by Apostolidis et al.[59] The results showed that each concentration of the 50% ethanol extract of *O. stamineus* (62.5, 31.25, 15.6, 7.8, 3.9, and 1.95 mg/ml) and sinensetin inhibited α-glucosidase. The percentage inhibition of the extract displayed a concentration-dependent reduction, with the highest inhibition percentage (81.4%) recorded by 62.5 mg/ml of extract concentration, and the lowest inhibition percentage (16.2%) was determined from 1.95 mg/ml. Besides, sinensetin revealed strong inhibition percentages (89%–32%) against α-glucosidase enzyme with concentration range of 2.5–0.31 mg/ml. However, 50% ethanolic extract of *O. stamineus* was determined to be the least potent at inhibiting the enzyme as opposed to that of acarbose and sinensetin. This was proved by IC$_{50}$ values of the inhibitor compounds; sinensetin (IC$_{50}$ 0.66 ± 0.025 mg/ml), acarbose (IC$_{50}$ 1.93 ± 0.281 mg/ml), and 50% ethanolic extract of *O. stamineus* (IC$_{50}$ 4.63 ± 0.413 mg/ml). The IC$_{50}$ of sinensetin was found to be significantly lower than acarbose and 50% ethanolic extract of *O. stamineus* (P < 0.01). The inhibitory activity of extract against the enzyme was presumably due to the presence of different compounds.[60] In addition, a previous study by Kwon et al.[8] showed that phenolics, flavonoids, and glycosides present in the extract and responsible as effective AGIs.

**Conclusion**

From this review, it has been shown that Malaysian plants have great and promising potential as pharmaceutical agent, particularly to be developed as antidiabetics through the inhibition of α-glucosidase enzyme. This natural approach is thought to be safer and more convenient compared to its synthetic version (e.g., acarbose and voglibose). Most studies reviewed in this paper demonstrated the *in vitro* tests of the AGI activity of the plants extract, which gives evidence and strong biochemical rationale of their potential. Therefore, the promising results shall be carried forward to *in vivo* test to further verify the activity. Besides, data generated from these studies further promote the traditional use of plants in medicine.

**Financial support and sponsorship**

We are grateful to Research Initiative Grant (RIGS15-099-0099) approved by the Research Management Centre, International Islamic University Malaysia, Kuantan.

**Conflicts of interest**

There are no conflicts of interest.

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