British Journal of Pharmaceutical Research
7(5): 365-374, 2015, Article no.BJPR.2015.118
ISSN: 2231-2919

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α-Glucosidase and α-Amylase Inhibitory Activities of Nine Sri Lankan Antidiabetic Plants

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Authors' contributions

This work was carried out in collaboration between all authors. Author JP Carried out the experiments. Author HKIP Concept and design of the study, manuscript preparation. All authors read and approved the manuscript.

Article Information

DOI: 10.9734/BJPR/2015/18645
Editor(s):
(1) Rafik Karaman, Bioorganic Chemistry, College of Pharmacy, Al-Quds University, USA.
Reviewers:
(1) G. Bupesh, King Institute of Preventive Medicine and Research, Chennai, India.
(2) Mathew Folaranmi Olaniyan, Medical Laboratory Science, Achievers University, Owo, Nigeria.
(3) A. Papazafiropoulou, Department of Internal Medicine and Diabetes Center, Tzaneio General Hospital of Piraeus, Greece.
(4) Anonymous, University of Mauritius, Mauritius.
Complete Peer review History: http://sciencedomain.org/review-history/10063

Original Research Article

Received 3rd May 2015
Accepted 29th May 2015
Published 6th July 2015

ABSTRACT

Aims: α-Amylase and α-glucosidase have been recognized as therapeutic targets for reduction of postprandial hyperglycaemia in diabetes mellitus. Objective of the study was to assess the α-amylase and α-glucosidase inhibitory potential of nine Sri Lankan antidiabetic plants.
Study Design: *In vitro* enzyme inhibitory assays.
Place and Duration of Study: Department of Biochemistry, Faculty of Medicine, University of Peradeniya, Sri Lanka, from October 2013 to December 2014.
Methodology: Methanol extracts of nine plant parts were used. *Pterocarpus marsupium* latex was used without extraction. Enzyme inhibition assays were conducted in the presence and absence of plant extracts using porcine pancreatic α-amylase and α-glucosidase from *Saccharomyces cerevisiae*. Acarbose was used as the standard inhibitor. Percentage inhibition of the two enzymes and the IC_{50} values were determined.
Results: The IC_{50} values of *Ficus racemosa* stem bark and *Pterocarpus marsupium* latex were significantly lower ($p< 0.05$) than the IC_{50} value of Acarbose for porcine pancreatic amylase.

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Lowest IC_{50} for amylase was observed with *P. marsupium.* The IC_{50} values of *Phyllanthus emblica* fruit*, Phyllanthus debilis* whole plant, *P. marsupium* and *F. racemosa* were significantly lower ($p<0.05$) than Acarbose for yeast glucosidase. *Musa paradisiaca* yam and *Tinospora cordifolia* leaves showed considerable inhibitory effects on glucosidase activity. *Coccinia grandis, Gymnema lactiferum, Gymnema sylvestre* and *Strychnos potatorum* seeds did not show considerable inhibitory effects on α-amylase and α-glucosidase.

Conclusion: A significantly high ($p< 0.05$) *in vitro* α-amylase and α-glucosidase inhibitory activities were observed with the methanol extracts of *F. racemosa, P. emblica*, *P. debilis* and *P. marsupium.*

Keywords: Medicinal plants; α-amylase; α-glucosidase; inhibitors; diabetes.

1. INTRODUCTION

Diabetes mellitus is a chronic disease which affected 382 million people worldwide and caused 5.1 million deaths in 2013 due to complications associated with diabetes [1]. Chronic hyperglycemia is the clinical hallmark of poorly controlled diabetes [2]. Primary goal in the management of diabetes is to regulate the blood glucose concentrations as close as to normal physiological levels, in order to prevent chronic diabetic complications such as retinopathy, nephropathy and cardio vascular diseases [2].

Digestion of dietary starch proceeds rapidly and leads to postprandial spikes in blood glucose. In diabetes, there is a much higher and prolong increase in blood glucose levels during postprandial phase. One of the therapeutic approaches used to lower blood glucose concentration is to decrease the postprandial rise in the blood glucose by inhibiting key enzymes hydrolyzing the dietary carbohydrates [3,4].

α-Amylase and α-glucosidase have been recognized as therapeutic targets for reduction of postprandial hyperglycaemia [4]. Inhibition of these enzymes delays carbohydrate digestion, decreasing the rate of glucose absorption and therefore blunting the post-prandial plasma glucose rise. The drugs available currently, as inhibitors of amylase and glucosidase show gastrointestinal side effects such as bloating, abdominal discomfort, diarrhoea, and flatulence making them less attractive as therapeutic agents [4].

α-Amylase is secreted by the pancreas and the salivary glands. It is a key enzyme in the carbohydrate digestion which catalyses the initial hydrolysis of starch by acting on the interior α-D-1,4 glucosidic linkages. Amylase converts starch in to α-limit dextrins, maltose, and maltotriose [5]. α-Glucosidase is an intestinal brush border enzyme. It catalyzes the liberation of absorbable monosaccharides such as glucose from the substrate which eventually facilitates the absorption by the small intestine [6].

Medicinal plants have been used since prehistoric times worldwide for the treatment of diabetes. The ethnobotanical studies of traditional herbal remedies used for diabetes around the world have identified more than 1,200 species of plants with hypoglycemic activity [7]. Approximately 126 antidiabetic plants are used to treat diabetes in Sri Lanka [8]. However, most of these plants are being used in traditional healing systems without proper scientific validation [9] despite recommendations by World Health Organization for further investigation. Most useful drugs derived from plants have been discovered by follow-up of ethnomedical uses [10]. Natural remedies for diabetes from plants are gaining popularity as they are effective, inexpensive and safe when compared to synthetic hypoglycaemic drugs [11]. Some of the antidiabetic plants could be important sources of amylase and glucosidase inhibitors.

The objective of the present study was to assess the α-amylase and α-glucosidase inhibitory potential of nine Sri Lankan antidiabetic plants.

2. MATERIALS AND METHODS

2.1 Plant Parts

Parts from ten plants including nine antidiabetic plants were collected from Ratnapura District, Sri Lanka (Table 1). Plants were authenticated (HKIP-CSH-2013-01 to HKIP-CSH-2013-10) and the voucher samples were deposited at the Royal Botanical Gardens, Peradeniya, Sri Lanka.

2.2 Preparation of Methanol Extracts

Plant parts were cleaned and dried under shade for approximately one week. Dried parts were

ground to a powder using a grinder. Powder (10 g) of nine plant parts other than *P. marsupium* latex was extracted three times with methanol (100 ml) using a sonicator. Methanol was filtered and the solvent was evaporated by rotary evaporator (Buchi RII) at 45-50°C [12]. Powder forms of the crude extracts were stored at room temperature until used for inhibitory assays. Methanol extracts and the dried *P. marsupium* latex were resuspended in phosphate buffer (pH 7.4) to the required working concentrations before the experiments. DMSO was used if necessary to solubilize the extracts.

Percentage α-amylase inhibition and α-glucosidase inhibition of the crude methanol extracts and the *P. marsupium* latex were analyzed using the methods described by Geethalakshmi et. al. [13] and Elya et al. [14] respectively.

2.3 α-Amylase Inhibition Assay

Inhibition of α-amylase by the crude methanol extracts and the *P. marsupium* latex was carried out using the pre incubation method described by Geethalakshmi et al. [13]. Briefly, porcine pancreatic α-amylase (Sigma) was dissolved in ice-cold distilled water (5 unit/ml solution). Potato starch (1% w/v) in 20 mM phosphate buffer (pH 6.9) containing 6.7 mM sodium chloride, was used as the substrate solution. Plant extract (40 µl) was mixed with 40 µl porcine pancreatic α-amylase and 80 µl of 20 mM phosphate buffered saline (pH 6.9). Tubes were pre incubated for 15 min at 37°C and then 1% potato starch (40 µl) was added to all the tubes. Final concentration of plant extract used during screening was 1 mg/ml. Series of final concentrations used for the extracts with higher inhibitory effects included 10, 20, 30, 40, 50 µg/ ml for *F. racemosa*, 250, 400, 500, 650, 1000 µg/ ml for *P. emblica* and 1, 2.5, 5, 7.5, 10 µg/ ml for *P. marsupium.* Control was carried out in the absence of plant extract or standard inhibitor. Test blanks were conducted in the presence of plant extracts without α-amylase. A blank reaction was carried out with 40 µl methanol replacing the plant extract. Acarbose (Sigma) (200 µg/ ml) was used as the standard inhibitor. Reaction mixtures were incubated for 15 min at 37°C. Dinitrosalicylic acid colour reagent (96 mM 3,5-dinitrosalicylic acid, 5.31 M sodium potassium tartarate in 2 M NaOH) was added (100 µl) to all the tubes and was kept immediately in a water bath at 85°C for 15 min. Distilled water (900 µl) was added to each tube and the absorbance was measured at 540 nm.

2.4 α-Glucosidase Inhibition Assay

The α-glucosidase inhibition was determined using the method as described by Elya et al. [14]. Briefly, 200 µl of 67 mM sodium phosphate buffer (pH 6.8) and 120 µl of 10 mM *p*-Nitrophenyl α-D-Glucopyranoside (Sigma) was added to tests, control and the blanks. Plant extract (40 µl) was added to the test and test blank. The mixtures were pre incubated for 15 min at 37°C. After incubation, 40 µl of 0.1 U α-glucosidase from *Saccharomyces cerevisiae* (Sigma) was added to the tests and control. Final concentration of plant extract used during screening was 0.5 mg/ml. Series of final concentrations used for the extracts with higher inhibitory effects included 10, 15, 20, 25, 40, 100 µg/ ml for *F. racemosa,* 0.25, 0.4, 0.5, 0.7, 0.8, 1, 10 µg/ ml for *P. emblica* and *P. debilis* and 0.25, 0.4, 0.5, 0.7, 0.8, 1 µg/ ml for *P. marsupium*. The reaction mixture was incubated for 15 min at 37°C. Reaction was terminated by adding 200 mM sodium carbonate (800 µl). The hydrolysis of α-D-glucopyranoside to *p*-nitrophenol was measured at 405 nm. Acarbose (200 µg/ ml) was used as the standard inhibitor.

Table 1. Plant parts used

Plant species	Common name*	Plant part
Coccinia grandis (L.) J. Voigt	*Kowakka*	Leaf
Ficus racemosa L.	*Attikka*	Stem Bark
Gymnema lactiferum (L.) R. Br. ex Schult	*Kurinnan*	Leaf
Gymnema sylvestre (Retz.) R. Br. Ex Schult	*Masbedda*	Leaf
Musa X *paradisiaca* L.	*Alu kesel*	Yam
Phyllanthus debilis Klein ex Willd	*Pitawakka*	Whole plant
Phyllanthus emblica L.	*Nelli*	Fruit
Pterocarpus marsupium Roxb.	*Gammalu*	Latex
Strychnos potatorum L. f.	*Ingini*	Seeds
Tinospora cordifolia (Willd.) Hook.f & Thoms.	*Rasakinda*	Leaf

**Commonly used Sri Lankan names of the plants are listed*

2.5 Calculation of Percentage Inhibition of Enzyme Activity

Percentage inhibition was calculated using the following formula.

$$\text{Percentage inhibition} = 100 - \left\{ \frac{(\text{Absorbance of Test-Absorbance of Test Blank}) \times 100}{(\text{Absorbance of Control-Absorbance of Control Blank})} \right\}$$

2.6 Calculation of IC_{50}

The concentration of the extract that inhibits 50% of the enzyme activity (IC_{50}) was calculated. Extracts with high inhibitory activity were analyzed using a series of suitable extract concentrations. IC_{50} values were determined by plotting percent inhibition (Y axis) versus log10 extract concentration (X axis) and calculated by logarithmic regression analysis from the mean inhibitory values [15].

2.7 Statistical Analysis

All experiments were performed three times. Each experiment was carried out in triplicates. Data are expressed as mean ± standard deviation. Statistical analysis was performed using ANOVA. Values of p which were <0.05 were considered as significant.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 α-Amylase inhibitory activity

F. racemosa stem bark and *P. marsupium* latex showed approximately 98% amylase inhibitory effects with 1 mg/ ml extract (Fig. 1). *P. emblica* fruit (73.9%) and *P. debilis* whole plant (53%) also showed significant amylase inhibitory effects at 1 mg/ ml. *T. cordifolia* leaves showed minor inhibitory effects (16.18%). Extracts of *C. grandis, G. lactiferum, G. sylvestre, M. paradisiaca and S. potatorum* showed negligible or minor inhibition (0.09-9.18%) at 1 mg/ ml concentration. IC_{50} values of the four plant parts with higher inhibitory effects are shown in Table 2. The other six plants did not exert sufficient inhibitory effects even with 10 mg/ ml extracts. Therefore IC_{50} for amylase was not determined with these six plants. The observed IC_{50} values of *F. racemosa stem bark* (19.73 µg/ml) and *P. marsupium* latex (2.97 µg/ml) were significantly lower ($p< 0.05$) than the IC_{50} value of the standard inhibitor Acarbose (262.54 µg/ml) for porcine pancreatic amylase. The percentage α-amylase inhibition (%) of *F. racemosa, P. emblica* and *P. marsupium* at varying concentrations are shown in Fig. 3. Accordingly the most significant amylase inhibitory effect was observed with *P. marsupium.*

3.1.2 α-Glucosidase Inhibitory Activity

P. emblica fruit, *P. marsupium* latex, *P. debilis* whole plant and *F. racemosa* stem bark showed approximately 98% glucosidase inhibitory effects with 0.5 mg/ ml extract (Fig. 2) with lower IC_{50} values (Table 2). *M. paradisiaca* yam (83.13%) and *T. cordifolia* leaves (41.48%) also showed significant ($p< 0.05$) glucosidase inhibitory effects at 0.5 mg/ml (Fig. 2). Leaves of *C. grandis, G. lactiferum, G. sylvestre and S. potatorum* seeds showed very low inhibition (2.91-10.91%) at 0.5 mg/ ml concentration (Fig. 2). IC_{50} values of the ten plant parts are shown in Table 2. The observed IC_{50} values of *P. emblica* fruit (0.48 µg/ml), *P. debilis* whole plant (0.57 µg/ml), *P. marsupium* latex (0.54 µg/ml) and *F. racemosa* stem bark (19.88 µg/ml) were significantly lower ($p< 0.05$) than that of the standard inhibitor Acarbose (208.53 µg/ml) for yeast glucosidase.

The percentage α-glucosidase inhibition (%) of *F. racemosa, P. debilis, P. emblica* and *P. marsupium* at varying concentrations are shown in Fig. 4. Concentrations at which >95% inhibition were obtained are 0.1 mg/ ml (Log -1) for *F. racemosa,* 0.01 mg/ ml (Log -2) for *P. emblica* and *P. debilis and* 0.001 mg/ ml (Log -3) for *P. marsupium* (Fig. 4). Even though *P. emblica* showed the lowest IC_{50}, for glucosidase, the concentration of the extract which has shown >95% glucosidase inhibition with *P. marsupium* was ten times less than that of *P. emblica*. This shows the rapid increase of inhibitory activity with higher concentration of *P. marsupium*.

F. racemosa stem bark, *P. emblica* fruit, *P. debilis* whole plant and *P. marsupium* latex showed higher inhibitory effects on both α-amylase and α-glucosidase activities.

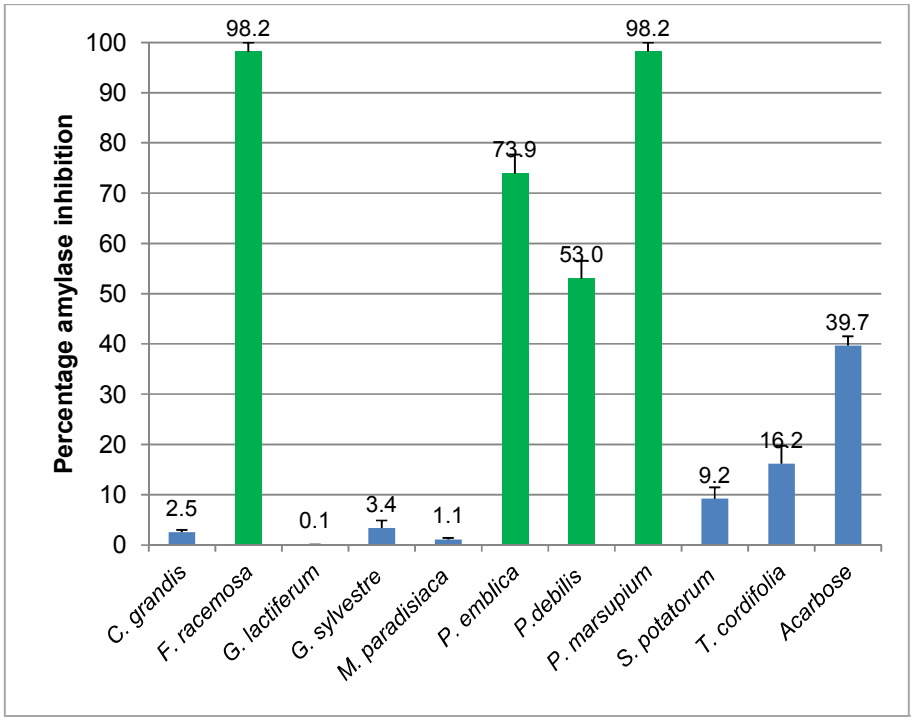

Fig. 1. Percentage α-amylase inhibitory activities of the plant extracts

α-Amylase inhibitory activities of the ten plant parts were measured using 1 mg/ ml extracts. Inhibitory activities are expressed as mean ± standard deviation. Extracts with > 50% inhibition are shown in green

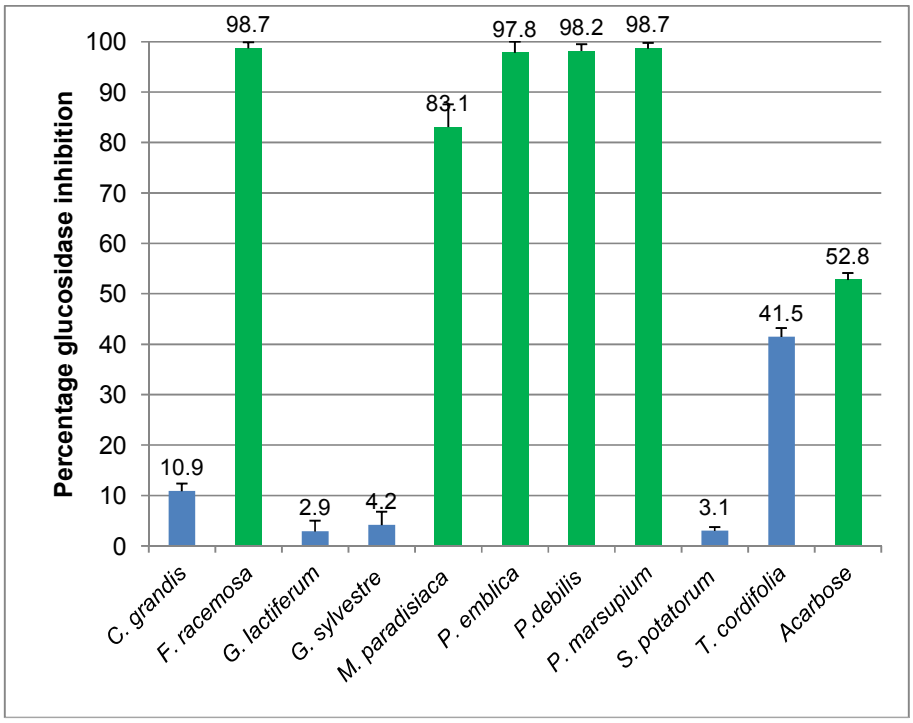

Fig. 2. Percentage α-glucosidase inhibitory activities of the plant extracts

α-Glucosidase inhibitory activities of the ten plant parts were measured using 0.5 mg/ ml extracts. Inhibitory activities are expressed as mean ± standard deviation. Extracts with > 50% inhibition are shown in green

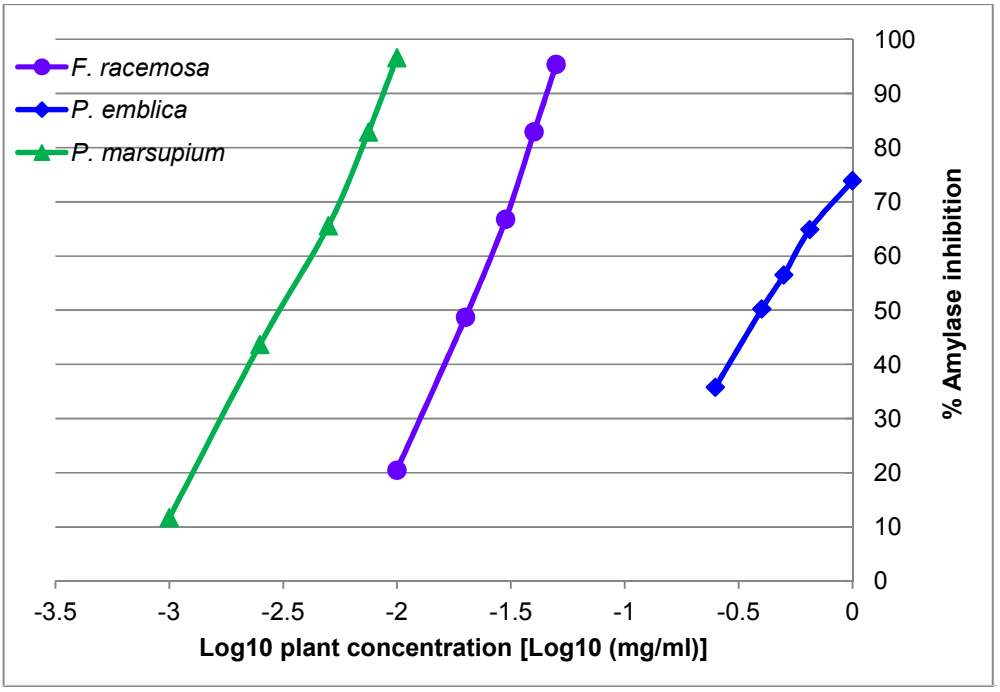

Fig. 3. The percent α-amylase inhibition (%) of different extracts at varying concentrations

Three extracts that showed higher inhibition were used. Data are indicated as mean percentage inhibition. Final concentrations used for the extracts included 10, 20, 30, 40, 50 µg/ ml for F. racemosa, 250, 400, 500, 650, 1000 µg/ ml for P. emblica and 1, 2.5, 5, 7.5, 10 µg/ ml for P. marsupium

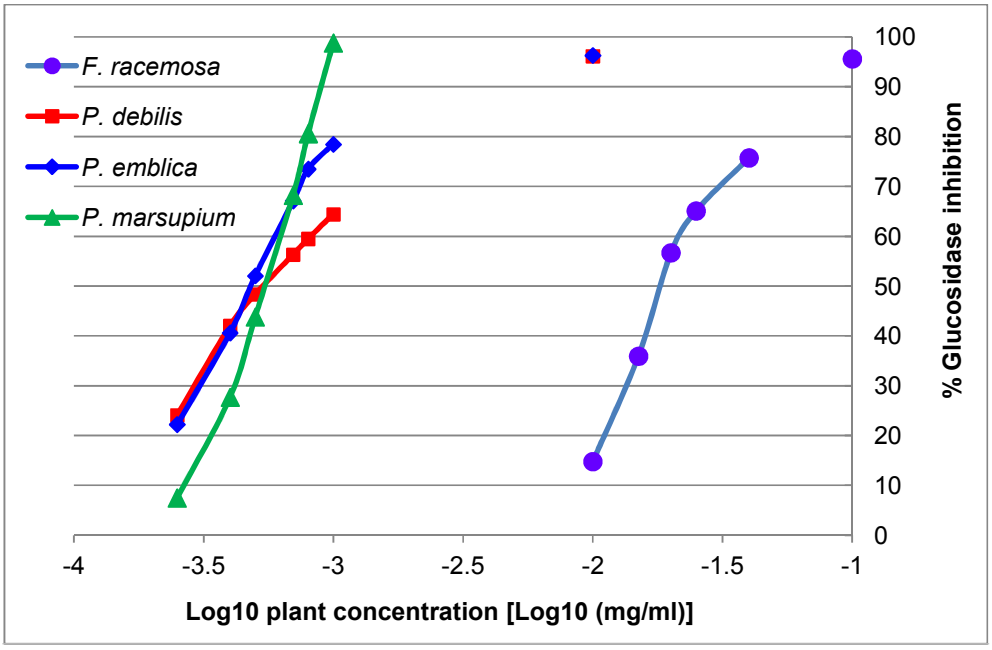

Fig. 4. The percent α-glucosidase inhibition (%) of different extracts at varying concentrations

Four extracts that showed higher inhibition were used. Data are indicated as mean percentage inhibition. Final concentrations used for the extracts included 10, 15, 20, 25, 40, 100 µg/ ml for F. racemosa, 0.25, 0.4, 0.5, 0.7, 0.8, 1, 10 µg/ ml for P. emblica and P. debilis and 0.25, 0.4, 0.5, 0.7, 0.8, 1 µg/ ml for P. marsupium

Table 2. IC_{50} values for α-glucosidase and α-amylase inhibitory activities of the plant extracts

Plant parts	IC_{50} µg/ml amylase inhibition	IC_{50} µg/ml glucosidase inhibition
Coccinia grandis leaves	*	1800
Ficus racemosa stem bark	19.73	19.88
Gymnema lactiferum leaves	*	2567
Gymnema sylvestre leaves	*	2737
Musa paradisiaca yam	*	178
Phyllanthus debilis whole plant	937	0.57
Phyllanthus emblica fruit	397.67	0.48
Pterocarpus marsupium latex	2.97	0.54
Strychnos potatorum seeds	*	2444
Tinospora cordifolia leaf	*	608
Acarbose	262.54	208.53

IC_{50} values for α-amylase inhibitory activities were measured only with the four plant extracts which showed higher inhibitory effects. The other six plants did not exert sufficient inhibitory effects even with 10 mg/ ml extracts. Therefore IC_{50} for amylase was not determined with those six plants. IC_{50} values were measured for α-glucosidase with all ten extracts*

3.2 Discussion

Prolonged hyperglycaemia is an independent risk factor in the development of chronic diabetic complications. The primary goal of the management of type 2 diabetes is to reduce the blood glucose concentration to a normal or near normal level [2]. Many plant extracts are known for their antidiabetic effects and were being used for the treatment of diabetes without scientific evidence. In the present study, ten plants were selected in which nine other than *G. lactiferum* were used to treat diabetes since ancient times without side effects [7,8,16,17]. They are also being used by Ayurvedic practitioners in Sri Lanka extensively to treat diabetes to date. The present study was conducted to investigate the potential inhibitory effects of nine antidiabetic plants on the major carbohydrate hydrolysing enzymes; α-amylase and α-glucosidase.

Results of the current study indicates that *F. racemosa, P. emblica, P. debilis* and *P. marsupium* have strong inhibitory effects on amylase and glucosidase activities even at very low concentrations of extracts. *M. paradisiaca* and *T. cordifolia* also showed inhibitory effects on glucosidase activity. These findings suggest that the known hypoglycaemic effects of these six plants could be exerted at least partly by their inhibitory effects on digestive enzymes. The present study does not provide evidence for a significant inhibition of amylase and glucosidase by *C. grandis, G. sylvestre* and *S. potatorum.* Hence, the hypoglycaemic effects known to exist with these three plants may be exerted by other mechanisms. Further studies to identify these mechanisms are necessary. *G. lactiferum* which is not considered as an antidiabetic plant did not show inhibitory effects on the two enzyme activities.

Our findings with *C. grandis, F. racemosa, P. emblica, P. debilis* and P*. marsupium* on amylase and glucosidase inhibition agreed with those of previous studies. Different solvent extracts including methanol extracts of *C. grandis* (*Coccinia indica*) fruit did not show inhibitory effects on porcine pancreatic amylase [15]. Ahmed and Urooj demonstrated that *F. racemosa* stem bark inhibits porcine pancreatic α-amylase and rat intestinal α-glucosidase, sucrase in a dose-dependent manner *in vitro* [18]. Ahmed and Urooj suggested that one of the mechanisms through which *F. racemosa* stem bark exerts the hypoglycemic effects *in vivo* is by inhibiting carbohydrate hydrolyzing enzymes [18]. In another study, five extracts of *F. racemosa* stem bark obtained using sequential extraction with hexane, chloroform, ethyl acetate, acetone and methanol showed α-amylase and α-glucosidase inhibitory activities [19]. *P. emblica* fruit ethanol extracts showed almost 100% yeast α-glucosidase inhibition at 1 mg/ml [20]. Methanol extract of *P. emblica* exhibited α-amylase and α-glucosidase inhibitory effects [21]. *P. debilis* aqueous plant extract significantly inhibited the glucose absorption from the small intestine in normoglycaemic mice [22]. In their study chronic administration of *P. debilis* extract did not induce toxicity on liver or kidney. *P. marsupium* latex water extracts has showed *in vivo* α-glucosidase inhibitory activity in Sprague-Dawley rats [23]. *P. marsupium* ethanol extracts showed a very high inhibitory activity against porcine pancreatic α-amylase (IC_{50} 5.16 µg/ ml)

and yeast α-glucosidase (IC_{50} 1.06 µg/ ml) [24]. The part of the plant used was not reported [24]. A remarkable inhibition of α-amylase by *P. marsupium* extract was observed in rabbits [25].

However, the results of the current study did not match with high inhibitory effects observed with *T. cordifolia* leaves previously. Methanol extract of the leaves of *T. cordifolia* showed high amylase inhibitory effect with an IC_{50} of 20 µg [26]. However, in the present study, only 16% inhibition was obtained even with 1 mg/ ml methanol extract of *T. cordifolia.*

Even though phytochemical analysis was not conducted in the current study, plant polyphenols such as flavonoids and tannins are known to have inhibitory effects on amylase and glucosidase. Potency of amylase inhibition by flavonoids; the major polyphenols present in plants is correlated with the number of hydroxyl groups on the B ring of the flavonoid skeleton. The interaction between amylase and the polyphenol ligands occurs with the formation of hydrogen bonds between the hydroxyl groups in certain positions of the polyphenol and the catalytic residues of the catalytic site [5]. Interaction between tannins and α-amylase is also suggested to be correlated with free OH groups in the tannin, that are likely to participate in making hydrogen bonds [5]. Hydroxylation of flavonoids is known to increase the inhibitory effects on glucosidase too [27]. *P. emblica* fruit is known to be rich in hydrolysable tannins, polyphenolic compounds such as gallic acid and ellagic acid, flavonoids such as quercetin and kaempferol. *P. emblica* fruit had the highest total polyphenolic content among twelve fruits [20]. Alpha amylase inhibitory activity of the tannin fraction of *P. emblica* fruit was found to be 410 µg/ml [28].

4. CONCLUSION

In the current study, ten plants which included nine plants used for the treatment of diabetes mellitus were tested. This study highlights the significantly high ($p< 0.05$) amylase and glucosidase inhibitory activity of the methanol extracts of *F. racemosa* stem bark*, P. emblica* fruit, *P. debilis* whole plant and *P. marsupium* latex exhibiting promising leads as inhibitory molecules with hypoglycaemic effects. The findings also provide scientific support for their use in traditional Ayurvedic medicine. *M. paradisiaca* yam and *T. cordifolia* leaves also showed considerable inhibitory effects on glucosidase activity. Therefore the known hypoglycaemic effects of these plants should be at least partly due to their effects on carbohydrate digestion and absorption. Leaves of *C. grandis, G. sylvestre* and seeds of *S. potatorum* did not show considerable inhibitory activity on the two enzymes and they may have other mechanisms responsible for their hypoglycemic effects. *G. lactiferum* which is not considered as an antidiabetic plant did not show inhibitory effect on both enzymes. Further studies are necessary to identify the compounds responsible for the enzyme inhibitory activities.

ACKNOWLEDGEMENTS

National Science Foundation Grant RG/2012/BS/01 for financial assistance. Mr. C.S. Handuwalge for collecting plant materials. Deputy Director, National Herbarium, Peradeniya for identification and authentication of plants.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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