 doi:10.20944/preprints201703.0116.v1

Potent Natural Inhibitors of Alpha-Glucosidase and Alpha-Amylase against Hyperglycemia *in Vitro* and *in Vivo*

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ABSTRACT

The inhibition of alpha-glucosidase and alpha-amylase is one of clinic strategies for remedy the type II diabetes. Herbal medicines are reported to alleviate hyperglycemia.

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However, the constituents from those sources whether are targeted to the alpha-glucosidase and alpha-amylase still unexplored. This study attempted to select the compounds for efficacy of hypoglycemia via cellular and mouse levels. The results illustrated that the cytotoxicity in all tested compounds at various concentrations except the concentration of 16-hydroxy-cleroda-3,13-dine-16,15-olide (HCD) at 30 μM were not significant difference ($p > 0.05$) when compared with the untreated control. Acarbose (reference drug), Antroquinonol, Catechin, Quercetin, Actinodaphnine, Curcumin, HCD, Docosanol, Tetracosanol, Berberine, and Rutin could effectively inhibit the alpha-glucosidase activity of Caco-2 cells when compared with the control (maltose). The compounds (Curcumin, HCD, Tetracosanol, Antroquinonol, Berberine, Catechin, Actinodaphnine, and Rutin) could reduce blood sugar level at 30 min in tested mice. The effects of tested compounds on area under curve (AUC) were significant ($p < 0.05$) among Acarbose, Tetracosanol, Antroquinonol, Catechin, Actinodaphnine, and Rutin along with Berberine and Quercetin. In *in vitro* (alpha-glucosidase) with *in vivo* (alpha-amylase) experiments suggest that bioactive compounds can be a potential inhibitor candidate of alpha-glucosidase and alpha-amylase for the alleviation of type II diabetes.

Keywords: *In vivo*; Alpha-glucosidase; Alpha-amylase; hyperglycemia

1. Introduction

Type II diabetes mellitus (TIIDM) or non-insulin dependent is a metabolic disease characterized by persistent hyperglycemia. In addition, TIIDM is a metabolic disorder trait by increased blood glucose level arising from insufficiency of insulin secretion or as known insulin resistance,[1] supporting perturbation of carbohydrate, protein and fat metabolism in the long term complexity of TIIDM is reduced risk of heart disease.[2] High blood sugar can produce long-term complications such as cardiovascular and renal disorders, retinopathy, and poor blood flow. Type II diabetes mellitus remains one of most health problems that 347

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million people worldwide have diabetes and there are more than 80% causes of death in low and middle income countries.[3] Diabetes is non-communicable diseases including the cause of death about 1.5 million or 4% of non-communicable diseases.[4] Its development can be prevented or delayed in people with impaired glucose tolerance by implementing lifestyle changes or the use of therapeutic agents. To date the prescription drugs for diabetic therapy such as insulin, biguanides (Metformin), sulfonylureas, thiazolidinediones (TZDs), and DPP-4 inhibitors are used for the treatment of diabetes which the advantage of Metformin can be combined with other drugs, for instance GLP-1 or insulin and even all of them have minimizing side effects.[5]

Currently, many drugs have been used for treatment of TIIDM and many problems involved in the adverse effects are related with their serial use.[6,7] Incidentally, the costly of those drugs is important issue for patient who must use them for long time.[8] Therefore, therapeutic strategies for the treatment of TIIDM consist of reduction of desire insulin, motivation of endogenous insulin secretion, enhancement of the handling of insulin at the target tissue and inhibition of deterioration of oligosaccharides and disaccharides.[9] The alternative medicine for anti-hyperglycemia as alpha-glucosidase inhibitor known starch blockers, which is consist of the function for absorption of exact carbohydrates in gastrointestinal tract, and is used to prolong rise in blood glucose after a meal.[10] In addition, alpha-glucosidase inhibitor two drugs such as acarbose (Precose) and Miglitol (Glyset)[11] have been used in clinic. Acarbose, a well-known and efficacious alpha-amylase and alpha-glucosidase inhibitor, is a post-prandial acting anti-diabetic drug. Importantly, acarbose works by slowing the action of certain chemicals the break down food to release glucose into blood. Additionally, the short-term effect of acarbose can reduce the pancreatic alpha-glucosidase and alpha-amylase enzymes for decreasing current of blood glucose level.[12] Alpha-amylase is also related to the breakdown of long chain carbohydrates and this inhibitor similar to acarbose which defers the digestion of carbohydrate and extends

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overall the time in the digestion of post-prandial plasma glucose increase.[13,14] Hence alpha-glucosidase and alpha-amylase inhibitors are vital medicines to inhibit the assimilation of carbohydrates in the intestines, can be used to treat TIIDM and impaired glucose tolerance (IGT).[10]

In nowadays, many reviewing issues are reported that efficacy medicines are the alternative one of active components for anti-diabetes agents from natural sources or folk herbal medicines.[15] Interestingly, anti-diabetic properties of non-polar *Toona sinensis* Roem (Meliaceae) extract[16] and leaf extract contains the hypoglycemia effect underlying an increment of insulin to regulate the adipose glucose transporter 4 (GLUT4) have been reported.[17] *Cortex Phellodendri* can reduce glucose level and prevent or retard the development of diabetic nephropathy in streptozotocin-induced diabetic rats[18] and reveals the potential alpha-glucosidase and xanthine oxidase inhibitors.[19] Curcumin is the yellow-colored bioactive constituent of the perennial plant, *Curcuma longa* L., which possesses a wide range of physiological and pharmacological properties such as antioxidant, anti-inflammatory, anticancer, neuroprotective and anti-diabetic activities. Anti-diabetic activity of curcumin may be due to its potent ability to suppress oxidative stress and inflammation.[20] Moreover, one study has reported that *Sarcandra glabra* (Thunb.) is a plant source of traditional folk herbal medicine, can restore the insulin resistance and glucose tolerance from oral glucose tolerance test (OGTT) as inhibitory effect on alpha-glucosidase activity.[21] Of note plants are crucial source of chemical components potent biological activity in remedy of diabetes by reducing post-prandial hyperglycemia[22] with potential for arrest of alpha-amylase be used as therapeutic or folk herb medicine by extraction compounds from plant sources that have been evaluated in alpha-amylase inhibitor activity.[14] From one recent review article reports that the most relevant clinical trials are performed with medicinal plants and natural products such as aloe, banana, bitter melon, caper, cinnamon, cocoa, coffee, fenugreek, garlic, guava, gymnema, nettle, sage, soybean,

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green and black tea, turmeric, walnut, and yerba mate. The active ingredients of high interest as potential anti-diabetics are: fukugetin, palmatine, berberine, honokiol, amorfrutins, trigonelline, gymnemic acids, gurmarin, and phlorizin.[23] To the best of our knowledge, the constituents from those natural sources whether are targeted to the alpha-glucosidase and alpha-amylase still unexplored. The aim of this study was to investigate anti-diabetic natural compounds from natural sources with inhibitory properties against alpha-amylase and alpha-glucosidase via the cellular and mouse levels.

2. Materials and methods

2.1. Sources of chemicals/reagents

The ten selected natural compounds were Antroquinonol, Actinodaphnine, Berberine, HCD, Docosanol, Tetracosanol, Curcumin, Catechin, Quercetin and Rutin isolated from *Antrodia cinnamonea*, *Cinnamomum insularimontanum Hayata, Cortex Phellodendri, Polyalthia longifolia, Saccharum sinensis* RoxB., *Curcuma longa* Linn., and *Toona sinensis* are shown as in Table 1. *In vitro* experiments, all tested compounds were dissolved in ethyl alcohol (EtOH) and diluted with Dulbecco's Modified Eagle Medium (DMEM, GIBCO, Carlsbad, CA, USA).

2.2 Bioactive compounds from natural sources isolation

All of sources that have been mentioned were isolated in this study. (1) Antroquinonol derivative, the culture conditions of *A. cinnamonea* and extraction method of this compound was performed as previously reported.[24] This compound was isolated from the dried power of cultured *A. cinnamonea* mycelium as was elucidated using a Hitachi Model L-7420 UV/VIS spectrophotometer (Hitachi Ltd., Japan) at 254 nm.[25] (2) Dried *C. insularimontanum Hayata* bark was grinded and extracted in hot water for 3 h in a hot water extractor. The extract was filtered and the supernatant was concentrated with a rotary evaporator. The substrate was then freeze-dried, resulting in a powder extract. The powder

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extract was suspended in sterilized distilled water at the suitable concentrations.[26] As was separate using a Hibar Lichrosorb RP-18 column (Kanto Chemical Co., Japan, 7 μm; 250x10 mm ID) and chromatographic data were collected and recorded by a D-7000 HPLC System Manager Software (Hitachi Ltd., Japan).[25] (3) Dried bark of *C. Phellodendri* was powdered and preparing one gram of powder was suspended in 20 mL deionized water in a 100 mL of Erlenmeyer flask. Mixed from their was extracted with ultrasound for 30 min, after that the ultrasonic extraction, the extract was filtered and diluted to 50 mL with water and obtained liquid solution was performed using chromatography a D-7000 HPLC System Manager Software (Hitachi Ltd., Japan) analysis.[19] (4) The bark of *P. longifolia* was used 100 gram of powdered sample was sodden in 250 mL of 95% ethanol solution for 24 h followed by cold maceration for further 48 h with provisional shaker (TS-560, ORBITAL SHAKER, Taiwan).[27] (5) The peel of *S. sinensis* RoxB. was derived from the filter peel of a sugar mill (Shangsi Sugar Mill, Guangxi, China) and purify by deliming, degreasing and decoloring. There is air-dried, crushed and homogenized. After, analysis of the purity sugarcane wax were carried out using the saponfication (hydrolysis with alkali), calcification, soxhlet refluxing extraction (SRE), purification, and crystallization methods.[28] (6) The dried rhizomes of *C. longa* Linn. were boiled with distilled water for 3 h. Total extract was centrifuged at5000 rpm for 30 min and the supernatant of the extraction was cryodesiccation. This process extract was dissolved in distilled water to use for this study.[29] (7) The leaves of *T. sinensis* were collected being powdered, then dissolved in a mobile phase consisting of methanol:water (50:50, v/v) before high performance liquid chromatography (HPLC) analysis. Chromatographic discrimination was obtained by isocratic elution with methanol:water (50:50, v/v) during the first 15 min followed by gradually increasing the methanol proportion to 100% over a period of 10 min. A flow rate of 4.0 mL/min at room temperature was used by A Hitachi Model L-7100 high-precision pump (Hitachi Ltd., Japan) at 254 nm. Isolation was conducted using a Hibar Lichrosorb RP-18 column (Kanto Chemical

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Co., Japan, 7 µM; 250 x10 mm ID). Finally, the compound was analyzed by MS, UV, IR, H-NMR, and C-NMR.[25]

2.3 Cell viability assay

Caco-2 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM, GIBCO), with 20% of the fetal bovine serum (FBS, GIBCO) and 1% of penicillin-streptomycin. The MTT (3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) (Invitrogen, Eugene, Oregon, USA) assay is used to analyze the viability of cells using colorimetric method. Caco-2 (1×10^4 cells/well) was seeded in 96-well plates and were incubated (37°C, 5% CO_2) overnight to allow the cells attached to the wells. Cells incubated with various concentrations of Acarbose (50, 100, and 300 µM) for 24 h, after incubation 20 µL/well of MTT solution (5 mg/mL)was added and further incubated for 4 h. The medium was removed, and formazan was solubilized using dimethyl sulfoxide, absorbance was measured at 570 nm using a microplate reader (ThermoLabsystems, Opsys MR, Thermofisher scientific, Waltham, MA, USA).

2.4 Cell glucose assay

The simulated maltose conditions were measured by production of glucose in Caco-2 cells. Caco-2 (1×10^4 cells/well) was used as a test model at total volume of 50 µL/well with glucose assay buffer in a 96-well plate.[30] After confluent, the cell culture medium was removed and washed 3 times with 200 µL of phosphate-buffered saline (PBS). The culture medium in the well was replaced with a reaction mixture containing 50 µL of test drug (a potent alpha-glucosidase inhibitor) and 28 mM maltose or 28 mM sucrose (a sugar solution) in PBS (0.95 mL) as a substrate. After the Caco-2 enzyme reaction at 37°C in 5% CO_2 for 2 h, the treatment solution in each well was removed for glucose determination. The glucose level of solution was determined by the glucose oxidase method. Briefly, the glucose standard curve was simultaneously generated as 0, 0.2, 0.4, 0.6, 0.8, and 1.0 nmol/50 µL/well with glucose assay buffer. The whole reaction was incubated at 37°C for 30 min. The claret color

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measured at 490 nm is proportional to the original glucose concentration.[31]

2.5 *In vivo* bio-compatibility model: oral starch tolerance test (OSTT)

The animal experiments were executed according to "The Guidelines for Care and Use of Laboratory Animals" approved by National Dong Hwa University Animal Ethics Committee. Male C57BL/6 mice (20-30 g) were obtained from the National Laboratory Animal center (Taipei, Taiwan), kept at controlled environmental conditions with room temperature (22 ± 2°C), humidity (60 ± 10%) and were subjected to this test after fasted 12 h. Blood glucose levels were measured at 0, 30, 60, 90, 120 and 10 min before (0 min) and after starch given. Mice were punctured blood from the tail vein for the determining blood glucose and then blood glucose was immediately determined by the glucose oxidase method using active blood glucose monitor (Accu-Chek®, Roche Diagnostics, USA). The animal experiment, mice were given starch as acontrol group. Oral starch tolerance test (OSTT) were proceeded in fasting condition for overnight in whichwas quick administration by oral gavage of a 90% corn starch solution[32]and mixed the 2.5 g/kg Bwt starch with acarbose as a positive control group, and 2.5 g/kg Bwt starch plus 17 mg/kg Bwt Acarbose, 0.3 mg/kg Bwt Curcumin, 3 mg/kg Bwt HCD, 4 mg/kg Bwt Docosanol, 4 mg/kg Bwt Tetracosanol, 1 mg/kg Bwt Antroquinonol, 100 mg/kg Bwt Berberine, 6 mg/kg Bwt Catechin, 60 mg/kg Bwt Quercetin, 5 mg/kg Bwt Actinodaphnine, and 4 mg/kg Bwt Rutin, respectively, as the experimental groups.

2.6 Statistical Analyses

GraphPad Prism is commercial scientific 2D graphing and statistics software published by GraphPad Software. Results were analyzed using one-way ANOVA followed by Tukey's test. Statistical significance was set as p <0.05. All statistical procedures were performed with GraphPad Prism 5 (GraphPad Software, INC., La Jolla, CA, USA).

3. Results

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3.1 The cytotoxicity of natural compounds on the Caco-2 cells

To investigate the cytotoxic effects of natural compounds on the Caco-2 cell, the viability was measured by MTT assay. The cells were incubated with various concentrations of natural compounds for 24 h. When compared with the untreated control, the viabilities of cells were not significant difference ($p > 0.05$) in all tested compounds at various concentrations except the concentration of HCD at 30 µM (Table 2). Additionally, the data also exhibited less cytotoxicity of tested compounds even high tested concentration at 300 µM including Acarbose, Docosanol, Tetracosonol, Catechin, Quercetin, and Rutin.

3.2 Alpha-glucosidase activity of natural compound inhibitors simulate the maltose condition in Caco-2 cells

Next to evaluate the inhibitory efficacy of natural compounds on the alpha-glucosidase activity of Caco-2 cells, the extracellular glucose concentration of the supernatant after various concentrations of tested compounds treatment was measured by the glucose oxidase assay. At 6, 12 and 24 h incubations, Acarbose (reference drug), Antroquinonol, Catechin, Quercetin, Actinodaphnine, Curcumin, HCD, Docosanol, Tetracosanol, Berberine, and Rutin could inhibit the alpha-glucosidase activity of Caco-2 cells when compared with the control (maltose) (Table 3). After 24 h incubation, Acarbose, Catechin, Quercetin, Curcumin, Docosanol, and Tetracosanol could potentially inhibit the alpha-glucosidase activity in dose- and time-dependent manner whereas Antroquinonol, Actinodaphnine, HCD, Berberine, and Rutin failed to suppress the alpha-glucosidase activity.

3.3 Effect of natural compounds administration on blood glucose level in OSTT

In order to test the effect of natural compounds on blood glucose levels of mice via OSTT was performed as alpha-amylase activity assay. Different natural compound combined with starch was orally administrated after fasting blood sugar measured at 0 min. The blood glucose level of mice was measured at 0, 30, 60, 90, and 120 min, respectively. The blood glucose concentrations were increased to 111.6 mg/dL at 30 to 60 min after starch given and

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were decreased at 90 min (Fig. 1a). These oral natural compounds (Curcumin, HCD, Tetracosanol, Antroquinonol, Berberine, Catechin, Actinodaphnine, and Rutin) could decrease blood sugar concentrations at 30 min. Furthermore, the blood glucose incremental curves were significantly different between Acarbose, Antroquinonol, and Quercetin. In addition, Curcumin, HCD, and Docosanol were not significantly different with Berberine and Quercetin. Moreover, Acarbose, Tetracosanol, Antroquinonol, Berberine, Catechin, Actinodaphnine, and Rutin were decreased whereas Berberine and Quercetin were increased in starch ingestion and absorption after starch given at 60 min (Fig. 1b). When the changes of glucose level are presented as the area under curve (AUC), Catechin, Actinodaphnine, and Rutin were sustained the hypoglycemic effect as the inhibition of**A**carbose. Additionally, the AUC of Curcumin, HCD, Docosanol, Berberine, and Quercetin were not higher than Acarbose or there were fewer than efficacy. Based on the inhibitory efficacy of blood sugar as compared with Acarbose (clinical drug as a reference), these ten tested compounds can be categorized into four classes. Our results revealed a number of folds (efficiency of drug) which were refined by the highest scoring is 206.0 (first group), 37.7-10.9 is second group, 7.2-4.4 is third group and at least is 1.2-0.7 (fourth group) as based on the design and statistical analysis of experiments. The resultant values led to (1) most potent group: Curcumin (206.0), (2) second group: Antroquinonol (37.7), HCD (17.6), Docosanol (15.5), and Tetracosanol (10.9), (3) third group: Rutin (7.2), Actinodaphnine (6.4), and Catechin (4.4), (4) fourth group: Quercetin (1.2) and Berberine (0.7)(Table 4). These results confirmed that the selected natural compounds possess the inhibition of alpha-amylase and alpha-glucosidase against hyperglycemia via cellular and mouse level.

4. Discussion

Type II diabetes mellitus (TIIDM) is the most common of gastrointestinal disorders as known chronic hyperglycemia. However, increasing of blood glucose levels are the results

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from entire or relative default of insulin secretion.[33] The inhibitory capability of alpha-amylase and alpha-glucosidase as these two carbohydrate-hydrolysing enzymes are known to be important molecular targets for attenuation of postprandial hyperglycemia to keep away from carbohydrate or starch to be digested and sucked in the body system has permitted to indicating these compounds as starch blockers are considered a therapeutic potential tool for treatment of TIIDM.[34] Currently, there are many anti-diabetic drugs that perform mostly for inhibiting carbohydrate digestion and absorption.[14] The pharmaceutical agents are found out as drugs to oppose TIIDM such as Metformin, Sylphonylureas, TZDs, GLP-1 analoges, DDP-4 inhibitors, insulin, Pramlintide, and SGLT-2 inhibitors.[35] These drugs help TIIDM people for maintaining blood glucose level while they still have side effect on the patients likewise.[36] In this study, we evaluated the inhibitory efficacy of alpha-amylase with acarbose (reference drug) which is renowned inhibitor and acarbose analogues have been found potential inhibitors of alpha-amylase[37], thereby the usage of acarbose may be alternative to change lifestyle in order to delay management of TIIDM.[38] Therefore, the tested agents or substances that reduce high blood glucose may exert as potential therapy drugs of diabetes.

Notably, the present study is associated with our recent work demonstrated that the top ten natural compounds (high scores docking) via molecular docking as shown in table 2 of this research showed high percentages inhibition against alpha-glucosidase and alpha-amylase activity when compared with commercial drug.[6] However, the eminent side effect of such treatments has driven importantly for candidate alternative medication with tiny severe or no side effects.[36] Hence the evidence for a candidate potent effect of folk herbal medicine occupy in dealing to anti-diabetes.[39] Moreover, the effectiveness of folk medicine must be herbal therapies as to build few adverse effects and reduce costly for alternative hyperglycemia agents. Particularly, curcumin (bis-α,β-unsaturated β-diketone), the chief constituent of turmeric plant (*C. longa*), plays a significant role in prevention of various

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diseases including diabetes by decrease blood glucose and increase plasma insulin level,[40] while different species has been taken as anti-diabetic agents in potent and safety on therapy of patient's diabetes.[41] Moreover, the bioactive compounds from *C. longa* and *C. insularimontanum*are identified as the best inhibitors of alpha-glucosidase and alpha-amylase enzyme activity.[42] Natural curcuminoids and curcumin analogs exert the inhibition of alpha-glucosidase [43] and further demonstrates that the alpha-glucosidase (0.4 µg/mL) and alpha-amylase (0.4 µg/mL) inhibitory potential of turmeric ethyl acetate extract is significantly higher than those of the reference drug acarbose (17.1 µg/mL and 290.6 µg/mL, respectively). In Table 4 of the present study also showed that curcumin can reduce blood glucose at lowering concentration (0.3 mg/kg Bwt) of drug doses as effective 206.0 fold as compared with acarbose (17 mg/kg Bwt) in OSTT.

Our recent results revealed that the rank of inhibiting alpha-amylase of natural compounds were Curcumin, Berberine, Docosanol, and HCD as 7.7, 5.9, 4.8, and 3.6 fold when compared to Acarbose.[6] Additionally, Curcumin had the highest fold of alpha-amylase inhibition and demonstrated that can promote PPARγ pathway associated with the NF-*k*B pathway.[44] From reviewing this theme, Curcumin also decreases inflammation, delays and prevents obesity-induced insulin resistance because this is the anti-oxidant of NF-*k*B inhibitor from turmeric.[45] Bisdemethoxycurcumin (BDMC) isolated from *C. longa* Linn**.**, can inactivate human pancreatic α-amylase,[46]and synthesized novel anti-diabetic curcumin derivatives with inhibitory properties against alpha-amylase and alpha-glucosidase are administrated for attenuation of postprandial hyperglycemia.[47] Additively, Curcumin and Antroquinonol can reduce blood glucose level by reducing the hepatic glucose source and stimulate glucose uptake by up-regulation of GLUT4 translocation.[48]

Berberine (delta alkaloids), the main effective composition of Chinese Goldthread Rhizome, is also effective in treating diabetes in today's clinical practice of Traditional Chinese Medicine. The acting mechanism of the hypoglycemic activity of Berberineis

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demonstrated by acutely inhibited the alpha-glucosidase to support this traditional use of berberine and Chinese Goldthread Rhizome for the treatment of diabetes mellitus.[49] Berberine could reduce fasting blood glucose from 10.6 to 6.9 mmol/L (190.8 to 124.2 mg/dL) which Berberine maintains the homeostasis of insulin resistance.[50] The anti-hyperglycaemic activity of Berberine is at least partly due to its ability to inhibit alpha-glucosidase and decrease glucose transport through the intestinal epithelium.[51] The inhibitory mechanisms of Berberine as an anti-hyperglycaemic agent might influence on intestinal disaccharidases and beta-glucuronidase.[52] Berberine could ameliorate renal dysfunction in diabetic nephropathy (DN) rats through controlling blood glucose, reduction of oxidative stress and inhibition of the activation of the polyol pathway.[53] Berberine promoted anti-diabetes potentials and AMP activated protein kinase (AMPK) in the liver and muscle cells.[54] In this study, diabetic mice models are also employed to show the effect of Rutin, Catechin, Actinodaphnine, Tetracosanol, and Antroquinonol on blood glucose-lowering effect.

Moreover, previous report also showed that oral administration at 100 mg/kg of Rutin for 45 days can help to decrease fasting plasma glucose and increase insulin levels of streptozotocin (STZ)-induced diabetic rats.[55] Rutin also decreased blood sugar concentration at 30 min and increased 111.6 mg/dL of blood glucose concentration at 30 to 60 min in this study. Surprisingly, taken Rutin and Quercetin together have been demonstrated an effective being of dual alpha-glucosidase and alpha-amylase inhibitors for reducing blood glucose.[56] While both of compounds were decreased blood glucose levels as the inhibition of alpha-glucosidase[57] as shown in Fig. 1b. Currently, several studies have reported that Rutin[58,59], Quercetin[60,61], and Catechin[62,63] are a group of flavonoids by isolated from *T. sinensis* plant, that have been shown to present blood glucose lowering properties in animal model and being potent compounds in the inhibition of alpha-amylase. Our recent work illustrates that Rutin may serve as a potential agent for glycemic control

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through enhancement of insulin receptor kinase (IRK) activity, thereby inducing the insulin signaling pathway causing increased GLUT4 translocation and increased glucose uptake.[48] One report also indicates that both Catechin and Quercetin can reduce with alpha-amylase and subsequently decrease the blood glucose level in mice after oral starch[64] as foregoing is similar to the efficacy results of natural compounds when compared to Acarbose. In one study has demonstrated that many polyphenolic compounds display a role alpha-amylase inhibitory activity[65] such as Catechin and Rutin[14] while Quercetin is bioflavonoid that has been used for relieving hyperglycemia activity to lead glucose homeostasis.[66] The alkaloids exhibited inhibitory activity against alpha-glucosidase, aldose reductase, alpha-amylase, and lipase. The flavonoids also showed mild inhibition on alpha-glucosidase, aldose reductase, alpha-amylase, and lipase.[67] Furthermore, the combination of Quercetin with curcumin is more effective to exert on controlling blood glucose levels in TIIDM.[68] Nevertheless, further *in vivo* studies in different models of hyperglycemia are required to evaluate the efficacy.

Conclusions

Of note the enhancing prevalence of hyperglycemia and negative clinical consequence were investigated with commercial anti-diabetic medicine for leading to new drugs discovery by focusing on the control of postprandial glucose levels. Ten natural compounds (Curcumin, HCD, Docosanol, Tetracosanol, Antroquinonol, Berberine, Catechin, Quercetin, Actinodaphnine, and Rutin) extracted from folk herbal medicine have been discovered in inhibitory potency of alpha-glucosidase and alpha-amylase. In addition the potent of natural compounds can reduce blood glucose level, are Catechin, Actinodaphnine, Rutin, Tetracosanol, and Antroquinonol when compared to Acarbose (clinical drug). Furthermore, the potential investigations of folk herbal medicine will provide valuable information to seek drug doses of natural sources for therapy TIIDM with less or no adverse effects.

 doi:10.20944/preprints201703.0116.v1

Conflict of interest

There are no conflicts of interest declare

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