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ORIGINAL ARTICLE

Antidiabetic effects of *Mukia maderaspatana* and its phenolics: An *in vitro* study on gluconeogenesis and glucose uptake in rat tissues

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Abstract

Context: Traditional medicine is used by over 60% of the world's population for health care. *Mukia maderaspatana* (L.) M. Roem. (Cucurbitaceae) (*Mukia*) is extensively used in folklore medicine as an antidiabetic plant. It is rich in phenolics that contribute to its medicinal properties.
Objective: *Mukia* extract and phenolics such as quercetin and phloroglucinol are investigated for their *in vitro* antidiabetic activity.
Materials and methods: Quercetin, phloroglucinol, and methanol extract of the dried whole plant (0.25 and 0.5 mg/ml) were studied for the inhibition of gluconeogenesis in rat liver slices and glucose uptake in isolated rat hemi-diaphragm (50 and 100 μg/ml). Phenolics of *Mukia* were analyzed by HPLC.
Results and discussion: Glucose (1.2 mg/g/h) was synthesized from pyruvate and the synthesis was completely inhibited by insulin (1 U/ml). Quercetin at 0.25 and 0.5 mg/ml caused 65% and 89% inhibition (0.42 mg/g/h and 0.13 mg/g/h glucose). Addition of insulin did not increase inhibition. Phloroglucinol inhibited 100% glucose production with or without insulin. *Mukia* (0.25 mg/ml) inhibited gluconeogenesis (0.65 mg/g/h) by 45%, and with insulin, inhibition increased to 50% (0.59 mg/g/h). At 0.5 mg/ml, glucose production was stimulated by1.2-fold, but with insulin it was inhibited by 89% (0.13 mg/g/h glucose). *Mukia* had no effect on glucose uptake, but potentiated the action of insulin mediated glucose uptake (152.82 ± 13.30 mg/dl/g/30 min) compared with insulin control (112.41 ± 9.14 mg/dl/g/30 min) ($p < 0.05$). HPLC analysis revealed the presence of phenolics.
Conclusion: Results provide scientific rationale for the use of *Mukia* in folk medicine as an antidiabetic nutraceutical.

Keywords

Hemi-diaphragm, liver, medicinal plant, phloroglucinol, quercetin, type 2 diabetes mellitus

History

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Introduction

Diabetes mellitus is a single most prevalent disease and a major cause of mortality and morbidity worldwide. It is estimated that there are over 350 million diabetics globally, and of them, over 90% have type 2 diabetes (Shaw et al., 2000). Type 2 diabetes represents a syndrome with disturbances in the metabolism of carbohydrates and fats and is also characterized by insulin resistance, especially in the muscle, adipose, and liver. Insulin resistance results in excess glucose output in the liver and impaired glucose utilization in muscle and peripheral tissues.

A change in lifestyle is at the forefront of management of type 2 diabetes, which includes exercise, weight control, and medical nutrition therapy (Nathan et al., 2006). Patients who are unable to achieve glucose homeostasis by diet and exercise are given oral antidiabetic drugs as a part of the conventional therapy. There are five classes of oral antidiabetic agents, namely, biguanides, sulphonylureas, α-glucosidase inhibitors, thiozolidine diones, and meglitinides. All these drugs have side effects (De Fonzo, 1999). Hence medicinal plants have increasingly becoming popular in the last several years as an alternate therapy (Dey et al., 2002). They have the same degree of efficacy as the antidiabetic drugs, but without the side effects. Moreover, many of the present day antidiabetic drugs were derived from medicinal plants. For example, metformin was synthesized based on the use of *Glega officinalis* (Linn.) (Fabaceace) to treat diabetes (Cusi & Defronzo, 1998).

Over 400 traditional plant-based antidiabetic therapies have been reported (Guptha et al., 2008). However, only a very few of them have been investigated scientifically to assess their efficacy. The physiological effects of plants and their extracts are because of the presence of specific phytochemicals in them. The phytochemicals such as phenolics (Yao et al., 2012), flavonoids (Chang et al., 2012), alkaloids (Sharma et al., 2010), and terpenoids (Periyasamy et al., 2012) possess diverse biological properties making them attractive candidates for therapeutic applications (Alexiou & Demopoulos, 2010). *Mukia maderaspatna* (L.) M. Roem. (Cucurbitaceae), commonly known as Madras pea

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pumpkin, is one such plant. It is a hepatoprotective (Thabrew et al., 1995), an anti-inflammatory, antiarthiritic (Ramakrishnamacharya et al., 1996), and antihypertensive agent and showed beneficial effects on lipid profile, fibrinogen, bilirubin, and body mass index in human volunteers (Raja et al., 2007). It is eaten as a leafy vegetable and traditionally used in antidiabetic therapy in some parts of India. It is rich in phenolics that contribute to its biological and medicinal properties.

In the present study, the *in vitro* antidiabetic effects of the methanol extract of *M. maderaspatana* (*Mukia* extract) and phytochemicals such as quercetin and phloroglucinol were studied. Their effect on gluconeogenesis in the rat liver tissues and glucose uptake in the isolated rat hemidiaphragm are presented. The antidiabetic effects of the *Mukia* extract are compared with those of insulin, quercetin, and phloroglucinol. The HPLC analysis was also carried out for the extract to identify and quantify the phenolic constituent(s).

Materials and methods

Chemicals

Quercetin and phloroglucinol were purchased from Sigma-Aldrich (Bangalore, India). Sodium pyruvate and glucose were purchased from SR Laboratories (Mumbai, India). Hank's Balanced Salt Solution (HBSS) and Tyrode-Ringer buffer were purchased from Hi-Media Laboratories (Mumbai, India). Glucose oxidase and peroxidase (GOD/POD) assay kit was purchased from AUTO SPAN Diagnostics (Mumbai, India). Human Insulin was purchased from Nova Nordisk (Bangalore, India). All other chemicals and reagents were purchased from SR Laboratories and Hi-Media Laboratories, and were of analytical grade.

Plant material and preparation of plant extract

The whole plant was collected from the Hassan district of Karnataka during the month of June, authenticated by botanist Dr. M.S. Sudarshana, University of Mysore. A voucher specimen (BOT-003-2010) has been deposited at the Botany Herbarium, University of Mysore, Mysore. The edible parts of the whole plant (leaves, stem and roots) were shade-dried and pulverized using a mechanical grinder. The powdered plant material (50 g) was extracted with methanol (200 ml) in a Soxhlet apparatus for 24 h. Solvent extract was filtered through Whatman No. 1 filter paper and the filtrate was evaporated to dryness using a rotary evaporator at 40 °C, which yielded a crude extract of 10% w/w. The dried extract was kept at −20 °C until further analysis.

Sequential extraction of plant material for HPLC analysis

The dried powder of whole plant material (50 g) was subjected to sequential Soxhlet extraction with solvents of increasing polarity such as petroleum ether (60−80 °C), chloroform, ethyl acetate, and finally with methanol, for 24 h. Each solvent extract was collected separately and filtered through Whatman No. 1 filter paper and the filtrate was evaporated to dryness using the rotary evaporator at 40 °C to yield crude extracts. The dried extracts were weighed and stored at −20 °C till further analysis.

HPLC analysis of *Mukia* extract

HPLC analysis of the different solvent extracts was carried out by the ISO method (ISO, 2005) for the identification of phenolics. Analysis were performed using an Agilent 1260 infinity series HPLC system comprising an autosampler (G13118), DI diode array detector (G4212B), and Agilent Eclipse Plus phenyl-hexyl column (4.6 × 250 mm, 5 µm). Samples or standards prepared in methanol (1 mg/ml) were injected in triplicate (20 µl) to the column. The mobile phase A consisted of 9% (volume fraction) acetonitrile, 2% (volume fraction) acetic acid with 20 µg/ml EDTA and mobile B consisted 80% (volume fraction) acetonitrile, 2% (volume fraction) acetic acid with 20 µg/ml EDTA. Separation was carried out at a 1 ml/min flow rate with an HPLC column maintained at 37 °C and a detection at 278 nm. HPLC analysis was carried out using a gradient elution. Binary gradient conditions: 100% mobile phase A for 10 min, then over 15 min, a linear gradient to 68% mobile phase A and 32% mobile phase B and held at this composition for 10 min. Then, reset to 100% mobile phase A over the next 5 min followed by 10 min equilibration before next injection.

Animals

Male albino rats weighing between 200 and 300 g were taken for the study from the Central Animal Facility, University of Mysore, Mysore. The animals were fed standard laboratory diet and water *ad libitum* and housed at room temperature. The rats were fasted overnight with free access to water prior to carrying out the *in vitro* experiments.

In vitro gluconeogenesis assay

Adult male albino rats were fasted overnight and were killed by cervical dislocation. The liver was excised and washed in ice cold saline and stored on ice. Liver slices were made as described by Peng et al. (1973) and Roobol and Alleyne (1972). The slices were weighed in a digital balance. The weights of tissue slices were between 100 and 150 mg. They were transferred to culture dishes containing Hank's Balanced Salt Solution (HBSS). Sodium pyruvate (10 mM) prepared in HBSS was added to the culture dish such that the final concentration of the pyruvate was 5 mM. The culture dishes were incubated at ambient temperature (27 °C) for up to 60 min. Aliquots were taken from the medium at 0, 30, and 60 min. The amount of glucose formed in the culture dish was assayed using the GOD–POD method described below.

Effect of insulin, phytochemicals and *Mukia* extract on *in vitro* gluconeogenesis

Gluconeogenesis in the liver was carried out as described above in the presence of 1 Unit (1 U) and 2 Units (2 U) of insulin (Nova Nordisk, Bangalore, Karnataka, India) added prior to the addition of pyruvate. Quercetin (0.25 and 0.5 mg/ml), phloroglucinol (0.25 and 0.5 mg/ml), and *Mukia* extract (0.25 and 0.5 mg/ml) were preincubated for 5 min individually with the liver slices before initiating

gluconeogenesis in the absence and presence of 1 U of insulin. Gluconeogenesis from pyruvate in the pre-treated liver slices was determined as described above.

In vitro glucose uptake by isolated rat hemi-diaphragm

Glucose uptake in isolated rat hemi-diaphragm was estimated essentially by the method described by Walaas and Walaas (1952) with some modifications (Chattopadhya et al., 1992). The glucose uptake studies were carried out using the rat-isolated hemi-diaphragm in Tyrode's solution containing 0.2% glucose. The glucose left over in the culture tubes after 30 min incubation at 37 °C in an atmosphere of 100% oxygen was determined as described below. Adult male albino rats were fasted overnight and killed by decapitation. The diaphragms were dissected quickly. The diaphragm isolated from each rat was divided into two equal halves. The isolated hemi-diaphragms were then rinsed in cold Tyrode's solution (without glucose) to remove any blood clot and weighed in a digital balance. The two halves of the hemi-diaphragms from the same rat were not used for the same set of experiments, but were used for two different set of experiments. The glucose uptake was determined using the isolated rat hemi-diaphragm (Tyrode solution with 0.2% glucose) in the presence of 0.4 units/ml of insulin (Nova Nordisk), 50 and 100 µg/ml of *Mukia* extract, and in the presence of both insulin (0.4 units/ml) and *Mukia* extract (100 µg/ml). The uptake was compared with normal control diaphragms that contained only glucose in Tyrode's solution. A total of five groups with eight sets in each group were compared. Milligram of glucose taken up per gram of rat hemi-diaphragm/30 min was calculated. The results are expressed as mean ± standard deviation (SD) ($n = 8$).

Glucose assay by GOD–POD method

Glucose in the culture dishes/tubes was assayed by the GOD–POD assay kit protocol. Briefly, 50 µl of the incubated medium was transferred to a 96-well ELISA plate. The color reagent (200 µl) was added to each well. The color was developed in the dark at RT for 30 min and then the optical density was measured at 505 nm.

Statistical analysis

Results are expressed as mean ± SD. The means between two groups were compared using Student's *t* test, assuming equal variance among the groups and differences were considered statistically significant at $p < 0.05$.

Results

Sequential extraction of plant material for HPLC analysis

The yield of the different solvent extracts per gram of dry material was as follows: petroleum ether 36.6 mg/g, chloroform 27.8 mg/g, ethyl acetate 12.0 mg/g, and methanol 53.4 mg/g.

HPLC analysis of *Mukia* extract

The HPLC analysis showed different polyphenolic constituents with respect to different solvent extracts. The HPLC chromatogram of chloroform extract was found to contain two major peaks at 3 min and 23.1 min (Figure 1). The major peaks at 3.0 min and at 23.1 min were identified as phloroglucinol and quercetin, respectively, by comparing their retention time and UV spectra with those of the reference standards. The content of phloroglucinol and quercetin was quantified as 1.3 and 16.1 mg/g, respectively, of the dry material.

In vitro gluconeogenesis

Glucose production in the absence and presence of pyruvate and in the presence of insulin is shown in Figure 2. In the absence of pyruvate there was no glucose synthesis, whereas glucose was synthesized in the presence of pyruvate at 30 min 0.57 mg/g glucose and at 60 min 1.2 mg/g. There was a linear increase in the production of glucose with time. The gluconeogenesis in the presence of insulin was inhibited, but there was no significant difference between the inhibition of gluconeogenesis in the presence of 1 U/ml and 2 U/ml of insulin. Inhibition of gluconeogenesis by quercetin and phloroglucinol in the absence and in the presence of 1 Unit insulin is shown in Figure 3. Quercetin at 0.25 mg/ml concentration inhibited gluconeogenesis completely in the first 30 min, but in the subsequent 30 min, the inhibition was overcome slightly. At 60 min, the amount of glucose produced was 0.42 mg/g tissue (65% inhibition). In the presence of insulin (1U/ml) along with quercetin (0.25 mg/ml), the inhibition of gluconeogenesis was overcome by producing 0.22 mg/g glucose (61% inhibition) at 30 min. At 60 min, the

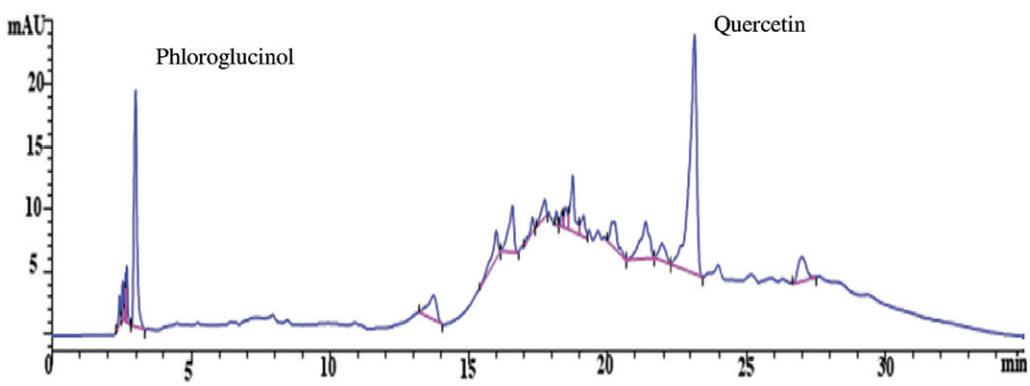

Figure 1. HPLC analysis of the chloroform extract of *Mukia* showing the presence of phloroglucinol and quercetin.

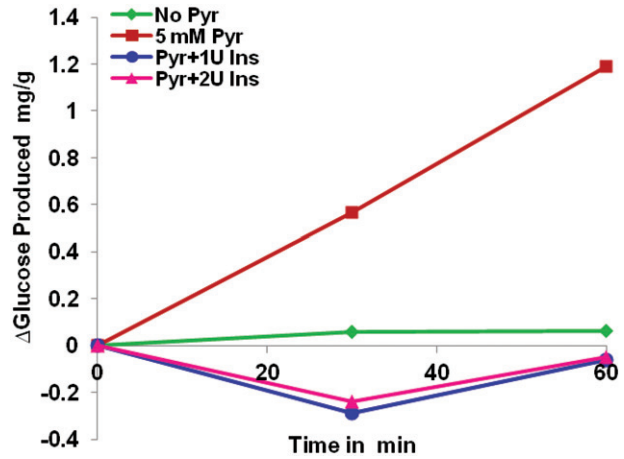

Figure 2. Gluconeogenesis from pyruvate in rat liver. *In vitro* gluconeogenesis in rat liver slices was tested in the absence and presence of pyruvate (5 mM) and in the absence and presence of 1 and 2 Units of insulin. Results are mg of glucose formed/g of liver.

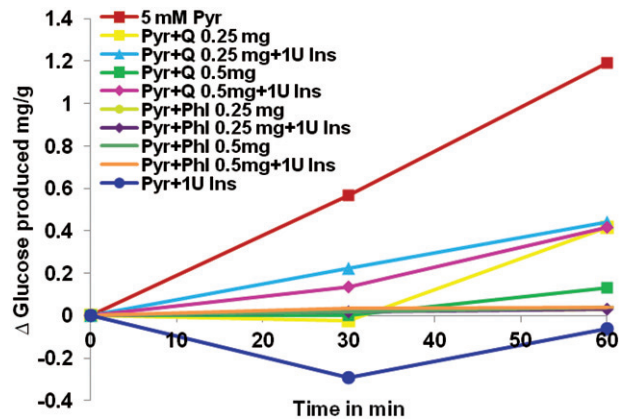

Figure 3. Inhibition of gluconeogenesis in rat liver by quercetin and phloroglucinol in the absence and presence of 1 Unit of insulin. Gluconeogenesis in rat liver was determined from pyruvate in the presence of 0.25 mg/ml and 0.5 mg/ml of quercetin or phloroglucinol preincubated with liver slices in the absence or presence of 1 Unit of insulin prior to determining gluconeogenesis from pyruvate (5 mM).

amount of glucose produced was 0.44 mg/g glucose (63% inhibition). At 0.5 mg/ml concentration, quercetin inhibited gluconeogenesis completely in the first 30 min, but the inhibition was slightly overcome at 60 min, resulting in the production of 0.13 mg/g glucose (89% inhibition). In the presence of insulin (1U/ml), at 30 min, 0.13 mg/g glucose (76% inhibition) was produced, and at 60 min, 0.42 mg/g (65% inhibition) glucose was produced when compared with pyruvate alone. Thus, in the presence of insulin, quercetin did not show any synergistic effect for the inhibition of gluconeogenesis. At 0.25 mg/ml, phloroglucinol inhibited gluconeogenesis completely at 30 min, and threrafter it continued for 60 min also. There was no change in the inhibition in the presence of insulin (1 U/ml) or when higher concentration of phloroglucinol (0.5 mg/ml) was present.

Inhibition of gluconeogenesis by *Mukia* extract in the presence and in the absence of 1 U insulin is shown in Figure 4. In the presence of 0.25 mg/ml *Mukia* extract, there was an initial inhibition of gluconeogenesis for the first

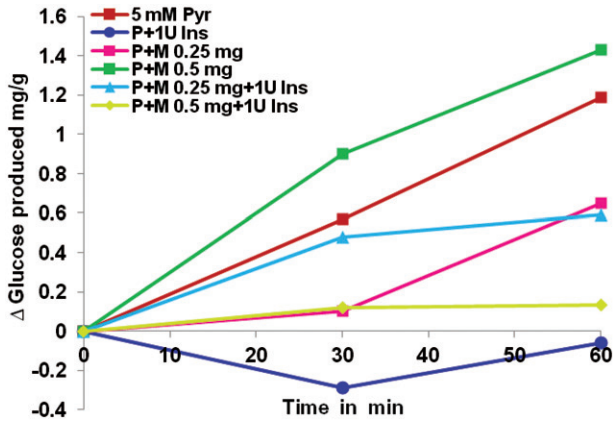

Figure 4. Inhibition of gluconeogenesis in rat liver by *Mukia* extract in the absence and presence of 1 Unit of insulin. Gluconeogenesis in rat liver was determined from pyruvate in the presence of 0.25 mg/ml and 0.5 mg/ml *Mukia* extract in the absence or presence of 1 U insulin preincubated with liver slices prior to determining gluconeogenesis from pyruvate (5 mM).

Table 1. *In vitro* glucose uptake by isolated rat hemi-diaphragm.

Group	Glucose uptake (mg/dl/g/30 min)
Normal control	101.29 ± 9.24*
Insulin control	112.41 ± 9.14*
Mukia 50 µg/ml	101.49 ± 8.29
Mukia 100 µg/ml	99.16 ± 12.72
Insulin + Mukia 100 µg/ml	152.82 ± 13.30*

Glucose uptake in the isolated rat hemi-diaphragm was carried out *in vitro* as described in the Methods section. Values are expressed as mean ± SD ($n = 8$). *Results are significantly different among groups at $p < 0.05$.

30 min producing 0.1 mg/g (82% inhibition) glucose. At 60 min, the inhibition was overcome producing 0.65 mg/g glucose (45% inhibition). In the presence of insulin (1U/ml), the initial inhibition seen with the *Mukia* extract alone was overcome by producing 0.48 mg/g glucose (15% inhibition), but at 60 min, the gluconeogenesis was slightly inhibited resulting in the production of 0.59 mg/g glucose (50% inhibition). At 0.5 mg/ml concentration, *Mukia* extract did not inhibit gluconeogenesis, instead it stimulated gluconeogenesis by 1.6-fold and 1.2-fold at 30 min and 60 min, respectively, compared with pyruvate alone. However, in the presence of insulin (1U/ml), it inhibited gluconeogenesis resulting in the production of 0.12 mg/g (79% inhibition) and 0.13 mg/g glucose (89% inhibition) at 30 min and 60 min, respectively, when compared with pyruvate alone. In the presence of insulin, *Mukia* extract showed synergistic effect on the inhibition of gluconeogenesis.

In vitro glucose uptake by isolated rat hemi-diaphragm

The results of glucose uptake by isolated rat hemi-diaphragm are shown in Table 1. Insulin caused stimulation of glucose uptake (112.41 ± 9.14 mg/dl/g/30 min) by isolated rat hemi-diaphragm in comparison with the normal control (101.29 ± 9.24 mg/dl/g/30 min). This difference was significant ($p < 0.05$). *Mukia* extract showed no significant increase

in the uptake of glucose at the two concentrations tested (50 and 100 μg/ml). However, a combination of insulin and 100 μg/ml of *Mukia* extract significantly ($p < 0.05$) potentiated the action of insulin on glucose uptake (152.82 ± 13.30 mg/dl/g/30 min) when compared with the insulin control (112.41 ± 9.14 mg/dl/g/30 min).

Discussion

Phytochemicals are a diverse class of compounds derived from different plant families but possessing similar functions. Many phytochemicals and plant extracts have been used in the treatment of type 2 diabetes. For example, isoflavone from soy, condensed tannins from tea, and phenolics from coffee have been tested for type 2 diabetes. Nutritional intervention studies performed in animals and humans suggest that ingestion of soy protein-associated isoflavones improved glucose control and insulin sensitivity (Hamden et al., 2011). Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, suppresses hepatic gluconeogenesis through 5′AMP-activated protein kinase (Collins et al., 2007). Hisperedin, naringenin, genestein, and diadzein have been shown to suppress gluconeogenic enzyme expression in liver and hepatocytes in culture (Narender et al., 2011). Polyphenol-like resveratrol has also been proposed as a potential antidiabetic agent (Szkudelski & Szkudelska, 2011). In a recent study, it was observed that resveratrol suppresses insulin signaling in adipocytes under insulin-sensitive state, but enhances it in insulin-resistant cells (Kang et al., 2012). In addition, extracts from berries have also been shown to possess antidiabetic activity (Johnston et al., 2005). *Eriobotrya japonica* (Thunb.) (Rosaceae) is used to treat diabetes in folk traditional medicine for a long time in China. A study of its antidiabetic activity in the total flavonoid fractions showed the presence of flavonoids having quercetin as their parent nuleus, such as quercetin-3-*O*-rutinoside and quercetin-3-*O*-rhamnoside (Lu et al., 2009).

Glucose is a fundamental source for cellular energy. It is supplied through the diet and may be stored as glycogen in the muscle and liver. During times of need, the glycogen is degraded to release glucose. Although all tissue and cells require glucose, about 50% of the glucose is used by the brain in the post-absorptive state (De Fonzo, 2004). Glucose is also endogenously produced mainly by the liver and to a small extent by the kidneys (De Fonzo, 2004). The anaerobic glycolytic products like lactate and pyruvate are the main precursors for gluconeogenesis in the liver. Amino acids such as alanine are also used for gluconeogenesis (Dong & Freedland, 1980).

Insulin and glucagon are the main hormones regulating glucose homeostasis. Although insulin is not needed for glucose uptake in the liver, it is required for glucose uptake in the peripheral tissues like muscle (Coomans et al., 2011; Triplett, 2012). In diabetes, particularly in type 2 diabetes, the insulin produced by the pancreas is unable to maintain glucose homeostasis, and hence hypoglycemic agents have to be used to reduce the levels of blood glucose (Wajchenberg, 2007).

In this *in vitro* study, we have investigated the ability of phytochemicals such as quercetin, phloroglucinol, and *Mukia* extract to inhibit gluconeogenesis in the rat liver and increase glucose uptake by *Mukia* extract in rat hemi-diaphragm. *In vitro* studies are useful in estimating the glucose metabolism since all the variables in the study can be controlled, especially the influence of hormones such as insulin and glucagon. We have shown that rat liver slices can convert pyruvate to glucose and in the absence of pyruvate, very little glucose was formed. Hence, the glucose present in the reaction medium would have come from gluconeogenesis and not from glycogen degradation. In the presence of insulin, there was an inhibition of gluconeogenesis. However, no significant difference was found between 1 U insulin and 2 U insulin. This may be because of the effect of 1 U insulin that could have been saturating, and hence additional insulin did not show any significant difference.

Pyruvate-dependent gluconeogenesis involves converting the pyruvate to phosphoenol pyruvate by the enzyme phosphoenolpyruvate carboxykinase (PEPCK), which is located in the cytosol. This may be the target of the phytochemicals as well as the *Mukia* extract. However, there is another pathway involving the mitochondrial dicarboxylic acids in pyruvate-mediated gluconeogenesis. *Mukia* extract and quercetin did not appear to inhibit gluconeogenesis after the initial inhibition, whereas phloroglucinol continued to inhibit gluconeogenesis suggesting that it is a potent antidiabetic phytochemical. *Mukia* (0.5 mg/ml) in the presence of 1 U insulin, on the other hand, potentiated the action of insulin on inhibition of gluconeogenesis. However, there was good synergestic effect on the inhibition of gluconeogenesis in the presence of insulin.

Isolated rat hemi-diaphragm is widely used as a model in the study of glucose uptake and is a reliable method for *in vitro* study of peripheral uptake of glucose. In our present study of *in vitro* glucose uptake by isolated rat hemi-diaphragm, *Mukia* extract by itself did not enhance glucose uptake in the isolated rat hemi-diaphragm but in the presence of 1 U insulin showed significantly ($p < 0.05$) higher level of glucose uptake than the insulin-treated group, suggesting a synergistic action. Such a synergestic action may also explain why we observed a decreased inhibition of gluconeogenesis at lower concentration of *Mukia* extract, but higher inhibition when the *Mukia* concentration was increased in the presence of insulin.

Altered glucose transport is associated with defective Glut-4 translocation and impaired insulin signaling cascade was evidenced as major defect in insulin resistance (Laville et al., 1996). The ability of phytochemicals to enhance the insulin sensitivity suggests that this may be a novel mechanisms to overcome insulin resistance.

Conclusion

Mukia maderaspatana extract has diverse antidiabetic effects based on its ability to inhibit gluconeogenesis and potentiate the action of insulin on glucose uptake. Plant phytochemicals, which are rich in phenolics, have potent antidiabetic properties and they can replace the synthetic drugs, as they have no proven side effects. Since *Mukia i*s an edible plant, rich in polyphenolics, traditional knowledge of its use in folk

medicine for its antidiabetic properties offer a potential therapeutic source for the treatment of diabetes. *Mukia* can be used as a natural antidiabetic nutraceutical.

Declaration of Interest

The authors report that they have no declarations of interest. Financial assistance from the Institution of Excellence (IOE) project of the University of Mysore is gratefully acknowledged. B. R. Srilatha is thankful to IOE for the award of research fellowship.

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