Polyphenols in madhumega chooranam, a Siddha medicine, ameliorates carbohydrate metabolism and oxidative stress in type II diabetic rats

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A B S T R A C T

Ethnopharmacological relevance: Present study was undertaken to demonstrate the mode of anti-diabetic action of a polyherbal Siddha Medicine, Madhumega chooranam (MMC).

Materials and methods: MMC was fractionated into phenolic (PMMC) and non-phenolic (NPMMC) portions in order to identify bioactive fraction. Study was performed in type II diabetic rats. Role of PMMC and NPMMC on liver glucose-6-phosphatase, fructose-1,6-bisphosphatase, glucokinase and glycogen content were determined. Their role on superoxide dismutase, reduced glutathione and lipid peroxidation were investigated. In addition, their effects on GLUT4 and PPARγ gene expression were studied. Pancreas and liver histopathology was studied using hematoxylin and eosin stain.

Results: PMMC improved carbohydrate metabolism by decreasing glucose-6-phosphatase and fructose-1,6-bisphosphatase and increasing glucokinase and glycogen contents in diabetic rats liver. It alleviated oxidative stress by increasing superoxide dismutase, glutathione and decreasing lipid peroxidation content. PMMC up-regulated liver GLUT4 and PPARγ mRNA expression in comparison to the vehicle or NPMMC rats.

Conclusion: Madhumega chooranam mediates its anti-diabetic action through the inhibition of gluconeogenesis and activation of glycolytic pathways in type II diabetic rats. Increased GLUT4 and PPARγ expressions provide additional information on its glucose uptake/sensitizing and hypolipidemic potential. Phenolic components of MMC were found to be the bioactive principles.

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1. Introduction

According to International Diabetes Federation, there were 40 million diabetics in India in 2007 and this number is predicted to rise to almost 70 million by 2025. Countries with largest number of diabetics will be India, China and USA by 2030 (King et al., 1998), which is alarming and needs immediate attention for the development of safer therapeutic regimens. World over there is a resurgence of traditional medical systems, based on the holistic nature of their approach to healing.

Siddha system of medicine is one of the major traditional medical systems of India, which is prevalent mainly in Tamilnadu. In Siddha, diabetes mellitus (DM) is termed as “Madhumegam” (Madhu means “sweet” and megam means “excessive urination”). Madhumega chooranam (MMC), a polyherbal Siddha medicine, is in vogue for the treatment of DM for more than five decades in Tamilnadu. It contains crude powders of Muraya koenigii, Terminalia chebula, Phyllanthus emblica, Tinospora cardifolia, Syzigium cumini, Cyperus rotundus and Phyllanthus amarus which were mixed in equal parts. Literature evidences on the therapeutic

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benefits of MMC reveal it has no or lesser side effects. Present study was undertaken to investigate role of MMC on carbohydrate metabolism and oxidative stress in a rat model of type II diabetes and also to identify its bioactive principles.

2. Materials and methods

2.1. Chemicals and reagents

Gallic acid and streptozotocin were purchased from Sigma-Aldrich chemical (USA). CMC, glucose-6-phosphate, TCA, ANSA, fructose 1,6-bisphosphate, BSA, PMS, NBT, NADH, GSH, DTNB, BHT, sulphanilamide, o-phosphoric acid, naphthyl ethylene diamine dihydrochloride were purchased from M/s. SISCO Research Laboratories, Mumbai, India. Tetra sodium pyrophosphate, TBA, SSA were supplied by M/s. Himedia laboratories, Mumbai, India. Glucose, triglycerides and cholesterol kits were procured from M/s. Accurex Biomedical Pvt. Ltd., India. Rat insulin ELISA kit was purchased from Crystal Chem Inc., USA. All other chemicals and reagents used were of analytical grade.

2.2. Animals and husbandry

Female Sprague Dawley rats weighing 120–130 g (initial weight) were housed in groups (3–5 animals/cage) in polypropylene cages in a well ventilated room (air cycles: 15/min; recycle ratio: 70:30) under an ambient temperature of 23 ± 2°C and 40%–65% relative humidity, with a 12 h light/dark artificial light cycle. They were provided with rodent feed (M/s. Provimi Animal Nutrition India Pvt. Ltd, Bengaluru) and purified water ad libitum, prior to dietary manipulation. Guidelines of “Guide for the Care and Use of Laboratory Animals” (Institute of Laboratory Animal Resources, National Academic Press 1996; NIH publication number #85-23, revised 1996) were strictly followed throughout the study. Institutional Animal Ethical Committee (IAEC), Sri Ramachandra University, Chennai, India approved the study (IAEC/XVIII/SRU/130/2010).

2.3. Madhumega chooranam

Madhumega chooranam was procured commercially from M/s. Arogya Healthcare Pvt. Ltd., Chennai and stored according to the manufacturer’s instruction (at room temperature).

2.4. Preparation of phenolic and non-phenolic fractions

Phenolic fraction was separated by refluxing MMC in 80% ethanol (pH 4.0) for 30 min in a reflux condenser. The solution was cooled and centrifuged at 3500 rpm for 10 min. Supernatant containing phenolic (PMMC) and the residue which contains non-phenolic (NPMMC) components were concentrated separately containing phenolic (PMMC) and the residue which contains non-phenolic (NPMMC) was determined by Folin–Ciocalteu method by HPTLC (Sawant et al., 2010). Acute oral toxicity test of MMC was standardised for gallic acid (McDonald et al., 2001). MMC was subjected to preliminary phytochemical, tannins, flavonoids and total phenols analysis. Total phenolic content in PMMC and NPMMC was determined by Folin–Ciocalteau method (McDonald et al., 2001). MMC was standardised for gallic acid content by HPTLC (Sawant et al., 2010). Acute oral toxicity test of MMC, PMMC and NPMMC was performed following OECD 423 guideline.

2.6. Induction of type II diabetes in rats

Type II diabetes was induced by following Srinivasan et al. (2005) method with minor modifications. Rats were allocated to two dietary regimens consisting of 10 and 80 animals by feeding either normal pellet diet (NPD) or high fat diet (HFD) ad libitum, respectively, for a period of four weeks. After 4 weeks of dietary manipulation, HFD rats with increased PTC (~3 fold) and PTG (~4 fold) levels were demarcated as hyperlipidemic and were injected with low dose (35 mg/kg, i.p) of streptozotocin. NPD animals were injected with citrate buffer (1 ml/kg, i.p). 72 h after STZ injection, rats with fasting glucose level ≥ 250 mg/dl were selected for study. Animals were kept on their respective diet till the end of the study.

2.6.1. Groups and treatment

Following confirmation of diabetes, rats were randomized into 7 groups of 6 in each group and scheduled to treatment protocol for 21 days. Weekly body weight, PG, PTC and PI were determined in the experimental rats.

1. Normoglycemic (0.3% CMC as vehicle; 5 ml/kg/day, p.o)
2. Hyperglycemic (0.3% CMC as vehicle; 5 ml/kg/day, p.o)
3. Metformin (50 mg/kg/day, p.o)
4. Metformin (100 mg/kg/day, p.o)
5. NPMMC (50 mg/kg/day, p.o)
6. NPMMC (100 mg/kg/day, p.o)
7. Metformin (250 mg/kg, p.o)

2.6.2. Plasma clinical chemistry

PG, PTC and PTG were analysed using commercial diagnostic kits (M/s. Accurex diagnostic kit, India) in a semi-automated biochemical analyser (Star 21S Plus, India). PI was measured using rat insulin kit (Crystal Chem Inc., USA) in a Multiskan Spectrum, Thermo Scientific, USA.

2.6.3. Key markers of carbohydrate metabolism

Glucose-6-Phosphatase (Swanson, 1955); Fructose 1, 6-bisphosphatase (Gancedo and Gancedo, 1971); Glucokinase (Newgard et al., 1983) and Glycogen content (Sadasivam and Manickam, 1996) were estimated in liver tissues.

2.6.4. Key markers of oxidative stress

Superoxide dismutase (Kakkab et al., 1984); reduced glutathione (Jollow et al., 1974); lipid peroxidation content (Ohkawa et al., 1979) and total protein (Lowry et al., 1951) were measured in liver tissues.

2.6.5. Gene expression of GLUT4 and PPARγ by reverse transcriptase PCR

GLUT4 and PPARγ mRNA expression were studied in liver tissues. Primers sequence used were as follows. PPARγ-sense, 5′–CAT TGT GGA GGA TAC AAG–3′; antisense, 5′–TTC TGA AAC CGA CAG TAC TGA CAT–3′. GLUT4: sense, 5′–GGA GGT GAA ACC CAG TAC AGA ACT–3′; antisense 5′–GGT GCC TCT CCC ACC ATT TT–3′ and β-actin: sense, 5′–TGC TGT CCC TAT AGT CCT CT–3′; antisense, 5′–AGG CCT TTA CCG ATG TCA ACG–3′. RT-PCR was carried out as described earlier (Hall et al., 1998).

2.6.6. Histopathology

At the end of treatment, animals were euthanized to collect liver and pancreas. Organs were blotted and freed from blood, fixed in 10% neutral buffered formalin for 48 h, trimmed and
phenolic content in PMMC and NPMMC were found to be 47.16%, 11.30% and 33% w/w, respectively. In particular, total presence of flavones, glycosides, quinones, phenolic compounds, 3. Results performed using GraphPad prism 5.0 (San Diego, USA).

2.7. Statistical analysis

Data were expressed as mean ± standard error of mean (SEM). Mean difference between the groups were analysed by one way ANOVA followed by Tukey’s multiple comparison as posthoc test. p value ≤ 0.05 was considered significant. Statistical analysis was performed using GraphPad prism 5.0 (San Diego, USA).

3. Results

Preliminary phytochemical analysis of MMC revealed the presence of flavones, glycosides, quinones, phenolic compounds, tannins, reducing sugars, alkaloids, proteins and saponins. Total phenolic, tannins and flavonoids contents of MMC were found to be 47.16%, 11.30% and 33% w/w, respectively. In particular, total phenolic content in PMMC and NPMMC were found to be 162.80 ± 5.95 and 25.74 ± 1.21 μg/mg, respectively. Gallic acid content of MMC, PMMC and NPMMC was found to be 0.91%, 1.69% and 0.2% w/w, respectively.

3.1. Acute oral toxicity of MMC, PMMC and NPMMC in rats

MMC, PMMC and NPMMC at 2000 mg/kg, p.o. caused neither mortality nor signs of toxicity. There were no significant differences in body weight gain. Gross pathological examination revealed no detectable abnormalities. Thus, in reference to the Globally Harmonised System of Classification and Labelling of Chemicals (OECD, 1998), MMC, PMMC and NPMMC can be classified as Category-5.

3.2. Anti-diabetic activity of PMMC

3.2.1. Effect of PMMC and NPMMC on body weight changes

PMMC prevented body weight loss in a non-significant and dose dependent manner in comparison to vehicle treated rats. NPMMC did not produce any such effect in diabetic rats. Metformin did not increase the body weight (Table 1).

3.2.2. Effect of PMMC and NPMMC on PG, PTC, PTG and PI levels

PMMC decreased plasma glucose significantly (p < 0.01) in a dose dependent manner from day 14 in comparison to vehicle treated hyperglycemic rats. On day 21, it decreased cholesterol and triglycerides levels (p < 0.05 and 0.01, respectively) and increased insulin levels (p < 0.05). NPMMC did not show such effects. Effect of PMMMC was comparable with metformin (Table 2).

3.2.3. Effect of PMMC and NPMMC on markers of carbohydrate metabolism

PMMC (100 mg/kg) decreased glucose-6-phosphatase and fructose-1,6-bisphosphatase and increased glucokinase and glycogen levels significantly (p < 0.01 and 0.05, respectively) in comparison to vehicle treated rats. NPMMC treatment did not show such effects. Effect of PMMMC is comparable with metformin (Table 3).

3.2.4. Effect of PMMC and NPMMC on markers of oxidative stress

PMMC (100 mg/kg) significantly increased superoxide dismutase (p < 0.05) and glutathione (p < 0.05) and decreased lipid peroxidation (p < 0.01) content in comparison to vehicle treated hyperglycemic rats. NPMMC failed to show such effects (Table 3).

3.2.5. Effect of PMMC and NPMMC on liver GLUT-4 and PPARγ expression

PMMC up-regulated mRNA expression of GLUT4 and PPARγ when compared to vehicle treated rats. NPMMC did not show such effects (Fig. 1).

3.2.6. Effect of PMMC and NPMMC on liver and pancreas histology in rats

Gross pathological examination of liver and pancreas of the experimental rats did not reveal any abnormalities. Histopathological examination of liver and pancreas of the normoglycemic rats revealed normal histological pattern. Vehicle treated hyperglycemic rats showed severe hepatocellular hypertrophy in conjunction with intracytoplasmic macrovesicular steatosis. Further they demonstrated multifocal bridging coagulative necrosis of centrolobular hepatocytes which were characterised by mononuclear cell infiltrations with cytoplasmic eosinophilia, pyknosis and karyolysis of hepatocellular nuclei. Pancreases of hyperglycemic rats showed 60%–75% atrophy of Islets of Langerhans. These cells were accompanied by decreased cellularity and marked vacuolar degeneration with mild to moderate multifocal mononuclear cells infiltration. Liver histology of PMMMC (50 mg/kg) and NPMMC rats revealed multifocal intracytoplasmic macrovesicular steatosis and multifocal inflammatory cells infiltration of various grades similar to those observed in hyperglycemic rats. Animals treated with PMMMC at 100 mg/kg revealed normal liver histology similar to those of normoglycemic rats. Degree of Islet cells atrophy, vacuolar degeneration and inflammatory cells infiltration in the pancreas of rats treated with NPMMC remained similar to those of hyperglycemic rats. Pancreas of rats treated

Table 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body weight (g)</th>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoglycemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMMC (50 mg/kg)</td>
<td></td>
<td>160.67</td>
<td>154.67</td>
<td>153.83</td>
<td>150.50</td>
</tr>
<tr>
<td>NPMMC (50 mg/kg)</td>
<td></td>
<td>162.33</td>
<td>154.67</td>
<td>153.83</td>
<td>150.50</td>
</tr>
<tr>
<td>Metformin (250 mg/kg)</td>
<td></td>
<td>159.00</td>
<td>154.67</td>
<td>153.83</td>
<td>150.50</td>
</tr>
</tbody>
</table>

n = 6/group; values are expressed in mean ± SEM. 

a Significance with Tukey’s test following one way ANOVA is indicated as p < 0.05 vs. normoglycemic group.

b Significance with Tukey’s test following one way ANOVA is indicated as p < 0.01 vs. normoglycemic group.
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4. Discussion

Present study demonstrates the safety and role of MMC on carbohydrate metabolism and oxidative stress in diabetic rats. In addition, we report that phenolic components of MMC are bioactive principles responsible for anti-diabetic action.

Severe atrophy of islets of Langerhans and decreased insulin levels reflect β cell dysfunctions which lead to disturbance of glucose uptake and lipids metabolism in hyperglycemic rats (Wellhinda et al., 1982; Ng et al., 1987; Bedoya et al., 1996). Ability of PMMC to increase PI levels indicate its protective effect on β cells function and its potential to release insulin from bound forms. This reflects insulin secretagogue nature of PMMC.

Decreased glucokinase level leads to suppression of glycogen synthesis and hence muscle wasting which in turn ends up in body weight loss (Jung et al., 2004). In the present study, increased hepatic glycogen with decreased plasma glucose levels demonstrate the cellular glucose influx in the diabetic rats which can be speculated to insulinomimetic nature of PMMC. Insulin deficiency triggers overactivation of fructose 1,6- bisphosphatase (Pari and Satheesh, 2006). In diabetic state, activated glucose-6-phosphatase donates hydrogen which binds with NADPH to form NADH and enhances lipogenesis (Bopanna et al., 1997). In this study, decreased glucose-6-phosphatase and fructose 1,6-bisphosphatase activity with simultaneously reduction in plasma cholesterol and triglycerides levels indicates the role of PMMC on lipid metabolism. HFD/STZ is an insulin deficient model with all the characteristic features of type II diabetes. PMMC augmented glucose uptake and decreased lipids levels emphasises its insulinomimetic and insulin sensitising nature.

Hypoinsulinaemia increases fatty acyl coenzyme A oxidase activity which initiates β-oxidation of fatty acids resulting in lipid peroxidation (Rahimi et al., 2005). Increased lipid peroxidation impairs cell membrane functions (Soon and Tan, 2002). SOD metabolises superoxide (O2•−) radical to H2O2 and molecular oxygen (Vincent et al., 2004; Lin et al., 2005). Glutathione peroxidase and glutathione-S-transferase decompose H2O2 or other organic hydroperoxides to non-toxic products using reduced glutathione as substrate. Several studies showed decreased antioxidant and increased lipid peroxidation status in DM (Sabu et al., 2002; Selvan et al., 2008). PMMC significantly decreased lipid peroxidation and increased SOD and GSH in diabetic rats. Phenolic principles by virtue of their redox potential readily donate electron or hydrogen to quench the singlet oxygen species or neutralise highly reactive radicals (Rice-Evans et al., 1996; Aiayegor and Okoh, 2009; Chis et al., 2009). High phenolic content in MMC will definitely render substantial benefits to counteract oxidative stress in diabetes.

Insulin regulates translocation of GLUT4 and in turn glucose into cells. On the other hand, PPARγ up-regulates GLUT4 expression and thereby increases glucose uptake (Kramer et al., 2001). Further, PPARγ encodes the proteins expression of lipoprotein lipase and fatty acid transport and enhances lipolysis and fatty acids uptake (Vikramadityan et al., 2005). PMMC treatment up-regulated GLUT4 and PPARγ expression with simultaneous decrease in PG level, which demonstrates its insulinomimetic and insulin sensitising nature once again clearly.

Dietary polyphenols such as resveratrol, catechins, epicatechins, gallic acid etc., possess wide therapeutic benefits (Postescu et al., 2007). Several studies demonstrated the anti-diabetic with PMMC and metformin were found to be histologically normal similar to normoglycemic rats. These findings suggest that the pathological progression induced by HFD/STZ were found to be suppressed by PMMC.

Table 2 Effect of PMMC and NPMMC on PG, PTC, PTG and PI levels in type II diabetic rats.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Glucose (mg/dl)</th>
<th>Cholesterol (mg/dl)</th>
<th>Triglyceride (mg/dl)</th>
<th>Insulin (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoglycemic</td>
<td>92.51</td>
<td>13.47</td>
<td>43.04</td>
<td>2.69</td>
</tr>
<tr>
<td>Hyperglycemic</td>
<td>253.33</td>
<td>136.69</td>
<td>255.63</td>
<td>7.08</td>
</tr>
<tr>
<td>Normoglycemic</td>
<td>258.92</td>
<td>100.83</td>
<td>242.01</td>
<td>14.19</td>
</tr>
<tr>
<td>Hyperglycemic</td>
<td>255.26</td>
<td>240.02</td>
<td>233.16</td>
<td>13.28</td>
</tr>
<tr>
<td>Hyperglycemic</td>
<td>257.37</td>
<td>235.57</td>
<td>250.01</td>
<td>182.74</td>
</tr>
</tbody>
</table>

a Significance with Tukey’s test following one way ANOVA is indicated as p < 0.01 vs. normoglycemic group.

b Significance with Tukey’s test following one way ANOVA is indicated as p < 0.05 vs. hyperglycemic group.
Table 3
Effect of PMMC and NPMMC on carbohydrate metabolism and oxidative stress markers level in type II diabetic rats.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Glucose-6-Phosphatase (μg/min/mg protein)</th>
<th>Fructose 1, 6-bisphosphatase (μg/min/mg protein)</th>
<th>Glucokinase (nmol/min/mg protein)</th>
<th>Glycogen (mg/g tissue)</th>
<th>Superoxide dismutase (Unit/min/mg protein)</th>
<th>Reduced glutathione (mg/g tissue)</th>
<th>Lipid peroxidation (μg/mg tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoglycemic</td>
<td>13.64 ± 3.96</td>
<td>0.48 ± 0.14</td>
<td>5.78 ± 0.78</td>
<td>1.52 ± 0.13</td>
<td>14.55 ± 1.31</td>
<td>3.01 ± 0.18</td>
<td>2.19 ± 0.03</td>
</tr>
<tr>
<td>Hyperglycemic</td>
<td>41.43 ± 4.72</td>
<td>1.69 ± 0.28</td>
<td>1.45 ± 0.32</td>
<td>0.73 ± 0.07</td>
<td>5.90 ± 1.35</td>
<td>1.25 ± 0.21</td>
<td>7.84 ± 1.40</td>
</tr>
<tr>
<td>PMMC (50 mg/kg)</td>
<td>34.37 ± 4.52</td>
<td>1.09 ± 0.26</td>
<td>2.56 ± 0.52</td>
<td>0.84 ± 0.10</td>
<td>10.05 ± 1.49</td>
<td>1.82 ± 0.45</td>
<td>4.48 ± 1.12</td>
</tr>
<tr>
<td>PMMC (100 mg/kg)</td>
<td>19.03 ± 1.88</td>
<td>0.69 ± 0.13</td>
<td>4.36 ± 0.65</td>
<td>1.25 ± 0.17</td>
<td>12.70 ± 1.01</td>
<td>2.87 ± 0.19</td>
<td>2.75 ± 0.37</td>
</tr>
<tr>
<td>NPMMC (50 mg/kg)</td>
<td>37.19 ± 2.81</td>
<td>1.43 ± 0.28</td>
<td>1.99 ± 0.57</td>
<td>0.84 ± 0.09</td>
<td>7.07 ± 0.89</td>
<td>1.50 ± 0.47</td>
<td>4.59 ± 0.79</td>
</tr>
<tr>
<td>NPMMC (100 mg/kg)</td>
<td>28.74 ± 2.15</td>
<td>1.29 ± 0.21</td>
<td>2.07 ± 0.35</td>
<td>0.89 ± 0.10</td>
<td>6.98 ± 2.21</td>
<td>1.62 ± 0.33</td>
<td>4.61 ± 0.82</td>
</tr>
<tr>
<td>Metformin (250 mg/kg)</td>
<td>21.95 ± 2.79</td>
<td>0.93 ± 0.19</td>
<td>5.03 ± 0.36</td>
<td>1.34 ± 0.07</td>
<td>13.59 ± 1.15</td>
<td>2.57 ± 0.23</td>
<td>2.05 ± 0.36</td>
</tr>
</tbody>
</table>

n=6/group; values are expressed in mean ± SEM.

* Significance with Tukey’s test following one way ANOVA is indicated as p < 0.01 vs. normoglycemic group.

† Significance with Tukey’s test following one way ANOVA is indicated as p < 0.05 vs. hyperglycemic group.

‡ Significance with Tukey’s test following one way ANOVA is indicated as p < 0.01 vs. hyperglycemic group.

5. Conclusion

This study reveals that Madhumega chooranam mediate its effects through inhibition of gluconeogenesis and activation of glycolytic pathway. Increased GLUT4 and PPARγ expression in diabetic livers provide additional information on its insulin mimetic and insulin sensitising nature. Phenolic components were found to be the bioactive principles of MMC. To our knowledge, the present study is the first of its kind to demonstrate the anti-diabetic action of MMC and thus the traditional claim is scientifically verified in an animal model of type II diabetes.

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Appendix A. Supplementary information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jep.2012.04.003

Reference


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