Preventive Effects of *Moringa oleifera* (Lam) on Hyperlipidemia and Hepatocyte Ultrastructural Changes in Iron Deficient Rats

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The effects of *Moringa oleifera* (MO), *Moringaceae* on hyperlipidemia and hepatocyte ultrastructural changes caused by iron deficiency were investigated. Four-week-old male Wistar-strain rats were fed a control diet based on AIN-93G (C), an iron deficient diet (FeD), a FeD + 0.5% MO (FeD-m) diet, or a FeD + MO 1% (FeD-M) diet for 4 weeks. It was found that MO reduced iron-deficient diet-induced increases in serum and hepatic lipids with dose-dependent increases of serum quercetin and kaempherol, but did not prevent anemia. By electron microscopy, in iron deficient hepatocytes, slightly swollen mitochondria and few glycogen granules were observed, but glycogen granules increased and mitochondria were normalized by treatment with MO. Furthermore, lipoproteins were observed in the Golgi complex under treatment with MO. These results suggest a possible beneficial effect of MO in the prevention of hyperlipidemia and ultrastructural changes in hepatocytes due to iron-deficiency.

Key words: *Moringa oleifera*; iron deficiency; hyperlipidemia; flavonoids; hepatocyte

Iron deficiency is a world-wide nutritional problem in more than two billion of persons, mainly women and children. The health consequences of anemia are multiple and include increased mortality rates, decreased physical capacity, infections, and so on. Secondary iron deficiency health problems, hyperlipidemia and bone loss, have received a great deal of attention.1–6 Swollen mitochondria have been described in rats and mice, and was linked to iron deficiency or copper deficiency.8,9 These biochemical and structural changes may be due to a lack of precursors of some mitochondrial enzymes.

Strategies to prevent anemia require costly logistical support out of reach in developing countries. Thus the advantages of vegetable varieties, which are rich in nutrients, are a strategy for poor countries to fight micronutrient malnutrition.

Originally from north India and Arabia, *Moringa oleifera* (MO) belongs to the *Moringacea* family, which accounts for 14 species. MO has been used in nutritional, industrial, and medical fields since a long time ago in Indian and African societies. It is a quick growing tree and is widely distributed in tropical areas. Several studies showed that MO contains several minerals, carotenoids, flavonoids, isothiocyanates, tocopherols, and ascorbic acid with good quality proteins.10,11 It has anti-cancer,12 anti-inflammatory,13 and thyroid status regulator proprieties.14 However, no studies have been carried out to investigate MO protective effects on secondary health problems due to iron deficiency. The purpose of this study was to evaluate the effects of MO on hyperlipidemia and hepatocyte ultrastructure changes in rats fed an iron deficient diet.

Materials and Methods

**Chemicals.** Kits for serum or liver total cholesterol (TC), triglyceride (TG), phospholipids (PL), and high-density lipoprotein-cholesterol (HDL-C) were purchased from Wako Pure Chemical Industries (Osaka, Japan). Pepsin, pancreatin, bile, and tannic acid for *in vitro* studies were purchased from Sigma Chemical (St. Louis, Missouri).

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Abbreviations: HDL-C, high density lipoprotein cholesterol; HPLC, high performance liquid chromatography; MeOH, methanol; MO, *Moringa oleifera*; TC, total cholesterol; TG, triglyceride; PCOOH, phosphatidylcholine hydroperoxides; PL, phospholipids
MO). Iron and copper standard solutions were obtained from Wako Pure Chemical Industries (Osaka, Japan), β-glucuronidase (Sigma), quercetin (Cayman Chemical, Ann Arbor, MI), kaempferol (Extrasynthese, Genay, France), and flavone (Acros Organics, Geel, Belgium) were used for serum quercetin and kaempferol determinations.

**Nutrient analyses in MO.** MO leaves were harvested from several trees in the south of Senegal. The leaves were dried in the traditional way in shade and pounded to yield a powder. Chemical compositions such as moisture, proteins, fats, cellulose, and mineral composition were determined according to AOAC methods. Minerals were determined by atomic absorption spectrophotometer (Perkin-Elmer 3110, Norwalk, CT). Total polyphenols were determined according to a modification of the method of Folin-Denis, and results are expressed as equivalent tannic acid. The types of polyphenols in MO powder were determined by HPLC with a photodiode array detector (Hitachi, Tokyo).16)

**Protein digestibility of MO.** Protein digestibility of MO was determined by the method of Mertz et al.17) The method involves pepsin digestion, then the undigested protein is determined by the Kjeldahl method.18)

**Iron bioavailability of MO** in vitro. Iron availability of MO was determined by the method of Kane and Miller.19) A double pepsin and pancreatin-bile digestion method was used. Iron passing through dialysis tubing and quantified by a bathophenanthroline disulfonate reaction is an indicator of iron bioavailability.

**Animals and diets.** Twenty-four 4-week-old male Wistar-strain rats were purchased from Clea Japan (Tokyo, Japan). The rats were divided into four groups of six each: control (C), iron deficiency (FeD), FeD plus 0.5% MO (FeD-m), and FeD plus MO 1% (FeD-M) (Table 1). The control group was pair-fed with respect to the iron deficient groups (FeD, FeD-m, and FeD-M). The rats were housed in individual stainless cages in a temperature and humidity controlled room with a 12 h light/dark cycle. The rats were allowed free access to lighted water for four weeks. The Animals Study Committee of Tokyo University of Agriculture approved this study, and the animals were maintained in accordance with the guidelines for the care and use of laboratory animals of Tokyo University of Agriculture. At the end of the experiment, the rats were killed by exsanguination. Blood was collected from the carotid artery and centrifuged at 3,000 rpm at 4°C for 15 min to obtain serum. The liver was perfused in situ with iced 0.9% saline and rapidly removed. Heart was also sampled. All samples were stored at −80°C until analysis.

**Minerals in liver.** Livers were ashed in muffle furnaces at 550°C for 48 h and minerals were extracted with 1 mol/l HCl. Iron and copper concentrations were determined with an atomic absorption spectrophotometer (Hitachi A2000, Tokyo).

**Serum quercetin and kaempferol.** As an internal standard, 10 µl of flavone (10 mmol/l) was added to tubes containing 200 µl of serum and 200 µl of hydrolysis reagent (0.1 M acetate buffer, pH 5.0, containing 0.2 U/ml β-glucuronidase, and 2 U/ml sulfatase). The mixture was hydrolyzed over night at 37°C, and then unconjugated fractions were extracted with diethyl ether (2 times). The ether fraction was dried and dissolved in 200 µl methanol (MeOH). A 10 µl sample of the solution was injected into the HPLC with an electrochemical detector (Coulochem II, ESA Biosciences (Boston, MA). The HPLC column was an MCM C18, (150 × 4.6 mm ID.; MC-medical, Tokyo; column oven temperature, 35°C). HPLC was carried out in the mobile phase with 50 mmol/l acetate buffer (pH 5.0)/MeOH/acetoni- trile (50/35/15). The flow rate was 1 ml/min. A UV detector was used for detection of flavone as the internal standard in 280 nm.

**Lipids in serum and liver.** Liver lipids were extracted quantitatively by the method of Folch et al.20) TG, TC, HDL-C, and PL21–23) were determined with reagent kits (Wako Pure Chemical Industries, Osaka, Japan).

**Electron microscopy.** The liver was cut to obtain a block (2 × 2 × 3 mm), which was fixed overnight with 2.5% glutaraldehyde at 4°C. The samples were then postfixed with 1% osmium tetroxide, dehydrated through a graded alcohol series, and embedded in Epok 812. Ultra-thin sections were cut on a Leica Ultracut F ultramicrotome (Leica, Wetzlar, Germany) with a diamond knife, and stained with uranyl acetate and lead citrate. The sections were examined at 80 kV under an H-7500 electron microscope (Hitachi, Tokyo).

**Statistical analyses.** Data were expressed as means ± SD. Fisher’s protected least significant difference

<table>
<thead>
<tr>
<th>Ingredient (g/kg diet)</th>
<th>C</th>
<th>FeD</th>
<th>FeD-m</th>
<th>FeD-M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casein</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Corn Starch</td>
<td>529.486</td>
<td>529.486</td>
<td>524.486</td>
<td>519.486</td>
</tr>
<tr>
<td>Sucrose</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Corn oil</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Cellulose</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Mineral mixture</td>
<td>35b</td>
<td>35b</td>
<td>35b</td>
<td>35b</td>
</tr>
<tr>
<td>Vitamin mixture</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Choline</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Tert-butyldihydroquinone</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
</tr>
<tr>
<td>MOP</td>
<td>—</td>
<td>—</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

*AIN-93 G mineral mixture, aAIN-93 G mineral mixture iron free, bAIN-93 vitamin mixture, MOP, Moringa oleifera powder*
Results

Nutritional values in MO

Nutritional values of MO powder are shown in Table 2. Transformation of leaves to powder increased mineral concentrations due to water loss. MO contained several minerals, such as iron, calcium, magnesium, potassium, sodium, and zinc, but iron availability was low.

Final body weight, heart and liver weights, hemoglobin level, and liver iron and copper concentrations

Growth and indicators for iron-deficiency are shown in Table 3. Significant differences were found in final body weights between the C and FeD, between the C and FeD-m, and between the FeD-m and FeD-M groups. The hemoglobin level was significantly decreased by iron deficiency (FeD, FeD-m, and FeD-M). Heart weight was significantly greater in the three iron deficient groups (FeD and FeD-m) than in the control group. Iron contents in liver as storage organ were significantly lower in the three iron-deficient groups than in the control group. Liver copper was significantly increased in the three iron deficient groups as compared with the control group.

Table 2. Nutritional Values in *Moringa oleifera* (MO)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>C</th>
<th>FeD</th>
<th>FeD-m</th>
<th>FeD-M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g/100 g)</td>
<td>35.03 ± 0.01</td>
<td>35.64 ± 0.86</td>
<td>35.03 ± 0.01</td>
<td>35.64 ± 0.86</td>
</tr>
<tr>
<td>Protein digestibility (%)</td>
<td>56.14 ± 8.86</td>
<td>56.14 ± 8.86</td>
<td>56.14 ± 8.86</td>
<td>56.14 ± 8.86</td>
</tr>
<tr>
<td>Lipids (g/100 g)</td>
<td>7.50 ± 0.21</td>
<td>7.50 ± 0.21</td>
<td>7.50 ± 0.21</td>
<td>7.50 ± 0.21</td>
</tr>
<tr>
<td>Cellulose (g/100 g)</td>
<td>4.02 ± 0.16</td>
<td>4.02 ± 0.16</td>
<td>4.02 ± 0.16</td>
<td>4.02 ± 0.16</td>
</tr>
<tr>
<td>Humidity (%)</td>
<td>4.53 ± 0.25</td>
<td>4.53 ± 0.25</td>
<td>4.53 ± 0.25</td>
<td>4.53 ± 0.25</td>
</tr>
<tr>
<td>Polyphenols (g/100 g)</td>
<td>1.72 ± 0.06</td>
<td>1.72 ± 0.06</td>
<td>1.72 ± 0.06</td>
<td>1.72 ± 0.06</td>
</tr>
<tr>
<td>Iron (mg/100 g)</td>
<td>18.39 ± 0.60</td>
<td>18.39 ± 0.60</td>
<td>18.39 ± 0.60</td>
<td>18.39 ± 0.60</td>
</tr>
<tr>
<td>Iron availability (%)</td>
<td>2.24 ± 0.65</td>
<td>2.24 ± 0.65</td>
<td>2.24 ± 0.65</td>
<td>2.24 ± 0.65</td>
</tr>
<tr>
<td>Calcium (mg/100 g)</td>
<td>1457.58 ± 47.77</td>
<td>1457.58 ± 47.77</td>
<td>1457.58 ± 47.77</td>
<td>1457.58 ± 47.77</td>
</tr>
<tr>
<td>Magnesium (mg/100 g)</td>
<td>395.45 ± 11.35</td>
<td>395.45 ± 11.35</td>
<td>395.45 ± 11.35</td>
<td>395.45 ± 11.35</td>
</tr>
<tr>
<td>Potassium (mg/100 g)</td>
<td>848.26 ± 36.57</td>
<td>848.26 ± 36.57</td>
<td>848.26 ± 36.57</td>
<td>848.26 ± 36.57</td>
</tr>
<tr>
<td>Sodium (mg/100 g)</td>
<td>73.68 ± 1.74</td>
<td>73.68 ± 1.74</td>
<td>73.68 ± 1.74</td>
<td>73.68 ± 1.74</td>
</tr>
<tr>
<td>Zinc (mg/100 g)</td>
<td>2.04 ± 0.07</td>
<td>2.04 ± 0.07</td>
<td>2.04 ± 0.07</td>
<td>2.04 ± 0.07</td>
</tr>
</tbody>
</table>

Values are Means ± SD, n = 3.

Table 3. Final Body Weight, Heart and Liver Weights, Hemoglobin (Hb) Level, and Liver Iron and Copper Concentrations

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>FeD</th>
<th>FeD-m</th>
<th>FeD-M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final BW (g)</td>
<td>200.2 ± 4.2</td>
<td>182.5 ± 15.5</td>
<td>180.7 ± 8.5</td>
<td>194.5 ± 10.8</td>
</tr>
<tr>
<td>Hb level (g/dl)</td>
<td>12.8 ± 0.6</td>
<td>4.59 ± 0.5</td>
<td>4.5 ± 0.8</td>
<td>4.5 ± 0.6</td>
</tr>
<tr>
<td>Heart Weight (g/100 gBW)</td>
<td>0.39 ± 0.03</td>
<td>0.58 ± 0.03</td>
<td>0.65 ± 0.08</td>
<td>0.62 ± 0.06</td>
</tr>
<tr>
<td>Liver Weight (g/100 gBW)</td>
<td>4.5 ± 0.3</td>
<td>3.6 ± 0.3</td>
<td>4.0 ± 0.6</td>
<td>4.3 ± 0.4</td>
</tr>
<tr>
<td>Liver Iron (µg/g dry wt)</td>
<td>527.9 ± 149.4</td>
<td>178.1 ± 54.5</td>
<td>160.0 ± 41.5</td>
<td>140.9 ± 20.8</td>
</tr>
<tr>
<td>Liver Copper (µg/g dry wt)</td>
<td>21.6 ± 1.8</td>
<td>110.6 ± 57.8</td>
<td>132.0 ± 88.3</td>
<td>80.8 ± 10.0</td>
</tr>
</tbody>
</table>

Values are means ± SD, n = 6 rats. Values with different letters are significantly different, P < 0.05. BW, body weight.

Table 4. Polyphenol Contents in *Moringa oleifera* (MO) (µmol/100 g dried leaf powder)

<table>
<thead>
<tr>
<th>Polyphenols</th>
<th>No hydrolysis</th>
<th>After hydrolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoquercitrin</td>
<td>1494.2</td>
<td>—</td>
</tr>
<tr>
<td>Rutin</td>
<td>1446.6</td>
<td>—</td>
</tr>
<tr>
<td>Kaempferol glycosides</td>
<td>394.4</td>
<td>—</td>
</tr>
<tr>
<td>Chlorogenic acid</td>
<td>134.5</td>
<td>—</td>
</tr>
<tr>
<td>Quercetin</td>
<td>—</td>
<td>2030.9</td>
</tr>
<tr>
<td>Kaempferol</td>
<td>—</td>
<td>336.7</td>
</tr>
</tbody>
</table>

HPLC analysis of MO polyphenols is represented in Table 4. MO contained isoquercitrin, rutin, kaempferol glycosides, and chlorogenic acids. Serum quercetin and kaempferol (Fig. 1A and B) increased with the concentration of MO in the diet. MO dose-dependently increased the serum concentration of quercetin and kaempferol in the FeD-m and FeD-M rats.
Fig. 1. Serum Quercetin and Kaempferol Concentrations.
A, Serum quercetin. Values are means ± SD, n = 6 rats, ND, not detected. Bars not sharing a letter differ significantly, P < 0.05. B, Serum kaempferol. Values are means ± SD, n = 6 rats, ND, not detected. Bars not sharing a letter differ significantly, P < 0.05.

Fig. 2. Serum Lipids.
A, Serum triglycerides (TG). Values are means ± SD, n = 6 rats, ND, not detected. Bars not sharing a letter differ significantly, P < 0.05. B, Serum phospholipids (PL). Values are means ± SD, n = 6 rats, ND, not detected. Bars not sharing a letter differ significantly, P < 0.05. C, Serum total cholesterol (TC). Values are means ± SD, n = 6 rats, ND, not detected. Bars not sharing a letter differ significantly, P < 0.05. D, Serum HDL-cholesterol (HDL-C). Values are means ± SD, n = 6 rats, ND, not detected. Bars not sharing a letter differ significantly, P < 0.05.
Hepatocytes by electron microscopy

The rough endoplasmic reticulum (rER) area, smooth endoplasmic reticulum (sER) area, and Golgi-complex area were observed in normal hepatocytes (Fig. 5A and B). sER appeared as a network of branching tubules and contained glycogen rosettes (arrows). The Golgi complex was formed by parallel smooth surface cisternae and vesicles (G). The rER lamellar plate did not contain glycogen granules. The mitochondria contained abundant or sparse cristae. In iron deficient rats (FeD), glycogen granules disappeared (Fig. 6A) and slightly swollen mitochondria showed cavitations of the mitochondrial matrix and loss of cristae (Fig. 6B). The FeD-m and FeD-M groups showed similar features as to hepatocytes. Many glycogen granules were evident in comparison with the control rats (Fig. 7A). Lipoproteins were present in the Golgi complex and mitochondria were normalized with MO (Fig. 7B).

Discussion

We examined the effects of powdered MO leaves on symptoms of iron deficiency in rats. MO has high protein and mineral contents as compared with common vegetables. The protein content of MO was reported previously.\textsuperscript{10,11} The iron bioavailability of MO was low, because vegetable iron is mainly non-heme iron with low absorption. MO did not prevent anemia, because MO did not improve symptoms such as reduction of hemoglobin level, low iron contents of organs, liver
copper accumulation, or heart hypertrophy due to iron deficiency.\textsuperscript{24,25} These phenomena also occurred in the MO groups (FeD-m and FeD-M) as shown in the FeD group. Iron in MO might be not well absorbed from the gut due to non-absorbable complexes with phytic acid, tannins, and certain dietary fibers that can bind iron in the intestinal lumen.

Serum and liver lipids increased in the iron deficient group without MO (Figs. 2–4). Sherman et al. found elevated plasma or serum TG, cholesterol, and PL in pups due to iron deficiency.\textsuperscript{24,25} Several authors\textsuperscript{24–26} have explained that hyperlipidemia, especially hypertriglyceridemia, is caused by increases in glucose turnover: in low oxygen concentrations due to iron

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**Fig. 5.** Hepatocyte from Normal Rats.
A, Rough endoplasmic reticulum (rER), smooth endoplasmic reticulum (sER), glycogen granules (arrows), and Golgi complex (G) were localized in the peribiliary regions. Nu, nucleus; M, mitochondria. B, Mitochondria.

**Fig. 6.** Hepatocytes from Iron Deficient Rats.
A, Glycogen granules disappeared. Nu, nucleus; rER, rough endoplasmic reticulum; G, Golgi complex. B, Mitochondria were slightly swollen.

**Fig. 7.** Hepatocytes from MO Group (FeD-M).
A, Many glycogen granules (arrows) and lipoproteins in Golgi complex (G) were observed. Nu, nucleus, M, mitochondria. B, Mitochondria recovered normal features.
deficiency, lactic acid accumulates and is converted to glucose. Excess glucose is degraded via glycolysis and pyruvate dehydrogenase into acetyl-CoA, which is converted into malonyl-CoA, fatty acids, triglycerides, phospholipids, and cholesterol. If no regulator system exists serum and liver lipids increase in response to these phenomena. MO inhibited iron-deficient diet-induced hyperlipidemia. The lipid lowering effects of MO might be due to its inhibition of lipid absorption or increased excretion of fecal bile acid and cholesterol. Non-digestible waxes and cuticles, and the binding capacity of dietary fibers with fats are potential lipid absorption inhibitors.27) Ghisi et al. reported that administration of crude leaf extracts of MO with a high fat diet decreased high-fat diet-induced increases in serum, liver, and kidney cholesterol levels.28,29) MO has definite hypocholesterolemic activity because it was found to increase the excretion of fecal cholesterol. We found the hypocholesterolemic effect of MO using iron-deficient rats, although we did not determine fecal cholesterol excretion.

Furthermore, some studies suggest beneficial effects of polyphenol-rich plant products on lipid metabolism.30–32) Grape seed,30) black and green olive phenolic extract,31) and flavonoid–rich extract of Hypericum perforatum32) rich in polyphenols affect lipid metabolism in rats by lowering the concentrations of serum and hepatic triglycerides and cholesterol. Igarashi and Ohmura33) reported lowering effects of quercetin, iso-rhamnetin, and rhamnetin in serum total cholesterol of rats fed a cholesterol-enriched diet and also in hepatic total cholesterol. MO contains quercetin glycosides, and serum quercetin increased in rats fed MO leaf powder in a dose-dependent manner in this study. Therefore, one of hypocholesterolemic effects of MO might be attributed to quercetin and other flavonoids, but further studies should be conducted using flavonoid extracts from MO leaves.

Through electron microscopy, liver glycogen was drastically reduced in the FeD group without MO (Fig. 6A) and restored by MO (Fig. 7A). The iron deficient diet with MO increased glycogen rosettes. Decreases in hepatocyte glycogen have been generally reported in fasted rats.7) A high rate of glucose turnover was also reported in iron deficiency.34) The iron deficient diet increased circulating glucose instead of glucose storage as glycogen in the liver. On the other hand, flavonoids are potent inhibitors of glycogen phosphorylase, which can break down glycogen.34) Quercetin, cyanidin, and delphinidin turned out to be the most potent inhibitors of glycogen phosphorylase, with concentration values where enzymatic activity was 50% of the respective control in the low μmolar range (< 5 μmol/L).34) Thus MO flavonoids might influence hepatic glycogen metabolism via this enzymatic control.

In the FeD rats, mitochondria appeared to be slightly enlarged with few cristae, resulting in enhanced electron lucency. These results are in accordance with previous studies.7–9) We have observed increased phosphatidylcholine hydroperoxides (PCOOH), a primary peroxide of biological membrane, in iron deficient rat liver.35) Damage to cell membranes by PCOOH might be a cause of swelling mitochondria, but this point needs to be clarified in further studies. Whatever it was due to, iron deficiency changed the morphological and structural organization of normal hepatocytes.36) Swollen mitochondria were improved by MO treatment. This might be related to antioxidative chemicals such as polyphenols and vitamins in MO.10,37–38) Increased lipoprotein was also observed in Golgi complex under MO treatment. Taxiforin, a plant flavonoid, stimulates hepatic apolipoprotein A-I (apoA-I) synthesis and secretion.39) apoA-I is associated mainly with HDL and is involved in the reverse cholesterol transport pathway. Although it is unclear whether increased lipoprotein due to MO is HDL or not, it is possible that flavonoids (quercetin and kaempferol) in MO play an important role in HDL metabolism, as well as taxifolin.

In conclusion, these results suggest that MO plays beneficial roles in the prevention of hyperlipidemia and ultrastructural changes in hepatocytes due to iron deficiency, but it is necessary to elucidate the details of the metabolism and physiological functions of MO.

Acknowledgment

The authors would like to thank Dr. Kazuki Kanazawa and his graduate students for analyzing the polyphenol contents in MO powder.

References

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