Mate Tea (*Ilex paraguariensis*) Promotes Satiety and Body Weight Lowering in Mice: Involvement of Glucagon-Like Peptide-1

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We previously investigated the effects of an aqueous extract of maté (mate) tea, made from the leaves of *Ilex paraguariensis*, on the diabesity and metabolic syndrome features in a mouse model. Mate induced significant decreases in body weight (BW), body mass index, and food intake (FI). In this study, to verify the mode of action of mate on FI and consequently on BW, we examined the anorexic effects of mate on the appetite and satiety markers glucagon-like peptide 1 (GLP-1) and leptin in high-fat diet-fed ddY mice. GLP-1 is a peptide signal generated by the gastrointestinal tract, which regulates appetite and influences BW, whereas leptin is an afferent signal from the periphery to the brain in a homeostatic feedback loop that regulates adipose tissue mass, thus leading to decreased appetite and FI and increased energy expenditure. Chronic administration of mate (50, 100 mg/kg) for 3 weeks significantly reduced FI, BW, and ameliorated blood fats, liver fats, and adipose tissue. Mate induced significant increases in GLP-1 levels and leptin levels compared with the control. Acute administration of major constituents of mate showed significant increases in GLP-1 levels by dicaffeoyl quinic acids and mateasaponins, and significant induction of satiety by caffeoyl quinic acids and caffeine in ddY mice. These findings suggest that mate may induce anorexic effects by direct induction of satiety and by stimulation of GLP-1 secretion and modulation of serum leptin levels.

**Key words** maté; satiety; glucagon-like peptide 1; leptin; *Ilex paraguariensis*; food intake

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*Ilex paraguariensis* St. Hill. (Aquifoliaceae) leaves, popularly known as maté (mate), yerba-mate, or erva-mate, are used in the preparation of several types of tea, beverage, and soft drink in South America. Mate trees grow naturally and have been cultivated in southern Brazil, Argentina, and Paraguay, and the popularity of its preparations is increasing worldwide, particularly in North America and Europe.† Mate has central nervous system-stimulant properties attributed to its content of methylxanthine alkaloids such as caffeine2) and it is known to contain compounds with antioxidant properties such as phenolic acids and caffeoylquinic acid derivatives, which are the most abundant compounds in the leaves.1,3) Other reported effects include hepatoprotective, choleretic, diuretic, hypcholesterolemic, antihypertensive, antithrombotic, antiinflammatory, antiobesity, and cardioprotective effects may partially explain its popularity.† Yerba-mate was suggested to have benefits over other weight-loss herbal medicines and supplements based on cited clinical evidence of adverse events.† In our previous studies, chronic administration of mate tea significantly decreased hyperglycemia and serum insulin levels and showed significant improvement in insulin sensitivity in a metabolic syndrome mouse model.6) The studies also indicated that mate slows gastric emptying (GE), lowers body weight (BW), and reduces food intake (FI).6) Evidence of weight loss induction with mate intake suggests possible roles of satiation increase and energy intake reduction. A number of satiety markers are implicated in the pathogenesis of appetite loss, anorexia, and FI reduction.

Glucagon-like peptide 1 (GLP-1) is an incretin secreted by the intestinal enteroendocrine L-cells predominantly found in the ileum and colon. GLP-1 is a satiety signal released into the circulation after a meal or upon nutrient ingestion; its bioactive form GLP-1(7—36) amide constitutes the majority of the circulating hormone. Peripheral administration of GLP-1 or long-acting GLP-1 receptor agonists, such as exendin-4, reduce blood glucose and FI in rodents and humans, and chronic administration results in loss of BW. A growing body of evidence demonstrates that the anorexic effect of GLP-1 could be attributable to both its effect on GE and a direct effect on neurons in the central nervous system involved in appetite regulation.7,8) Leptin, an adipocytokine hormone that has both central and peripheral actions, has important roles in the regulation of appetite and energy balance, and is implicated in obesity.9,10)

In this study, we investigated the effects of oral administration of mate on biomarkers of satiety, obesity, and hyperlipidemia and their correlation with the antimetabolic syndrome effects and mechanisms of action of mate in high-fat diet (HFD)-fed ddY mice. We also carried out preliminary tests on the major constituents of mate to verify the role and mechanisms of the active ingredients. To the best of our knowledge, this is the first report on the effects of mate and its constituents on satiety and GLP-1 in vivo.

**MATERIALS AND METHODS**

**Mate Extract** An aqueous extract of mate was provided by Tamura Pharmaceutical Co., Ltd. (Nara, Japan). The extract was prepared from powdered dry fresh leaves of *I. paraguariensis* by infusion with boiling water (at 95 °C for 30 min), followed by filtration and vacuum-pressurized evaporation. The yield of the powdered aqueous extract was 25.7% of the extracted leaves, as described in our previous report.5) The administered dose was calculated based on the amount of the aqueous powdered extract dissolved or sus-
pended in a vehicle of 5% arabic gum solution.

**Major Constituents of Mate Extract** Major constituents of the aqueous extract were isolated and purified by repeated column chromatography. Briefly, mate aqueous extract (140 g) was subjected to silica gel column chromatography [4 kg, Silica gel BW-200 (Fuji Silysia Chemical, Ltd., Kasugai, Japan; 150—350 mesh), CHCl₃; MeOH: H₂O, (6: 4: 0)→(6: 4: 1)→(5: 4: 1); EtOAc: MeOH: H₂O, (2: 1: 0)→(2: 1: 1)→(1: 1: 1)→(1: 2: 1)] and octadecyl silica gel (ODS) column chromatography [2 kg, Chromatorex ODS DM1020T (Fuji Silysia Chemical, Ltd., 100—200 mesh), MeOH: H₂O, (25: 75)→(0: 100)]. Finally, HPLC was repeatedly used [pump: Hitachi L-2130 Elite LaChrom, Hitachi, Tokyo, Japan; detector: Shimadzu SPD-10A UV–VIS Detector/Shimadzu RID-10A Refractive Index Detector, Shimadzu, Kyoto, Japan; recorder: Shimadzu C-R6A; column: YMC-Pack ODS-A (250×20 mm i.d. S-5 μm, 12 nm); temperature: 25 °C; mobile phase: MeOH: H₂O, (25: 75)→(80: 20)] to give neochlorogenic acid (=3-O-caffeoyl-D-quinic acid) (312 mg, 0.22%), chlorogenic acid (2, 356 mg, 0.25%), cryptochlorogenic acid (=4-O-caffeoyl-D-quinic acid) (353 mg, 0.25%), 3,4-O-dicaffeoyl-D-quinic acid (1.46 g, 1.04%), 3,5-O-dicaffeoyl-D-quinic acid (1, 1.72 g, 1.23%), 4,5-O-dicaffeoyl-D-quinic acid (1.21 g, 0.86%), rutin (0.68 g, 0.49%), and caffeine (4, 4.95 g, 3.54%). Purification by repeated ODS column chromatography and HPLC afforded saponins, of which matesaponin 2 (684 mg, 0.49%) was identified as the major saponin. The isolated constituents were identified by comparison with spectral data (1H-NMR, 13C-NMR, and MS) previously reported and those of standard compounds [chlorogenic acid (2), matesaponin 2 (3), caffeine (4), and rutin]. Of the major constituents isolated, we tested 3,5-O-dicaffeoyl-D-quinic acid (1), chlorogenic acid (2), matesaponin 2 (3), and caffeine (4).

**Drugs and Chemicals** The following analytical grades of reagents were used in the experiments: normal saline (parenteral 0.9% sodium chloride solution, Otsuka, Tokyo, Japan), pentobarbital sodium (Tokyo Chemical Industry, Tokyo, Japan), arabic gum (Wako Pure Chemical Industries, Ltd., Osaka, Japan), aprotonin (RR-APRO, Phoenix Pharmaceuticals, Inc., Burlingame, CA, U.S.A.), dipetidyl peptidase-4 (DPP-IV) inhibitor (Millipore, St. Charles, MO, U.S.A.), α-linolenic acid (Cayman Chemical Company, Ann Arbor, MI, U.S.A.), enzyme DPP-IV (DPP4[CD26], 39-766 aa, ATGen Co., Ltd., Seongnam, Republic of Korea), GPNT substrate (Gly-Pro-pNA.Tos, Peptide Institute Inc., Osaka, Japan), Tris-maleate-NaOH buffer (Nacalai Tesque, Kyoto, Japan), and diprotin-A (Ile-Pro-Ile, Peptide Institute Inc.).

**Animals** Male ddY mice (6 weeks of age) weighing about 27—30 g were purchased from Kiwa Laboratory Animal Co., Ltd. (Wakayama, Japan) and used in this study. The animals were housed for 1 week before the experiments and fed a normal diet (MF, Oriental Yeast Co., Ltd., Tokyo, Japan) and water ad libitum. Housing conditions were thermostatically maintained at 24±1 °C with a 12 h-light/dark cycle (lights on: 07:30—19:30). BW and FI were measured daily throughout the experimental period. After the 1-week adaptation period, the animals were divided into four groups of two control groups and two mate-treated groups. One of the control groups was fed a normal control diet (D12450B, 10 kcal% fat, Research Diets Inc., New Brunswick, NJ, U.S.A.) and referred to as the normal group. The other three groups were fed an HFD (D12451, 45 kcal% fat, Research Diets Inc.). Of the HFD-fed groups, one group was administered mate extract dissolved or suspended in 5% arabic gum solution at a dose of 50 mg/kg/d, per os (p.o.); the second group was administered the extract at a dose of 100 mg/kg/d, p.o.; and the third group was administered equivalent volumes of the vehicle and used as a control. All experimental procedures were performed in accordance with the standards approved by the Experimental Animal Research Committee of Kyoto Pharmaceutical University.

**Measurement of BW and FI** BW and FI were measured daily between 11:00 and 13:00 throughout the experimental period.

**Mid-Light Phase Satiety Test and Blood Sample Assays** A group of mice was fasted overnight with free access to water (from 18:00—10:00). In the experiment (performed at 10:00), a simple satiety test was carried out where the fasted mice were given the HFD for 30 min, and the FI within the 30-min period was measured. The mice were then immediately anesthetized with pentobarbital sodium (50 mg/kg, intraperitoneally (i.p.)). Blood sampling was performed within 30 min after the FI measurement by withdrawing blood from the portal vein in syringes containing DPP-4 inhibitor (20 μl/ml blood), mixed, and transferred into microtubes containing ethylenediaminetetraacetic acid (EDTA)-Na (1 mg/ml blood) and aprotinin (100 μl/ml blood). The blood was centrifuged at 1600 g for 10 min at 4 °C, and the plasma was separated, divided into microtubes, and kept at −80 °C as HFD-state plasma. A second group of mice was treated similarly but without HFD feeding, and fasting-state plasma was prepared. The retroperitoneal white adipose tissues (epidymal, inguinal, and perirenal tissues) were separated, excised, and weighed. The liver was weighed and kept at −80 °C for further tests. Enzyme-linked immunosorbent assay (ELISA) kits were used for the measurement of blood levels of GLP-1 (GLP-1 Active, Shibayagi Co., Ltd., Gunma, Japan) and leptin (Leptin-Mouse, Shibayagi Co., Ltd., Gunma, Japan) and free fatty acids (FA), and total cholesterol (T-Cho) levels were determined using the Triglyceride E-Test Wako, NEFA C-Test Wako, and Total Cholesterol E-Test Wako, respectively (Wako Pure Chemical Industries Ltd.). Measurements were performed using a microplate reader (SH-1000 Lab Microplate Reader, Corona Electric Co., Ltd., Ibaraki, Japan) and the computer software SF6 (SH-1000 Software, Corona Electric Co., Ltd.).

**Measurement of Liver TGs** The liver TG contents were determined using a simplified method. Briefly, liver samples (ca. 100 mg) from similar lobes and portions were first processed in 1 ml of distilled water using a tissue-lyser (Tissuelyser, Qiagen, Haan, Germany). The mixture was centrifuged for 15 min at 8000 g and left to stand. The supernatant layer was used for TG determination using the Triglyceride E-Test Wako (Wako Pure Chemical Industries, Ltd.).

**Assessment of Acute Administration of Constituents of Mate. Effects on Satiety and GLP-1 Levels in Vivo** Male ddY mice (6 weeks of age) weighing about 27—30 g purchased from Kiwa Laboratory Animal Co., Ltd. were housed as described above and fed an HFD (D12451, 45 kcal% fat,
Research Diets Inc.) for 7 d before the experiments. A normal group was selected and given a normal diet (MF, Oriental Yeast Co., Ltd.). In the experiments, the test mice were fasted overnight with free access to water. Test samples were given orally to the mice 45 min before the mid-light satiety test. The constituents (1–4) were given at a dose of 100 mg/kg. The positive control α-linolenic acid was given at a dose of 20 mg/kg. The negative control and normal groups were given equivalent volumes of vehicle. The HFD was then given to the mice for 30 min, and FI within the 30-min period was measured for each group. The normal group was given the normal diet in the satiety test. Then the mice were anesthetized with pentobarbital sodium (50 mg/kg, i.p.), blood samples were collected, the plasma was separated, and GLP-1 levels were measured as described above.

**Assay of Inhibitory Effects on DPP-IV in Vitro** The modified assay method of Umezawa et al. was used. Briefly, the assay was performed in 96-well microplates. Preincubation of 25 μl of DPP-IV enzyme (10 mU/ml) or a blank buffer (50 mM Tris-maleate-NaOH, pH 7.2) with 25 μl of sample or control (0.4% dimethyl sulfoxide (DMSO) in buffer) was carried at 37 °C for 3 min. Fifty microliters of Gly-Pro-pNA.Tos (GPNT) substrate was added, and the mixture was incubated at 37 °C for 30 min. The absorbance was measured at 410 nm. Diprotin-A (Ile-Pro-Ile) was used as a reference inhibitor.

**Statistical Analysis** One-way analysis of variance (ANOVA) was performed for multiple comparisons between groups, followed by Dunnett’s method or Dunn’s method for multiple comparisons vs. the control group. A p value of less than 0.05 was considered to represent a statistically significant difference. Statistical analyses were carried out with the software SigmaStat for Windows ver. 3.0.1. (SPSS Inc., Chicago, IL, U.S.A.).

**RESULTS**

**Effects of Mate on BW** In this study, mate extract had a significant lowering effect on BW throughout the administration period, as shown in Fig. 1. The BW gain was significantly lowered by mate (control group, 5.8 ± 0.51; 50-mg mate group, 4.9 ± 0.43; 100-mg mate group, 3.5 ± 0.47 g/20 d, representing weight percentages of 19.3 ± 1.73, 16.3 ± 1.44, 11.8 ± 1.57%, respectively) (Table 1).

**Effects of Mate on FI** A significantly lower daily FI was seen in mate-administered groups (control, 2.70 ± 0.02; 50-mg mate group, 2.53 ± 0.01; 100-mg mate group, 2.43 ± 0.01 g/d/mouse) (Table 1, Fig. 2).

**Effects of Mate on Satiety at Mid-Light Phase** In the test of satiety, only the 100-mg mate group showed a significant decrease in FI during the 30-min feeding period compared with the control group (control group, 0.70 g/30 min; 50-mg mate group, 0.57 g/30 min; 100-mg mate group, 0.53 g/30 min) (Fig. 3).

**Effects of Mate on Obesity and Dyslipidemia-Related Metabolic Parameters** The fasting blood plasma of mate-administered groups showed significant decreases in TG levels compared with the control group (control group, 49.8 ± 3.2; 50-mg mate group, 33.6 ± 3.8; 100-mg mate group, 30.5 ± 2.3 mg/dl) (Fig. 4A). The levels of free FA, measured as nonesterified free fatty acids, showed a significant decline in mate-treated mice compared with the control group.

Table 1. Effects of Mate on Parameters and Weights of the Body and Organs in Mice

<table>
<thead>
<tr>
<th>Parameter/organ</th>
<th>Normal-fed</th>
<th>HFD-fed mice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Mate (50 mg/kg)</td>
</tr>
<tr>
<td>Final body weight (g)</td>
<td>36.8 ± 0.64</td>
<td>36.0 ± 0.47***</td>
</tr>
<tr>
<td>Body weight gain (g/20 d)</td>
<td>5.4 ± 0.72</td>
<td>5.8 ± 0.51††</td>
</tr>
<tr>
<td>Body weight (%)</td>
<td>17.4 ± 2.33</td>
<td>19.3 ± 1.73†</td>
</tr>
<tr>
<td>Food intake (g/d/mouse)</td>
<td>3.48 ± 0.01</td>
<td>2.70 ± 0.02††</td>
</tr>
<tr>
<td>White adipose tissue (g)</td>
<td>0.62 ± 0.04*</td>
<td>0.96 ± 0.15‡</td>
</tr>
<tr>
<td>Adiposity index (a)</td>
<td>1.78 ± 0.10*</td>
<td>2.75 ± 0.37†</td>
</tr>
<tr>
<td>Liver (g)</td>
<td>1.30 ± 0.04</td>
<td>1.13 ± 0.05†</td>
</tr>
<tr>
<td>Hepatic index (HI) (b)</td>
<td>3.69 ± 0.16</td>
<td>3.31 ± 0.09</td>
</tr>
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* p<0.05, † p<0.01, †† p<0.001 between groups (one-way ANOVA).

Fig. 1. Effects of Mate Extract on Body Weight Gain in Mice

Weight was measured daily throughout the administration period in the mate 50-mg/kg-treated group (○), mate 100-mg/kg-treated group (●), control vehicle group (■), and normal group (○). Data are mean±S.E.M. (n=12–18 mice per group). * p<0.05 vs. control group (Dunnett’s method). † p<0.05 between groups (one-way ANOVA).
(1.15±0.06, 0.58±0.01, 0.49±0.02 mg/dl, respectively) (Fig. 4B). However, only the 100-mg mate group exhibited a significant decrease in T-Chol levels compared with the controls (122±3.2, 116.5±6.7, 89.6±1.4 mg/dl, respectively) (Fig. 4C). Compared with the control group, both the 50- and 100-mg mate-administered groups had significant decreases in liver TG contents (29.3±2.6, 16.5±2.7, 15.1±2.1 mg/g liver, respectively), as shown in Fig. 4D.

The 100-mg mate-treated group showed significant decreases in the adiposity index and in the weights of the white adipose tissue (WAT) and liver compared with the control. The 50-mg mate group had a significant decrease only in the WAT weight. All the groups showed no change or nonsignificant decreases in the hepatic index during the experimental period (Table 1).

**Effects of Mate on Satiety-Related Metabolic Markers.**

**Effects on GLP-1 Levels** The mate-administered groups exhibited significant increases in GLP-1 levels compared with the control group (control group, 10.8±1.1; 50-mg mate group, 24.3±1.3; 100-mg mate group, 40.0±3.8 pg/ml) (Fig. 5A).

**Effects on Leptin Levels** The 50-mg and 100-mg mate-treated groups showed significant increases in leptin levels compared with the vehicle-treated control (control group, 1554±44; 50-mg mate group, 1959±72; 100-mg mate group, 2141±89 pg/ml) (Fig. 5B).

**Effects of Acute Administration of Major Constituents of Mate on Satiety** In the mid-light phase satiety test,
compounds 1, 2, and 4 (3,5-O-dicaffeoyl-D-quinic acid, chlorogenic acid, and caffeine, respectively), and the positive control α-linolenic acid showed significant inhibitory effects on FI (1, 1.40 ± 0.05; 2, 1.25 ± 0.04; 4, 0.39 ± 0.03; positive control, 1.25 ± 0.05 g/30 min) (Figs. 6, 7).

**Effects of Acute Administration of Mate Constituents on GLP-1 Levels** Compounds 1 and 3 (3,5-O-dicaffeoyl-D-quinic acid and matesaponin 2, respectively) and the positive control (α-linolenic acid) showed significant increases in GLP-1 levels vs. the vehicle control group (1, 16.71 ± 1.64; 3, 20.44 ± 3.44; positive control, 16.60 ± 1.11 pg/ml) (Fig. 8).

**Effects of Mate Constituents on DPP-IV in Vitro** The reference inhibitor (diprotin-A) showed a potent inhibitory effect on DPP-IV (90.6 ± 0.1% inhibition at 100 μg/ml; IC₅₀ = ca. 8.8 μg/ml). The tested major compounds 1—4 showed weak inhibitory effects or no inhibition at 100 μg/ml (-2.4 ± 1.9, 9.3 ± 8.1, -4.6 ± 0.4, 3.4 ± 1.8, respectively).

**DISCUSSION**

In this study, to clarify the antiobesity and BW-lowering mode of action of mate, we investigated the effects of mate on satiety and FI, and their correlation with BW and body lipids. Consistent with our previous findings, 6) 3-week chronic administration of mate (50, 100 mg/kg) significantly reduced BW, FI, and ameliorated plasma lipids (TG, FA, and T-Chol). It also reduced liver TG and the weights of the liver and WAT. The most significant finding in this study was that chronic administration of mate induced significant increases in GLP-1 levels and leptin levels in HFD-fed ddY mice compared with the controls.

It is well known that GLP-1 is secreted from the intestinal L-cells in response to FI and that its effects, although rapid in onset, are short-lived in part because the active form of GLP-1 is rapidly degraded by the circulating protease DPP-IV. Therefore a DPP-IV inhibitor was used to enable the estimation of GLP-1 levels in the blood. In addition, aprotinin was used to deactivate the proteolytic effects of the circulating protease enzymes. Our current findings indicate that mate administration increases GLP-1 levels, possibly by inducing GLP-1 secretion and/or enhancing its levels.

GLP-1 and its receptors are present in both the central...
nervous system and peripheral tissues, and the feeding effects of GLP-1 could be mediated at either or both sites. The impact of these effects on GLP-1 and satiety may be affected by some factors related to mid-light-phase and dark-phase cycles, as well as circadian rhythm and ambient temperature. In this study, we monitored the proliferative effects of mate administration on FI in the postfasting state at the mid-light-phase cycle, i.e., during daytime, and these effects are probably based on the peripheral stimulation of GLP-1. Our study highlights a significant correlation between FI and circulating levels of GLP-1 in presence or absence of the anorexic constituents of mate tea. Nonetheless, the anorexic effect of mate could be partly due to the presence of GLP-1 agonists and/or GLP-1 stimulatory substances. Moreover, we previously reported inhibitory effects of mate administration on GE in mice. 6) GLP-1 induction is known to inhibit GE 17) as well as increase satiety with reduced FI and reduced appetite. This finding suggests that mate could also induce satiety by inhibition of GE through the increase in GLP-1 levels.

Another interesting finding is that mate administration was accompanied by increased levels of leptin. Leptin is known to enhance the suppressive effects of gut peptides and their agonists on FI, as well as to stimulate GLP-1 release from L-cells. 5) On the other hand, it was suggested that peripherally released GLP-1 may mediate the effect of leptin and augment the leptin-dependent satiety signals. Both hormones have an additive effect on the decrease in FI in experimental animals. 19) Based on these findings, it could also be postulated that the increase in circulating levels of leptin with mate administration stimulates the secretion of appetite-suppressing GLP-1 and therefore indirectly alters the appetite.

Leptin is an adipocyte-derived hormone that is essential for the normal regulation of BW. It is anafferent signal from the periphery to the brain in a homeostatic feedback loop that regulates adipose tissue mass. In this study, the leptin level was positively correlated with the decrease in body fat mass, where mate-administered mice showed reduced retropertioneal WAT with increased circulating leptin levels. Elevated leptin levels signal the brain that excess energy is being stored, thus leading to decreased appetite and FI and increased energy expenditure. Similar findings indicated that rising levels of leptin signal the brain that excess energy is being stored, and this signal brings about adaptations of decreased appetite and increased energy expenditure that prevent obesity. 20) Basically there are two systems that operate in the regulation of FI: short-term regulation that concerned with overeating at each meal; and long-term regulation, which is related with the maintenance of normal quantities of energy stores as body fat. Our study implicates beneficial effects of mate administration on both short- and long-term FI regulation.

The findings of our experiments on the effects of acute administration of the major constituents of mate indicate that the short-term satiety effects could be attributed to dicaffeoylquinic acids (DCQAs), matesaponins, and caffeine, whereas the GLP-1 proliferative effects could be related to the DCQAs and matesaponins. It worth mentioning that Hirasa wa et al. 21) reported a short-term stimulatory effect of α-linolenic acid on GLP-1 levels at a similar dose. In our study, DCQAs and matesaponin 2 (at 100 mg/kg) led to significant increases in GLP-1 levels, similar to the control α-linolenic acid (at 20 mg/kg). Moreover, in vitro tests of the major constituents (1—4) did not show significant inhibitory effects on DPP-IV, indicating the possibility of other mechanisms rather than DPP-IV inhibition. The data also indicate that the significant satiety-inducing and appetite-suppressive effects of caffeine are most likely induced by direct central mechanisms and are less likely related to GLP-1 levels.

Early reports stated that decaffeinated coffee increased GLP-1 concentrations upon chronic administration in a randomized crossover study in healthy humans. 22) This effect was suggested to be attributed to chlorogenic acid, which increased GLP-1. 23) Recently, decaffeinated coffee has been shown to increase the total GLP-1 concentration slightly 30 min after ingestion in a randomized, crossover trial. 24) Meanwhile, caffeine was reported to enhance the appetite-suppressant effect of nicotine, 25) and its intake was positively related to satiety in both sexes in a randomized clinical trial. 26)

In conclusion, it is suggested that the anorexic and FI-lowering effects of mate could be exerted through mechanisms including induction and/or enhancement of intestinal GLP-1, modulation of serum leptin levels, and a possible direct central satiety-stimulatory role. Further detailed studies on the effects of chronic administration of mate constituents on GLP-1 and satiety are warranted.

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