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Anti-fatigue properties of the water extract of *Codonopsis pilosula* leaves in mice

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ABSTRACT: *Codonopsis pilosula* is a herbal plant with its roots utilized in food and medicine across Asia for the recognized healthy properties. However, the leaves contain fatigue-reducing chemicals and oxidative metabolism scavenger, while the potential anti-fatigue effects remain unexplored. The anti-fatigue function of water extract of *C. pilosula* leaves (WCL) was investigated in mice model. Swimming endurance, biochemical parameters and the genes of AMPK signaling pathway were determined. And the chemical components were identified and analyzed by UPLC-MS/MS. WCL exhibited remarkable anti-fatigue properties with a high safety. Compared to normal group (3.43 min), WCL significantly prolonged swimming time, with the best performance observed at a dosage of 1 g/kg/day (17.74 min), followed by 2 g/kg/day (6.69 min), and 0.5 g/kg/day (3.90 min) which showed no significant effect. The anti-fatigue effect was primarily observed by increasing indicators in the blood of antioxidant effects through enhancing SOD enzyme activity, and reducing MDA levels, and also by decreasing blood metabolites of BUN, LDH, and BLA, and upregulating expression levels of *PGC-1α*, *PPARα* and *MHC-1* genes. Overall, orally administering WCL at dose of 1–2 g/kg/day in mice demonstrated significant anti-fatigue effects. Flavonoids, phenolic acids, and amino acids may play important roles in their anti-fatigue ability by components analysis. Therefore, WCL is a promising natural product with anti-fatigue properties, and these findings provide novel insights into the high-value, health-promoting use of the non-medicinal parts of *C. pilosula*.

KEYWORDS: anti-fatigue effect, *Codonopsis pilosula*, swimming model, medicinal plants

INTRODUCTION

Codonopsis pilosula is a herbal plant mainly distributing in Asia, and the dried roots have been utilized in both food and medicine for centuries for addressing various health conditions [1]. The dried roots have been included in the list of the Pharmacopoeia of People's Republic of China since 1963 [2]. Pharmacological studies proved that anti-fatigue effect is one of the notable function of *C. pilosula*'s roots, which has been proved by clinical experience [3]. The roots also have other effects, including memory enhancing effects, anti-fatigue, regulating and improving immune function, etc. [4]. In practical production, typically only the roots are utilized, while the above-ground parts such as leaves, stems, and flowers have not been utilized until now, resulting in a waste of resources. However, recent studies related to medicinal materials have shown that the non-medicinal parts of medicinal plants contain a lot of chemical substances, even some active substances are higher than the medicinal parts. In our former studies, when comparing the chemical composition and antioxidant properties of *C. pilosula* leaves (CL) and roots, we observed that CL exhibited higher levels of bioactive compounds such as lobetyolin, proteins, amino acids, polysaccharides, flavonoids, and polyphenols [5]. It is worth noting that these chemical components, particularly amino acids, polysaccharides, flavonoids, and polyphenols, are known as effective physiological regulators that can alleviate fatigue [6]. Additionally, it has been determined that the antioxidant activity of CL is significantly higher compared to the roots. Studies have confirmed that oxidative stress and free radical damage play a critical role in the development of fatigue [7], while the antioxidant activity of CL is strong, the high content of amino acid and polysaccharide in CL are also important factors with potential anti-fatigue effect. However, the anti-fatigue effects of CL have not previously been reported.

Fatigue is affecting more than 20% of people worldwide [8], which can be caused by intense physical exercise [9]. Extensive research on natural materials has demonstrated their ability to enhance athletic performance and combat fatigue with minimal side effects. Therefore, the exploration of natural functional materials with anti-fatigue properties is crucial for promoting overall health. Investigating the health benefits of CL can pave the way for the development of new, health-promoting foods while offering valuable

insights for the *Codonopsis* industry's advancement, holding significant economic and research value [10]. This study aims to evaluate the anti-fatigue effects of CL. The anti-fatigue function was investigated in an endurance swimming mice model by measuring weight-loaded swimming time. To explore the primary mechanism, biochemical parameters including blood urea nitrogen (BUN), blood lactic acid (BLA), serum lactate dehydrogenase (LDH), liver glycogen (LGL), malonaldehyde (MDA) and superoxide dismutase (SOD) of the liver were analyzed. The mRNA expression levels of *PGC-1α*, *PPARα*, and *MHC-1* were also determined. These findings provide an experimental basis for the use of CL as a functional material and offer insights into the bioactive utilization of the non-traditional medicinal parts of *C. pilosula*.

MATERIALS AND METHODS

Preparation of WCL

C. pilosula leaves were collected in mid-August from a two-year-old planting field in Huining, Gansu Province, China. Leaves of various sizes were cut, mixed, washed with distilled water, and dried to a constant weight. For animal experiments, 100 g of powdered leaves were boiled in 1 l distilled water for 30 min [11], filtered through six layers of gauze, and repeated three times. The combined extract was concentrated in a vacuum drying oven, freeze-dried, and stored at −80 °C. The extract was then diluted with distilled water to the required experimental concentrations [12].

Acute toxicity test of WCL

A total of 40 Kunming mice of 18–22 g (from the same source and housing condition as described in the next subsection) were randomly selected and divided into a control group and WCL group. The WCL group was fasted 12 h (but allowed to get water) before gavage fed. They were administered at a concentration of 26.72 g/kg for every 24 h. The control group was given with ultra-pure water. The mouse's appearance, behavior, response to stimuli, secretions, excrement, etc. and death (time of death, pre-death reaction, etc.) were observed every day. The weight was measured on the 1, 3, 7, and 14 d. At the end (14 days), the experimental animals were generally dissected to observe and record the changes in the volume, weight, and color of the tissues and organs, and a detailed pathological examination of the tissues were conducted.

Animal housing for testing anti-fatigue effect

Fifty male Kunming mice of no specific pathogen (SPF) grade of 18–22 g [11] were purchased from Lanzhou Veterinary Research Institute (Lanzhou, China). They were housed in a room where the temperature and relative humidity environment (20±2 °C, 55±10% relative humidity) were controlled with a 12 h light-dark cycle. The animals were kept in polypropylene cages, they can get food and water freely. Fresh water and food were added every day. The animal feeding experiments were conducted by Lanzhou Food and Drug Administration. All experiments in this study followed the National Institutes of Health Guide for Care and Use of Laboratory Animals and were approved by Lanzhou Food and Drug Administration. After 5 d of acclimation, the mice were randomly divided into 5 groups with 10 animals for each group and kept for 30 d. The body weight of the mice was recorded every week. The food intake was recorded every day.

Experimental groups of testing anti-fatigue effect

The mice were divided into 5 groups: negative control group (NC), treated with distilled water; positive control (PC), treated with ascorbic acid, 1 g/kg/day, low-dose group (LG), treated with WCL of 0.5 g/kg/-day; medium-dose group (MG), treated with WCL of 1 g/kg/day; high-dose group (HG), treated with WCL of 2 g/kg/day. All treatments were administered by oral gavage at 0.1 ml/10 g body weight.

Endurance swimming test

Mice were trained to swim for 30 min, three times a week, in plastic containers (50 cm height, 30 cm diameter) with 20 cm water depth and a temperature of 22–25 °C [9]. On the 28th day, after oral administration, mice rested for 30 min, then underwent a weight-loaded swimming test with a lead sheet (7% of body weight) attached to their tails. The swimming time was recorded when they failed to surface for air within 7 s [13]. Afterward, they were removed from the water, dried, and rested for 48 h. On day 30, after the final oral dose, mice swam for 30 min without weight-loaded. They were dried, rested for 30 min, anesthetized with ether, and blood was collected from their eyes for serum analysis. Livers were frozen in liquid nitrogen and stored at −80 °C for later analysis [14].

Determination of biochemical parameters

The levels of BUN, BLA, serum LDH, LGL, liver and MDA and SOD were measured according to the procedures provided by the assay kits. All the assay kits used were purchased from Solarbio Life Science Co., Ltd. (Beijing, China). All other reagents were of analytical grade.

Quantitative real-time PCR analysis

All reagents, RNA extraction, and PCR methods were provided by Wuhan Servicebio Technology Co., Ltd. (Wuhan, China). For RNA extraction, 100 mg liver tissue was homogenized with 1 ml Trizol Reagent on ice, then centrifuged at 12,000 rpm for 10 min to

collect the supernatant. After adding 250 µl chloroform, 400 µl supernatant was transferred to a new tube, mixed with 0.8 times the volume of isopropanol, and incubated at −20 °C for 15 min. The precipitate was washed with 1.5 ml of 75% ethanol and dissolved in 15 µl RNase-free water at 55 °C for 5 min. RNA concentration and purity were measured using Nanodrop 2000 and diluted to 100–500 ng/µl. For reverse transcription, 2 µg RNA was incubated with 0.5 µl Oligo (dT)18 Primer and 0.5 µl Random Hexamer Primer at 65 °C for 5 min, then cooled on ice. Reaction buffer (4 µl) and RT enzyme mixture (1 µl) were added, followed by incubation at 42 °C for 60 min, then at 70 °C for 5 min. RNA quantification was performed with an initial denaturation at 95 °C for 10 min, followed by 40 cycles of denaturation at 95 °C for 15 s and annealing at 60 °C for 60 s. The gene expression was calculated using the $2^{-\Delta\Delta t}$ method, β-actin was used as an endogenous reference gene [15].

The sequences of forward primers for *PGC-1α*, *PPARα*, *MHC-1* and β-*actin* were: GAGAGGCAGAAGCAGAAAGC, GCATGTGAAGGCTGTAAGGG, CCAAGGGCCTGAATGAGGAG, and GCAAGCAGGAGTACGATGAGT, respectively. The sequences of reverse primer were: CTCAATTCTGTCCGCGTTGT, TTGTGTGACATCCCGACAGA, GCAAAGGCTCCAGGTCTGAG and GGTGTAAAACGCAGCTCAGTA, respectively [15].

Sample preparation and extraction and conditions for UPLC-MS/MS analysis

Biological samples were freeze-dried using a vacuum freeze-dryer (Scientz-100F, Scientz Biotechnology, Ningbo, China) and crushed with a zirconia bead in a mixer mill (MM 400, Retsch, Haan, Germany) for 1.5 min at 30 Hz. 100 mg of lyophilized powder was dissolved in 1.2 ml 70% methanol, vortexed for 30 s every 30 min for 6 cycles, and stored at 4 °C overnight. After centrifugation at 12,000 rpm for 10 min, the extracts were filtered (SCAA-104, 0.22 µm) before UPLC-MS/MS analysis. LIT and triple quadrupole (QQQ) scans were performed using a Q TRAP mass spectrometer (Q TRAP 4500, AB Sciex, Foster City, CA, USA), with ESI Turbo Ion-Spray interface in both positive and negative modes, controlled by Analyst 1.6.3 software. ESI parameters included a source temperature of 550 °C, ion spray voltage of 5500 V (positive)/−4500 V (negative), and gases set at 50, 60, and 25 psi for GSI, GSII, and CUR, respectively. Mass calibration was performed using 10 and 100 µmol/l polypropylene glycol solutions in QQQ and LIT modes. MRM scans were conducted with medium collision gas; the declustering potential (DP) and collision energy (CE) were optimized for each transition and monitored according to metabolite elution.

Statistical analysis

The data was analyzed by SPSS 20.0 software. Significant differences and mean values were analyzed using One-way ANOVA, the significance in differences were determined by Duncan test ($p < 0.05$ and $p < 0.01$ were both tested for all the indicators in this study). All experiments were conducted in triplicate.

RESULTS AND DISCUSSION

Acute toxicity test of WCL

To evaluate the safety of WCL, the acute toxicity test was conducted [16]. Compared with the control group, the physiological reactions and behaviors of mice in WCL group were all normal, and there was no abnormal reaction or death. No obvious organ changes were observed after autopsy. The changes in animal weight are shown in Table 1. The weight of the administration group increased normally during the test. Therefore, WCL has a good safety guarantee for later test.

Effects of WCL on body weight and food intake during test of anti-fatigue effect

During the anti-fatigue test, daily food intake was recorded, and weekly averages were calculated for all groups (Table 2). The body weight of mice in each experimental group was measured weekly (Table 3). The results showed that body weight increased for all mice, with stable food intake across groups during the feeding stages. From the second week, the LG and MG groups showed lower body weight compared to other groups, but no significant differences were observed between experimental and control groups. However, the MG group had significantly lower body weight than the LG and HG groups, likely due to its potential lipid-lowering effect. Many natural plant ingredients, such as green tea and olive leaves, have various health benefit [12].

Effect of WCL on weight-loaded swimming time

The swimming time recorded from endurance weight-loaded experiment is commonly used as an indicator of anti-fatigue activity in mice model [16]. The results of the endurance weight-loaded swimming time of this study are presented in Fig. 1. The positive control (PC) group treated with VC demonstrated an effective anti-fatigue effect, which was higher than the control group treated with distilled water ($p < 0.05$). For WCL treated groups, LG (3.90 min) had no difference with that of the negative control NC (3.43 min), the swimming time was almost consistent with that of NC, suggesting that intake of the low dose of WCL had no effect on swimming time. Interestingly, the swimming time of MG (17.74 min) was much significantly longer than all the other groups ($p < 0.01$). Compared with the control group (3.43 min), WCL prolonged swimming time significantly, even over 2 times higher than the positive control group (7.05 min), meaning that WCL can improve the exercise endurance of mice to a certain extent over the dose of 1 g/kg/day. However,

Table 1 Body weight of experimental groups of mice for acute toxicity test of WCL.

	Control		Treated group	
	Female (g)	Male (g)	Female (g)	Male (g)
Initial weight	19.34 ± 0.55	19.17 ± 0.50	19.11 ± 0.46	19.03 ± 0.50
1st day	22.90 ± 0.82	25.56 ± 0.60	23.38 ± 1.17	25.11 ± 0.86
3rd day	24.28 ± 0.71	26.84 ± 0.83	24.04 ± 1.11	27.26 ± 1.00
7th day	25.95 ± 0.88	31.88 ± 1.09	26.44 ± 1.60	30.59 ± 1.14
14th day	29.55 ± 1.32	36.38 ± 1.34	30.46 ± 1.93	36.46 ± 1.53

Data are presented as mean ± SD, $n = 10$.

Table 2 Average food intake recorded weekly for the experimental groups of mice.

	NC (g)	PC (g)	LG (g)	MG (g)	HG (g)
First week	2.67 ± 0.14	2.67 ± 0.18	2.70 ± 0.13	2.73 ± 0.09	2.71 ± 0.09
Second week	2.88 ± 0.06	2.87 ± 0.04	2.86 ± 0.05	2.88 ± 0.03	2.85 ± 0.03
Third week	2.91 ± 0.05	2.92 ± 0.03	2.92 ± 0.02	2.90 ± 0.03	2.93 ± 0.03
Fourth week	2.95 ± 0.07	2.96 ± 0.04	2.95 ± 0.04	2.97 ± 0.08	2.98 ± 0.08

Data are presented as mean ± SD, $n = 10$. NC, negative control group, treated with distilled water; PC, positive control, treated with ascorbic acid, 1 g/kg/day; LG, low-dose group, treated with samples of 0.5 g/kg/day; MG, medium-dose group, treated with samples of 1 g/kg/day; HG, high-dose group, treated with samples of 2 g/kg/day. The different small letters indicate significant differences at $p < 0.05$ and $p < 0.01$, respectively, based on ANOVA-Duncan multiple comparison results.

the swimming time of the HG group (6.69 min) was much shorter than that of the MG group but longer than that of NC and LG groups, which was almost the same as PC group. This means high dose of intake of WCL could prolong swimming time but it did not increase with the increase of dose. The most appropriate dose was 1 g/kg/day. This result was similar to the weight-loaded swimming test of arabinan-rich pectin from acerola [17], of which the middle dose group obtained the highest swimming time and the high dose group obtained longer time than the control group but shorter than the middle-dose group. The phenomenon where the high-dose group exhibited a lower efficacy than the middle-dose group is a classic concept in pharmacology and toxicology, commonly referred to as "a pattern of decreased effect with increased dose" [18]. This may be related to the fact that the intake of high concentrations of bioactive substances can impose an additional burden on metabolic organs, such as the liver and kidneys. There is a threshold for the absorption and utilization of the active components in WCL by the body; once this threshold is exceeded, the excess not only fails to exert beneficial effects but also consumes energy for metabolism and excretion [18, 19]. Another possibility is side effects: a high dose may induce mild physiological discomfort or metabolic disorders (non-lethal but affecting the optimal exercise state of the mice), leading to a shortened exhaustive swimming time. Additionally, immune response mechanisms could be another contributing factor, as high doses might trigger an adverse or opposite immune reaction [18, 19]. From these results, WCL could prolong the exhaustive swimming time efficiently, thus it had a prominent anti-fatigue effect over the dose of 1 g/kg/day. What's more, the effect was closely determined by the dose of WCL, low dose did not have meaningful function.

Effect of WCL on biochemical parameters of blood samples

To analyze anti-fatigue mechanism of WCL, the biochemical parameters of blood samples are shown in Fig. 2. The muscle produces plenty of lactic acids when doing high-intensity exercise. The increased level of lactic acid will bring about a reduction of pH in muscle tissue and blood, and also induce many side effects of various biochemical and physiological processes [20]. Therefore, the levels of BUN, LDH, and BLA of blood samples were detected. BUN is the nitrogen content in urine from the breakdown of

Table 3 Body weight of mice in the experimental groups recorded weekly.

Group	Initial (g)	First week (g)	Second week (g)	Third week (g)	Fourth week (g)
NC	21.73 ± 1.55^{a}	33.50 ± 1.84^{a}	41.73 ± 2.71^{ab}	43.51 ± 2.57^{ab}	43.57 ± 2.51^{ab}
PC	21.42 ± 1.59^{a}	33.65 ± 2.23^{a}	41.46 ± 2.74^{ab}	43.13 ± 2.41^{ab}	43.40 ± 2.23^{ab}
LG	21.12 ± 1.37^{a}	33.95 ± 2.59^{a}	42.87 ± 2.67^{a}	41.33 ± 2.88^{ab}	41.72 ± 2.80^{ab}
MG	21.20 ± 1.33^{a}	32.94 ± 2.37^{a}	39.82 ± 2.26^{b}	40.98 ± 3.37^{b}	41.03 ± 2.73^{b}
HG	22.18 ± 1.97^{a}	34.06 ± 3.05^{a}	40.86 ± 2.50^{ab}	44.14 ± 3.07^{a}	44.08 ± 2.72^{a}

Data are presented as mean ± SD, $n = 10$. NC, PC, LG, MG, and HG are the same as those described under Table 2.

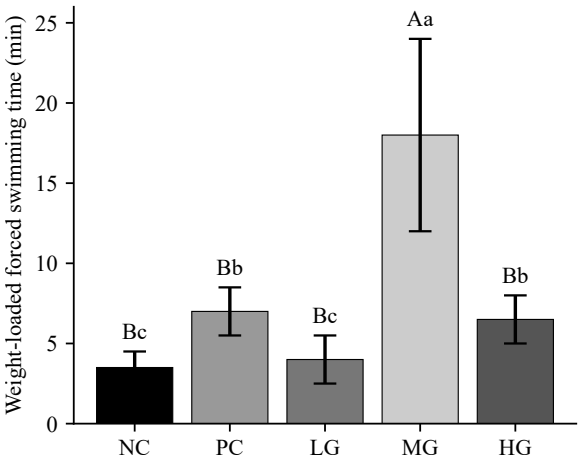


Fig. 1 The weight-loaded swimming time of mice treated with different doses in an endurance swimming mice model. NC, negative control group, treated with distilled water; PC, positive control, treated with ascorbic acid, 1 g/kg/day; LG, low-dose group, treated with samples of 0.5 g/kg/day; MG, medium-dose group, treated with samples of 1 g/kg/day; HG, high-dose group, treated with samples of 2 g/kg/day. Above each column, the different small and capital letters in the mean column indicate significant and great significant differences at $p < 0.05$ and $p < 0.01$, respectively, based on ANOVA-Duncan multiple comparison results.

proteins, which occurs when energy production from sugar and fat metabolism is insufficient to support the body [21]. Serum LDH is considered to be an accurate indicator of muscle injury. The normal function of LDH in cells is to catalyze the mutual conversion of pyruvate and lactate, thereby reducing the accumulation of LA in muscles [22]. The blood test index results showed that the serum index test results were in good agreement with the conclusion of swimming experiment. The levels of these 3 indicators of the control group (17.14 mmol/l, 12.87 U/ml, 7.66 mmol/l) were higher than those of other groups ($p < 0.01$), except for the LG group (16.17 mmol/l, 12.56 U/ml, 6.38 mmol/l). But different from the weight-loaded experiment, with the WCL dose increased, the blood indicators showed a decreasing trend and did not increase with the increase of the dose. There is no significant difference between the MG group (11.38 mmol/l, 8.39 U/ml, 3.41 mmol/l) and the HG group (11.48 mmol/l, 8.96 U/ml, 4.35 mmol/l). Similar to the swimming time, the levels of 3 blood indicators of the LG group were all significantly higher than those of other experimental groups ($p < 0.01$), which proved that the LG group did not significantly change the blood indicators of the mice. This is in agreement with the study result of other anti-fatigue research, like hairtail (*Trichiurus lepturus*) hydrolysate [9]. The result indicated that intake of WCL could reduce the level of the above 3 indicators. According to the theory of accumulation of metabolites of fatigue, fatigue is an accumulation effect caused by the production of a large number of metabolites in the body after a lot of exercise [23]. WCL reduces the levels of BUN, serum LDH, and BLA accumulated during high-intensity exercise to a certain extent to alleviate the fatigue effect. Moreover, this effect has a significant dose-effect relationship. The 1 g/kg/day dose was most effective, followed by 2 g/kg/day; the 0.5 g/kg/day dose had no significant effect.

Effect of WCL on biochemical parameters of liver samples

The effects of WCL on biochemical parameters of liver samples are shown in Fig. 3. SOD is an important antioxidant enzyme to clean superoxide anion free radicals [24]. And SOD also plays an important role in physiological process, which is localized immunohistochemically in the human and rat tissues [25]. As shown in Fig. 3A, the levels of SOD activity of WCL increased with the increase of dose, and it was correlating with the dose positively. This result is consistent with that of *in vitro* antioxidant activity of WCL in our previous study [11]. The PC group has the highest SOD activity, the value was 268.80 U/g, which may be due to the strong antioxidant activity of VC, which is a well-known strong antioxidant. There is no significant difference between the HG group (247.40 U/g) and PC group, indicating that the antioxidant activity of WCL at high doses can reach the level as high as that of VC, this is also the same as *in vitro* antioxidant activity of WCL. There were no significant differences among LG group (47.37 U/g), MG group (112.30 U/g) and NC group (79.19 U/g), ($p < 0.01$), indicating that WCL has no obvious effect on SOD activity when the gavage dose is low. MDA is one of the end-products in the lipid peroxidation process, and its levels will increase while fatigue occurs [25]. As shown in Fig. 3 (B), the MDA levels of the experimental groups were significantly lower than that of the NC group. The MDA levels of MG group (1.61 nmol/mgprot) and HG group (2.10 nmol/mgprot) were significantly lower than that of PC group (2.99 nmol/mgprot) ($p < 0.01$). And MG group was significantly lower than HG group ($p < 0.01$); LG group (4.25 nmol/mgprot) had higher MDA level than other experimental groups, but still significantly lower than NC group ($p < 0.01$). Therefore, WCL has a strong effect on reducing MDA. The MG group has the most obvious reduction effect, then was the HG group and the LG group. As the degree of fatigue increases, the LGL decomposition also increases, so the level of LGL can reflect the degree of fatigue to a certain extent. From Fig. 3 (C), it can be seen that the LGL level in the MG group (9.77 mg/g) and the HG group (8.31 mg/g) were higher than other groups ($p < 0.01$). PC group (7.72 mg/g) was higher than NC group (5.34 mg/g) and LG group ($p < 0.01$). There was no significant difference between LG group

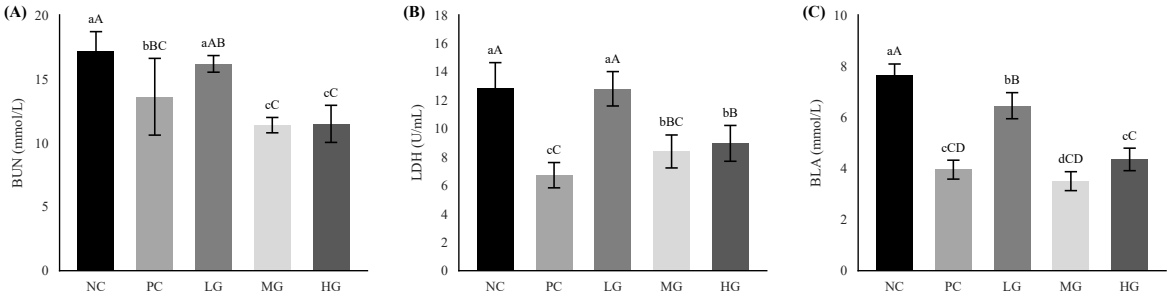


Fig. 2 The levels of BUN (A), LDH (B), and BLA (C) of the mice treated with different doses. BUN, blood urea nitrogen; LDH, lactate dehydrogenase; BLA, blood lactic acid; NC, PC, LG, MG, HG, and letters above bar graph which indicate statistics are the same as those described under Table 2.

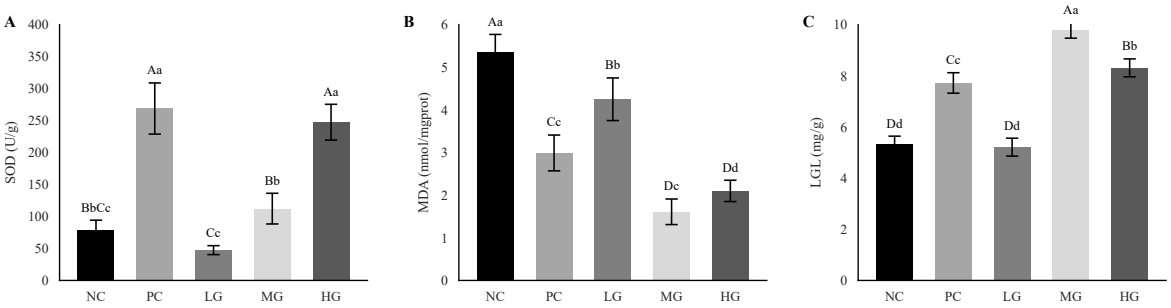


Fig. 3 The levels of SOD (A), MDA (B), and LGL (C) of the mice treated with different doses. SOD, superoxide dismutase; MDA, malonaldehyde; LGL, liver glycogen; NC, PC, LG, MG, HG, and letters above bar graph which indicate statistics are the same as those described under Table 2.

(5.21 mg/g) and NC group. From the above results, WCL can significantly increase liver SOD enzyme activity, and the activity increases with the increase of dose. There is no significant difference in enzyme activity between HG group and VC group. WCL also reduced liver MDA content significantly. The consumption of LGL level was lower in WCL treated groups. The theory of fatigue caused by free radicals believes that active oxygen free radicals produced by exercise can induce protein oxidation and lipid peroxidation to destroy cell membranes and organelles, resulting in muscle fatigue [23]. Therefore, WCL increases the antioxidant enzyme activity of fatigued mice and reduces oxidized lipid metabolites, this is an important mechanism for its anti-fatigue activity.

Effect of WCL on anti-fatigue related mRNA expression

The AMPK signaling pathway is crucial for energy metabolism, phosphorylating PGC-1α to activate downstream factors, promoting mitochondrial biosynthesis, and enhancing energy supply [26]. Upregulation of the AMPK/PGC-1α pathway correlates with exercise endurance and fatigue regulation. PPARα, a nuclear hormone receptor, collaborates with PGC-1α to balance energy metabolism [27]. Endurance training increases *MHC-1* expression in muscle fibers, as seen in mice gavaged with *Rhodiola rosea* [28]. To explore WCL's anti-fatigue mechanism, *PGC-1α*, *PPARα*, and *MHC-1* expressions were measured. RT-PCR showed WCL upregulated *PGC-1α* dose-dependently (Fig. 4A). While the HG group had the highest *PGC-1α* expression, its swimming time was shorter than the MG group, indicating other genes influence the mechanism. The MG group significantly upregulated *PPARα* compared to NC and HG (Fig. 4B), with the PC group showing the highest expression. WCL treatment upregulated *MHC-1*, with MG having the strongest effect (1.39-fold vs. blank, $p < 0.01$; Fig. 4C). In summary, WCL upregulated *PGC-1α* and *MHC-1* in all treated groups, with MG specifically enhancing *PPARα*. The MG group showed the longest swimming time and highest *MHC-1*/*PPARα* expression, while HG's high *PGC-1α* did not correlate with endurance. This suggests the anti-fatigue mechanism involves synergistic regulation of PGC-1α, PPARα, and MHC-1 in the AMPK pathway, balancing energy production and improving exercise endurance.

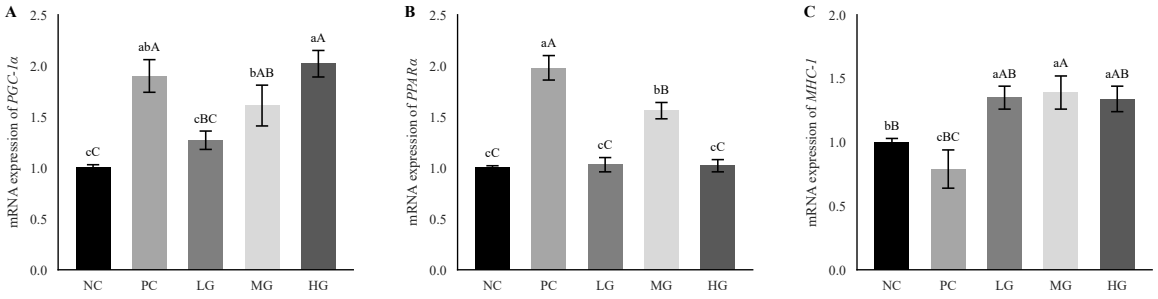


Fig. 4 Expression levels of *PGC-1α* (A), *PPARα* (B), and *MHC-1* (C) genes measured by RT-PCR. NC, PC, LG, MG, HG, and letters above bar graph which indicate statistics are the same as those described under Table 2.

Table 4 Metabolites detected in *C. pilosula* leaves.

	m/z Q3 (Da)	Formula	Ionization mode	Compound name	Compound class	Peak area ratio (%)
1	283.09	$C_{10}H_{13}N_5O_5$	[M+H]+	2-Hydroxyadenosine	Nucleotides and derivatives	4.13 ± 0.21
2	448.10	$C_{21}H_{20}O_{11}$	[M+H]+	Luteolin-7-O-glucoside (Cynaroside)	Flavonoids	3.46 ± 0.59
3	448.10	$C_{21}H_{20}O_{11}$	[M+H]+	Aureusidin-4-O-glucoside	Flavonoids	3.21 ± 0.12
4	286.05	$C_{15}H_{10}O_6$	[M+H]+	Luteolin (5,7,3′,4′-Tetrahydroxyflavone)	Flavonoids	1.89 ± 0.56
5	354.10	$C_{16}H_{18}O_9$	[M-H]-	1-Caffeoylquinic acid	Phenolic acids	1.76 ± 0.14
6	202.22	$C_{10}H_{26}N_4$	[M+H]+	Spermine	Alkaloids	1.69 ± 0.54
7	448.10	$C_{21}H_{20}O_{11}$	[M+H]+	Luteolin-3′-O-glucoside	Flavonoids	1.59 ± 0.15
8	286.05	$C_{15}H_{10}O_6$	[M+H]+	Aureusidin	Flavonoids	1.59 ± 0.11
9	354.10	$C_{16}H_{18}O_9$	[M-H]-	Cryptochlorogenic acid (4-O-Caffeoylquinic acid)	Phenolic acids	1.33 ± 0.23
10	354.10	$C_{16}H_{18}O_9$	[M-H]-	Neochlorogenic acid (5-O-Caffeoylquinic acid)	Phenolic acids	1.14 ± 0.14
11	280.24	$C_{18}H_{32}O_2$	[M-H]-	Linoleic acid	Lipids	1.03 ± 0.14
12	300.06	$C_{16}H_{12}O_6$	[M+H]+	Diosmetin (5,7,3′-Trihydroxy-4′-methoxyflavone)	Flavonoids	1.00 ± 0.46

Chemical components analysis of the extract

The UPLC-MS/MS analysis was applied to analyze the chemical substances in the extracts. The total ion chromatogram and multi-peak graphs from UPLC-MS/MS analysis are shown in Fig. S1(A,B). Screening was conducted using primary and secondary mass spectrometry in both positive and negative ion modes, with removal of isotopic signals and redundant signals from NH_4^+, Na^+, and K^+. Compounds were identified by database comparison based on molecular weight and m/z. Components with a peak area ratio >0.01% are listed in Table 4 and Table S1, classified as follows: flavonoids (44 types) and phenolic acids (41 types) were the most abundant, followed by lipid compounds (37 types), nucleotides and derivatives (23 types), amino acids and derivatives (16 types), as well as alkaloids, organic acids, lignans, and coumarins. These substances align with our previous publication [11]. Among extract components, 2-hydroxyadenosine had the highest peak area ratio, followed by luteolin-7-O-glucoside (Cynaroside), with flavonoids comprising a large proportion among the top 20 components. Thus, active ingredients for anti-fatigue effects are likely polyphenols, flavonoids, alkaloids, amino acids, nucleotides, and derivatives. Amino acids enhance physical strength and combat fatigue by supplying energy via deamination (producing NH_3 and CO_2) when carbohydrate/lipid catabolism is insufficient, and regulating the TCA cycle [26]. Exercise generates ROS (e.g., hydroxyl and superoxide anion radicals), and natural plants with antioxidant activity eliminate fatigue by improving antioxidant defense system activity, clearing ROS, reducing MDA content, balancing the antioxidant system and ROS, inhibiting lipid peroxidation, and protecting cell membranes [29]. This aligns with the blood and enzyme activity indicators in mice from this study. Flavonoids and phenolic acids exhibit strong antioxidant activity, significantly improving oxidative metabolic damage from fatigue. Thus, the flavonoids, phenolic acids, and amino acids in CL extracts may exert anti-fatigue effects in mice through this mechanism.

CONCLUSION

C. pilosula leaves exhibit a significant anti-fatigue effect with a dose-response relationship. The water extracts notably prolonged swimming time, with the best effect at 1 g/kg/d, while 0.5 g/kg/d showed no significant effect. The anti-fatigue mechanism involves regulating energy metabolism by reducing liver glycogen consumption, enhancing antioxidant effects through increased liver SOD activity, and lowering MDA levels.

It also decreases blood metabolites like BUN, LDH, and BLA during fatigue, and upregulates *PGC-1α* expression in the AMPK pathway. Flavonoids, phenolic acids, and amino acids contribute to the anti-fatigue effect. CL shows potential as a health-promoting material, and the non-medicinal parts of *C. pilosula* offer valuable bioactive properties for future development.

Appendix A. Supplementary data

Supplementary data associated with this article can be found at https://dx.doi.org/10.2306/scienceasia1513-1874.2026.095.

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Appendix A. Supplementary data

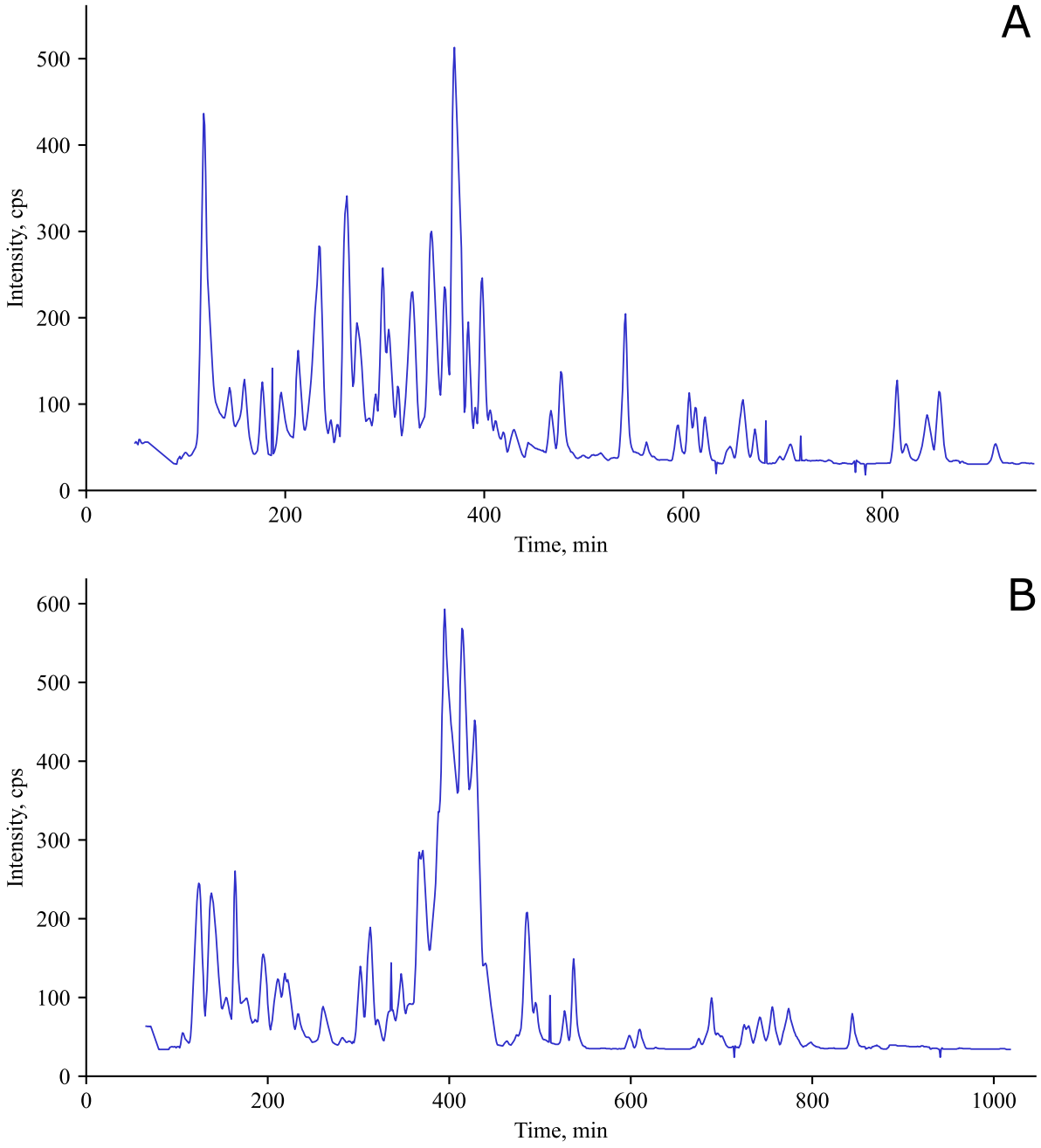


Fig. S1 Total ion current diagram of the extract by UPLC-MS/MS analysis. A, negative mode; B positive mode.

Table S1 Identified compounds and their peak area ratios.

	m/z Q3 (Da)	Formula	Ionization mode	Compound name	Compound class	Peak area ratio (%)
1	283.09	$C_{10}H_{13}N_5O_5$	[M+H]+	2-Hydroxyadenosine	Nucleotides and derivatives	4.13 ± 0.21
2	448.10	$C_{21}H_{20}O_{11}$	[M+H]+	Luteolin-7-O-glucoside (Cynaroside)	Flavonoids	3.46 ± 0.59
3	448.10	$C_{21}H_{20}O_{11}$	[M+H]+	Aureusidin-4-O-glucoside	Flavonoids	3.21 ± 0.12
4	286.05	$C_{15}H_{10}O_6$	[M+H]+	Luteolin (5,7,3′,4′-Tetrahydroxyflavone)	Flavonoids	1.89 ± 0.56
5	354.10	$C_{16}H_{18}O_9$	[M-H]-	1-Caffeoylquinic acid	Phenolic acids	1.76 ± 0.14
6	202.22	$C_{10}H_{26}N_4$	[M+H]+	Spermine	Alkaloids	1.69 ± 0.54
7	448.10	$C_{21}H_{20}O_{11}$	[M+H]+	Luteolin-3′-O-glucoside	Flavonoids	1.59 ± 0.15
8	286.05	$C_{15}H_{10}O_6$	[M+H]+	Aureusidin	Flavonoids	1.59 ± 0.11
9	354.10	$C_{16}H_{18}O_9$	[M-H]-	Cryptochlorogenic acid (4-O-Caffeoylquinic acid)	Phenolic acids	1.33 ± 0.23
10	354.10	$C_{16}H_{18}O_9$	[M-H]-	Neochlorogenic acid (5-O-Caffeoylquinic acid)	Phenolic acids	1.14 ± 0.14
11	280.24	$C_{18}H_{32}O_2$	[M-H]-	Linoleic acid	Lipids	1.03 ± 0.14
12	300.06	$C_{16}H_{12}O_6$	[M+H]+	Diosmetin (5,7,3′-Trihydroxy-4′-methoxyflavone)	Flavonoids	1.00 ± 0.46
13	610.15	$C_{27}H_{30}O_{16}$	[M+H]+	Kaempferol-3-O-galactoside-4′-O-glucoside	Flavonoids	0.99 ± 0.01
14	300.06	$C_{16}H_{12}O_6$	[M+H]+	Hispidulin (5,7,4′-Trihydroxy-6-methoxyflavone)	Flavonoids	0.96 ± 0.03
15	519.33	$C_{26}H_{50}NO_7P$	[M+H]+	LysoPC 18:2(2n isomer)	Lipids	0.94 ± 0.03
16	300.06	$C_{16}H_{12}O_6$	[M+H]+	Rhamnocitrin (7-Methylkaempferol)	Flavonoids	0.93 ± 0.10
17	548.12	$C_{25}H_{24}O_{14}$	[M+H]+	Kaempferide-3-O-(6″-malonyl)glucoside	Flavonoids	0.89 ± 0.08
18	329.05	$C_{10}H_{12}N_5O_6P$	[M-H]-	Cyclic 3′,5′-Adenylic acid	Nucleotides and derivatives	0.86 ± 0.03
19	243.09	$C_9H_{13}N_3O_5$	[M+H]+	Cytarabine	Nucleotides and derivatives	0.77 ± 0.32
20	345.05	$C_{10}H_{12}N_5O_7P$	[M-H]-	Guanosine 3′,5′-cyclic monophosphate	Nucleotides and derivatives	0.70 ± 0.06
21	283.09	$C_{10}H_{13}N_5O_5$	[M+H]+	Guanosine	Nucleotides and derivatives	0.70 ± 0.01
22	448.10	$C_{21}H_{20}O_{11}$	[M-H]-	Kaempferol-3-O-galactoside (Trifolin)	Flavonoids	0.70 ± 0.04
23	131.10	$C_6H_{13}NO_2$	[M+H]+	6-Deoxyfagomine	Alkaloids	0.67 ± 0.02
24	251.10	$C_{10}H_{13}N_5O_3$	[M+H]+	2′-Deoxyadenosine	Nucleotides and derivatives	0.66 ± 0.06
25	181.07	$C_9H_{11}NO_3$	[M+H]+	4-Hydroxy-5-(2-oxo-1-pyrrolidinyl)benzoic acid	Alkaloids	0.65 ± 0.06
26	270.05	$C_{15}H_{10}O_5$	[M+H]+	Apigenin	Flavonoids	0.63 ± 0.04
27	122.05	$C_6H_6N_2O$	[M+H]+	Nicotinamide	Others	0.62 ± 0.01
28	119.07	C_8H_9N	[M+H]+	N-Benzylmethylene isomethylamine	Alkaloids	0.62 ± 0.01
29	534.10	$C_{24}H_{22}O_{14}$	[M+H]+	Kaempferol-3-O-(6″-malonyl)galactoside	Flavonoids	0.62 ± 0.02
30	135.05	$C_5H_5N_5$	[M+H]+	Adenine	Nucleotides and derivatives	0.60 ± 0.03
31	534.10	$C_{24}H_{22}O_{14}$	[M+H]+	Kaempferol-3-O-(6″-malonyl)glucoside	Flavonoids	0.59 ± 0.03
32	772.21	$C_{33}H_{40}O_{21}$	[M+H]+	Kaempferol-6,8-di-C-glucoside-7-O-glucoside	Flavonoids	0.57 ± 0.00
33	278.23	$C_{18}H_{30}O_2$	[M-H]-	α-Linolenic Acid	Lipids	0.56 ± 0.01
34	278.23	$C_{18}H_{30}O_2$	[M-H]-	γ-Linolenic Acid	Lipids	0.55 ± 0.03
35	267.10	$C_{10}H_{13}N_5O_4$	[M+H]+	Adenosine	Nucleotides and derivatives	0.54 ± 0.04
36	327.13	$C_{15}H_{21}NO_7$	[M+H]+	N-benzoyl-2-aminoethyl-β-D-glucopyranoside	Others	0.53 ± 0.06
37	448.10	$C_{21}H_{20}O_{11}$	[M+H]+	Kaempferol-4′-O-glucoside	Flavonoids	0.53 ± 0.08
38	594.16	$C_{27}H_{30}O_{15}$	[M+H]+	Apigenin-6,8-di-C-glucoside (Vicenin-2)	Flavonoids	0.52 ± 0.06
39	176.10	$C_{10}H_{12}N_2O$	[M+H]+	Serotonin	Alkaloids	0.51 ± 0.07
40	432.11	$C_{21}H_{20}O_{10}$	[M+H]+	Galangin-7-O-glucoside	Flavonoids	0.49 ± 0.01

Table S1 Continued ...

	m/z Q3 (Da)	Formula	Ionization mode	Compound name	Compound class	Peak area ratio (%)
41	490.11	$C_{23}H_{22}O_{12}$	[M+H]+	Kaempferol-3-O-(2″-acetyl)glucoside	Flavonoids	0.49 ± 0.01
42	495.33	$C_{24}H_{50}NO_7P$	[M+H]+	LysoPC 16:0(2n isomer)	Lipids	0.47 ± 0.00
43	477.29	$C_{23}H_{44}NO_7P$	[M+H]+	LysoPE 18:2(2n isomer)	Lipids	0.47 ± 0.01
44	204.09	$C_{11}H_{12}N_2O_2$	[M-H]-	L-Tryptophan	Amino acids and derivatives	0.46 ± 0.11
45	174.11	$C_6H_{14}N_4O_2$	[M+H]+	L-Arginine	Amino acids and derivatives	0.46 ± 0.04
46	176.10	$C_{10}H_{12}N_2O$	[M+H]+	N-Hydroxytryptamine	Alkaloids	0.45 ± 0.06
47	148.02	$C_8H_4O_3$	[M+H]+	Phthalic anhydride	Phenolic acids	0.42 ± 0.01
48	145.09	$C_5H_{11}N_3O_2$	[M+H]+	4-Guanidinobutyric acid	Organic acids	0.40 ± 0.00
49	477.29	$C_{23}H_{44}NO_7P$	[M+H]+	LysoPE 18:2	Lipids	0.39 ± 0.00
50	453.29	$C_{21}H_{44}NO_7P$	[M+H]+	LysoPE 16:0	Lipids	0.38 ± 0.04
51	118.03	$C_4H_6O_4$	[M-H]-	Succinic acid	Organic acids	0.37 ± 0.01
52	180.04	$C_9H_8O_4$	[M-H]-	Caffeic acid	Phenolic acids	0.37 ± 0.00
53	610.15	$C_{27}H_{30}O_{16}$	[M+H]+	Orientin-2″-O-galactoside	Flavonoids	0.37 ± 0.11
54	118.03	$C_4H_6O_4$	[M-H]-	Methylmalonic acid	Organic acids	0.37 ± 0.01
55	187.06	$C_{11}H_9NO_2$	[M+H]+	3-Indoleacrylic acid	Alkaloids	0.36 ± 0.11
56	117.08	$C_5H_{11}NO_2$	[M+H]+	L-Valine	Amino acids and derivatives	0.36 ± 0.10
57	278.15	$C_{16}H_{22}O_4$	[M+H]+	Dibutyl phthalate	Phenolic acids	0.36 ± 0.13
58	342.12	$C_{12}H_{22}O_{11}$	[M-H]-	Galactinol	Others	0.35 ± 0.01
59	516.13	$C_{25}H_{24}O_{12}$	[M-H]-	Isochlorogenic acid B	Phenolic acids	0.35 ± 0.06
60	278.15	$C_{16}H_{22}O_4$	[M+H]+	Diisobutyl phthalate	Phenolic acids	0.34 ± 0.01
61	135.05	$C_5H_5N_5$	[M+H]+	2-Aminopurine	Nucleotides and derivatives	0.33 ± 0.01
62	432.11	$C_{21}H_{20}O_{10}$	[M+H]+	Apigenin-7-O-glucoside (Cosmosiin)	Flavonoids	0.32 ± 0.01
63	192.03	$C_6H_8O_7$	[M-H]-	Isocitric Acid	Organic acids	0.29 ± 0.01
64	316.12	$C_{14}H_{20}O_8$	[M-H]-	Vanilloside	Phenolic acids	0.28 ± 0.01
65	624.17	$C_{28}H_{32}O_{16}$	[M+H]+	Chrysoeriol-7-O-gentiobioside	Flavonoids	0.28 ± 0.01
66	516.13	$C_{25}H_{24}O_{12}$	[M-H]-	Isochlorogenic acid A	Phenolic acids	0.27 ± 0.01
67	432.11	$C_{21}H_{20}O_{10}$	[M+H]+	Apigenin-8-C-Glucoside (Vitexin)	Flavonoids	0.26 ± 0.01
68	180.06	$C_6H_{12}O_6$	[M-H]-	D-Mannose	Others	0.25 ± 0.01
69	316.08	$C_{13}H_{16}O_9$	[M-H]-	1-O-Gentisoyl-D-glucoside	Phenolic acids	0.24 ± 0.01
70	187.06	$C_{11}H_9O_2N$	[M+H]+	3-amino-2-naphthoic acid	Alkaloids	0.24 ± 0.01
71	342.12	$C_{12}H_{22}O_{11}$	[M-H]-	D-Maltose	Others	0.24 ± 0.01
72	610.15	$C_{27}H_{30}O_{16}$	[M+H]+	Luteolin-7-O-gentiobioside	Flavonoids	0.24 ± 0.01
73	376.14	$C_{17}H_{20}N_4O_6$	[M+H]+	Riboflavin (Vitamin B2)	Others	0.24 ± 0.01
74	154.03	$C_7H_6O_4$	[M-H]-	2,3-Dihydroxybenzoic Acid	Phenolic acids	0.24 ± 0.01
75	475.27	$C_{23}H_{42}NO_7P$	[M+H]+	LysoPE 18:3	Lipids	0.24 ± 0.01
76	180.06	$C_6H_{12}O_6$	[M-H]-	D-Galactose	Others	0.23 ± 0.01
77	154.03	$C_7H_6O_4$	[M-H]-	3,4-Dihydroxybenzoic acid (Protocatechuic acid)	Phenolic acids	0.22 ± 0.01
78	316.08	$C_{13}H_{16}O_9$	[M-H]-	Protocatechuic acid-4-O-glucoside	Phenolic acids	0.22 ± 0.01
79	342.12	$C_{12}H_{22}O_{11}$	[M-H]-	Isomaltulose	Others	0.22 ± 0.01
80	772.21	$C_{33}H_{40}O_{21}$	[M+H]+	Kaempferol-3-O-sophorotrioside	Flavonoids	0.22 ± 0.01

Table S1 Continued ...

	m/z Q3 (Da)	Formula	Ionization mode	Compound name	Compound class	Peak area ratio (%)
81	326.10	$C_{15}H_{18}O_8$	[M-H]-	p-Coumaric acid-4-O-glucoside	Phenolic acids	0.22 ± 0.01
82	342.12	$C_{12}H_{22}O_{11}$	[M-H]-	Lactobiose	Others	0.20 ± 0.01
83	517.32	$C_{26}H_{48}NO_7P$	[M+H]+	LysoPC 18:3(2n isomer)	Lipids	0.20 ± 0.01
84	495.33	$C_{24}H_{50}NO_7P$	[M+H]+	LysoPC 16:0	Lipids	0.18 ± 0.01
85	432.11	$C_{21}H_{20}O_{10}$	[M-H]-	Apigenin-6-C-glucoside (Isovitexin)	Flavonoids	0.18 ± 0.01
86	181.07	$C_9H_{11}NO_3$	[M+H]+	N-(2-Hydroxy-4-methoxyphenyl)acetamide	Alkaloids	0.18 ± 0.01
87	188.11	$C_9H_{16}O_4$	[M-H]-	Azelaic acid	Organic acids	0.17 ± 0.06
88	134.02	$C_4H_6O_5$	[M-H]-	L-Malic acid	Organic acids	0.17 ± 0.03
89	342.12	$C_{12}H_{22}O_{11}$	[M-H]-	D-Sucrose	Others	0.17 ± 0.01
90	475.27	$C_{23}H_{42}NO_7P$	[M+H]+	LysoPE 18:3(2n isomer)	Lipids	0.16 ± 0.02
91	342.10	$C_{15}H_{18}O_9$	[M-H]-	Vanillic Acid-4-O-Glucuronide	Phenolic acids	0.16 ± 0.06
92	342.10	$C_{15}H_{18}O_9$	[M-H]-	1-O-Caffeoyl-β-D-glucose	Phenolic acids	0.16 ± 0.07
93	134.02	$C_4H_6O_5$	[M-H]-	3-Dehydro-L-Threonic Acid	Others	0.16 ± 0.01
94	144.12	$C_8H_{16}O_2$	[M-H]-	Valproic Acid	Organic acids	0.15 ± 0.01
95	326.10	$C_{15}H_{18}O_8$	[M-H]-	1-O-p-Coumaroyl-β-D-glucose	Phenolic acids	0.15 ± 0.00
96	338.10	$C_{16}H_{18}O_8$	[M-H]-	5-O-p-Coumaroylquinic acid	Phenolic acids	0.15 ± 0.03
97	180.06	$C_6H_{12}O_6$	[M-H]-	D-Fructose	Others	0.15 ± 0.01
98	244.07	$C_9H_{12}N_2O_6$	[M-H]-	Uridine	Nucleotides and derivatives	0.14 ± 0.13
99	131.10	$C_6H_{13}NO_2$	[M+H]+	L-Leucine	Amino acids and derivatives	0.14 ± 0.11
100	594.16	$C_{27}H_{30}O_{15}$	[M+H]+	Vitexin-2″-O-glucoside	Flavonoids	0.14 ± 0.08
101	131.10	$C_6H_{13}NO_2$	[M+H]+	L-Norleucine	Amino acids and derivatives	0.14 ± 0.02
102	756.21	$C_{33}H_{40}O_{20}$	[M+H]+	Apigenin-6-C-glucoside-7-O-Sophoroside	Flavonoids	0.14 ± 0.00
103	370.09	$C_{16}H_{18}O_{10}$	[M-H]-	Fraxetin-8-O-glucoside (Fraxin)	Lignans and Coumarins	0.14 ± 0.00
104	338.10	$C_{16}H_{18}O_8$	[M-H]-	3-O-p-Coumaroylquinic acid	Phenolic acids	0.13 ± 0.00
105	228.21	$C_{14}H_{28}O_2$	[M-H]-	Myristic Acid	Lipids	0.13 ± 0.00
106	180.06	$C_6H_{12}O_6$	[M-H]-	D-Glucose	Others	0.13 ± 0.06
107	521.35	$C_{26}H_{52}NO_7P$	[M+H]+	LysoPC 18:1	Lipids	0.13 ± 0.00
108	138.03	$C_7H_6O_3$	[M-H]-	4-Hydroxybenzoic acid	Phenolic acids	0.13 ± 0.02
109	516.13	$C_{25}H_{24}O_{12}$	[M+H]+	1,3-Dicaffeoylquinic acid	Phenolic acids	0.13 ± 0.00
110	516.13	$C_{25}H_{24}O_{12}$	[M+H]+	Isochlorogenic acid C	Phenolic acids	0.13 ± 0.03
111	610.15	$C_{27}H_{30}O_{16}$	[M+H]+	Kaempferol-3,7-di-O-glucoside	Flavonoids	0.13 ± 0.03
112	131.10	$C_6H_{13}NO_2$	[M+H]+	L-Isoleucine	Amino acids and derivatives	0.13 ± 0.02
113	180.06	$C_6H_{12}O_6$	[M-H]-	Inositol	Others	0.13 ± 0.01
114	517.32	$C_{26}H_{48}NO_7P$	[M+H]+	LysoPC 18:3	Lipids	0.13 ± 0.07
115	342.12	$C_{12}H_{22}O_{11}$	[M-H]-	D-Trehalose	Others	0.13 ± 0.01
116	490.11	$C_{23}H_{22}O_{12}$	[M-H]-	Kaempferol-3-O-(6″-acetyl)glucoside	Flavonoids	0.12 ± 0.03
117	133.04	$C_4H_7NO_4$	[M-H]-	L-Aspartic Acid	Amino acids and derivatives	0.11 ± 0.01
118	176.07	$C_7H_{12}O_5$	[M-H]-	2-Isopropylmalic Acid	Organic acids	0.11 ± 0.03
119	498.12	$C_{25}H_{22}O_{11}$	[M+H]+	Dicaffeoylshikimic acid	Phenolic acids	0.11 ± 0.04
120	520.19	$C_{26}H_{32}O_{11}$	[M+H]+	Dehydrodiconiferyl alcohol-γ′-O-glucoside	Phenolic acids	0.11 ± 0.03

Table S1 Continued ...

	m/z Q3 (Da)	Formula	Ionization mode	Compound name	Compound class	Peak area ratio (%)
121	194.06	$C_{10}H_{10}O_4$	[M-H]-	Ferulic acid	Phenolic acids	0.11 ± 0.02
122	521.35	$C_{26}H_{52}NO_7P$	[M+H]+	LysoPC 18:1(2n isomer)	Lipids	0.10 ± 0.09
123	453.29	$C_{21}H_{44}NO_7P$	[M+H]+	LysoPE 16:0(2n isomer)	Lipids	0.10 ± 0.05
124	186.16	$C_{11}H_{22}O_2$	[M-H]-	Undecylic Acid	Lipids	0.09 ± 0.04
125	626.15	$C_{27}H_{30}O_{17}$	[M+H]+	Quercetin-3-O-(2″-O-galactosyl)glucoside	Flavonoids	0.09 ± 0.01
126	474.12	$C_{23}H_{22}O_{11}$	[M+H]+	Apigenin-7-O-(6″-acetyl)glucoside	Flavonoids	0.09 ± 0.00
127	418.09	$C_{20}H_{18}O_{10}$	[M+H]+	Kaempferol-3-O-arabinoside	Flavonoids	0.08 ± 0.02
128	204.09	$C_{11}H_{12}N_2O_2$	[M+H]+	1-Methoxy-indole-3-acetamide	Alkaloids	0.08 ± 0.01
129	148.04	$C_5H_8O_5$	[M-H]-	L-Citramalic acid	Organic acids	0.08 ± 0.00
130	281.11	$C_{11}H_{15}N_5O_4$	[M+H]+	2′-O-Methyladenosine	Nucleotides and derivatives	0.08 ± 0.00
131	154.03	$C_7H_6O_4$	[M-H]-	2,5-Dihydroxybenzoic acid; Gentisic Acid	Phenolic acids	0.08 ± 0.03
132	297.09	$C_{11}H_{15}N_5O_3S$	[M+H]+	5′-Deoxy-5′-(methylthio)adenosine	Nucleotides and derivatives	0.08 ± 0.01
133	278.23	$C_{18}H_{30}O_2$	[M+H]+	Punicic acid (9Z,11E,13Z-octadecatrienoic acid)	Lipids	0.07 ± 0.00
134	136.04	$C_4H_8O_5$	[M-H]-	D-Threonic Acid	Others	0.07 ± 0.01
135	436.14	$C_{21}H_{24}O_{10}$	[M-H]-	Phloretin-4′-O-glucoside (Trilobatin)	Flavonoids	0.07 ± 0.01
136	354.10	$C_{16}H_{18}O_9$	[M-H]-	Chlorogenic acid (3-O-Caffeoylquinic acid)	Phenolic acids	0.07 ± 0.00
137	181.07	$C_9H_{11}NO_3$	[M+H]+	L-Tyrosine	Amino acids and derivatives	0.07 ± 0.01
138	504.15	$C_{21}H_{28}O_{14}$	[M-H]-	1-O-Caffeoyl-(6-O-glucosyl)-β-D-glucose	Phenolic acids	0.07 ± 0.01
139	260.03	$C_6H_{13}O_9P$	[M-H]-	D-Glucose 6-phosphate	Others	0.07 ± 0.00
140	132.04	$C_5H_8O_4$	[M-H]-	2-Methylsuccinic acid	Organic acids	0.07 ± 0.01
141	260.03	$C_6H_{13}O_9P$	[M-H]-	Glucose-1-phosphate	Others	0.06 ± 0.00
142	230.16	$C_{11}H_{22}N_2O_3$	[M+H]+	L-Valyl-L-Leucine	Amino acids and derivatives	0.06 ± 0.02
143	278.16	$C_{15}H_{22}N_2O_3$	[M+H]+	L-Leucyl-L-phenylalanine	Amino acids and derivatives	0.06 ± 0.01
144	155.07	$C_6H_9N_3O_2$	[M+H]+	L-Histidine	Amino acids and derivatives	0.06 ± 0.01
145	493.32	$C_{24}H_{48}NO_7P$	[M+H]+	LysoPC 16:1	Lipids	0.05 ± 0.01
146	282.26	$C_{18}H_{34}O_2$	[M-H]-	11-Octadecanoic acid(Vaccenic acid)	Lipids	0.05 ± 0.01
147	523.36	$C_{26}H_{54}NO_7P$	[M+H]+	LysoPC 18:0	Lipids	0.05 ± 0.01
148	383.11	$C_{14}H_{17}N_5O_8$	[M+H]+	Succinyladenosine	Nucleotides and derivatives	0.05 ± 0.01
149	347.06	$C_{10}H_{14}N_5O_7P$	[M+H]+	Adenosine 5′-monophosphate	Nucleotides and derivatives	0.05 ± 0.01
150	260.03	$C_6H_{13}O_9P$	[M-H]-	D-Fructose 6-Phosphate	Others	0.05 ± 0.01
151	368.11	$C_{17}H_{20}O_9$	[2M-H]-	5-O-Feruloylquinic acid	Phenolic acids	0.05 ± 0.01
152	464.10	$C_{21}H_{20}O_{12}$	[M+H]+	Quercetin-3-O-glucoside (Isoquercitrin)	Flavonoids	0.04 ± 0.01
153	448.10	$C_{21}H_{20}O_{11}$	[M-H]-	Kaempferol-7-O-glucoside	Flavonoids	0.04 ± 0.01
154	165.07	$C_9H_{11}NO_2$	[M+H]+	L-Phenylalanine	Amino acids and derivatives	0.04 ± 0.00
155	340.08	$C_{15}H_{16}O_9$	[M-H]-	Esculin (6,7-DihydroxyCoumarin-6-glucoside)	Lignans and Coumarins	0.04 ± 0.01
156	148.04	$C_5H_8O_5$	[M-H]-	3-Methylmalic acid	Organic acids	0.04 ± 0.01
157	340.08	$C_{15}H_{16}O_9$	[M-H]-	Daphnin	Lignans and Coumarins	0.04 ± 0.00
158	236.12	$C_{12}H_{16}N_2O_3$	[M+H]+	L-Alanyl-L-Phenylalanine	Amino acids and derivatives	0.04 ± 0.01
159	148.04	$C_5H_8O_5$	[M-H]-	2-Hydroxyglutaric Acid	Organic acids	0.04 ± 0.01
160	330.10	$C_{14}H_{18}O_9$	[M-H]-	2,4,6-trihydroxy-acetophenone-6-O-β-D-glucopyranoside	Phenolic acids	0.04 ± 0.01

Table S1 Continued ...

	m/z Q3 (Da)	Formula	Ionization mode	Compound name	Compound class	Peak area ratio (%)
161	352.26	$C_{21}H_{36}O_4$	[M+H]+	1-α-Linolenoyl-glycerol	Lipids	0.04 ± 0.02
162	281.11	$C_{11}H_{15}N_5O_4$	[M+H]+	N6-methyladenosine	Nucleotides and derivatives	0.04 ± 0.01
163	493.32	$C_{24}H_{48}NO_7P$	[M+H]+	LysoPC 16:1(2n isomer)	Lipids	0.04 ± 0.00
164	326.10	$C_{15}H_{18}O_8$	[M-H]-	Phenylpropionic acid-O-β-D-glucopyranoside	Phenolic acids	0.04 ± 0.00
165	520.19	$C_{26}H_{32}O_{11}$	[M-H]-	Pinoresinol-4-O-glucoside	Lignans and Coumarins	0.04 ± 0.02
166	296.24	$C_{18}H_{32}O_3$	[M-H]-	13(S)-HODE;13(S)-Hydroxyoctadeca-9Z,11E-dienoic acid*	Lipids	0.04 ± 0.01
167	330.10	$C_{14}H_{18}O_9$	[M-H]-	2,4,6-trihydroxy-acetophenone-4-O-β-D-glucopyranoside	Phenolic acids	0.04 ± 0.00
168	122.04	$C_7H_6O_2$	[M-H]-	4-Hydroxybenzaldehyde	Phenolic acids	0.04 ± 0.00
169	242.23	$C_{15}H_{30}O_2$	[M-H]-	Pentadecanoic Acid	Lipids	0.03 ± 0.01
170	148.04	$C_5H_8O_5$	[M-H]-	2-Dehydro-3-deoxy-L-arabinonate	Others	0.03 ± 0.01
171	296.24	$C_{18}H_{32}O_3$	[M-H]-	9S-Hydroxy-10E,12Z-octadecadienoic acid	Lipids	0.03 ± 0.00
172	210.04	$C_6H_{10}O_8$	[M-H]-	D-Saccharic acid	Others	0.03 ± 0.00
173	580.22	$C_{28}H_{36}O_{13}$	[M-H]-	Syringaresinol-4′-O-glucopyranoside	Lignans and Coumarins	0.03 ± 0.01
174	284.08	$C_{10}H_{12}N_4O_6$	[M-H]-	Xanthosine	Nucleotides and derivatives	0.03 ± 0.00
175	210.04	$C_6H_{10}O_8$	[M-H]-	D-Galactaric acid	Others	0.03 ± 0.00
176	180.08	$C_{10}H_{12}O_3$	[M-H]-	Propyl 4-hydroxybenzoate	Phenolic acids	0.03 ± 0.00
177	462.12	$C_{22}H_{22}O_{11}$	[M+H]+	6-C-MethylKaempferol-3-glucoside	Flavonoids	0.03 ± 0.00
178	324.04	$C_9H_{13}N_2O_9P$	[M-H]-	Uridine 5′-monophosphate	Nucleotides and derivatives	0.03 ± 0.01
179	462.12	$C_{22}H_{22}O_{11}$	[M+H]+	Diosmetin-7-O-glucoside	Flavonoids	0.03 ± 0.00
180	462.12	$C_{22}H_{22}O_{11}$	[M+H]+	Diosmetin-7-O-galactoside	Flavonoids	0.03 ± 0.00
181	311.12	$C_{12}H_{17}N_5O_5$	[M+H]+	2-(Dimethylamino)guanosine	Nucleotides and derivatives	0.03 ± 0.01
182	462.12	$C_{22}H_{22}O_{11}$	[M+H]+	Hispidulin-7-O-Glucoside	Flavonoids	0.03 ± 0.01
183	176.03	$C_6H_8O_6$	[M-H]-	L-Ascorbic acid (Vitamin C)	Others	0.03 ± 0.01
184	311.12	$C_{12}H_{17}N_5O_5$	[M+H]+	N6-(2-Hydroxyethyl)adenosine	Nucleotides and derivatives	0.03 ± 0.00
185	218.13	$C_9H_{18}N_2O_4$	[M+H]+	L-Seryl-L-Isoleucine	Amino acids and derivatives	0.03 ± 0.00
186	268.08	$C_{10}H_{12}N_4O_5$	[M-H]-	9-(Arabinosyl)hypoxanthine	Nucleotides and derivatives	0.02 ± 0.01
187	264.15	$C_{14}H_{20}N_2O_3$	[M+H]+	L-Valyl-L-Phenylalanine	Amino acids and derivatives	0.02 ± 0.00
188	174.05	$C_7H_{10}O_5$	[M-H]-	Shikimic acid	Organic acids	0.02 ± 0.00
189	436.14	$C_{21}H_{24}O_{10}$	[M-H]-	Dihydrocharcone-4′-O-glucoside	Flavonoids	0.02 ± 0.00
190	330.24	$C_{18}H_{34}O_5$	[M-H]-	9,10,13-Trihydroxy-11-Octadecenoic Acid	Lipids	0.02 ± 0.00
191	310.21	$C_{18}H_{30}O_4$	[M-H]-	13(s)-hydroperoxy-(9z,11e,15z)-octadecatrienoic acid	Lipids	0.02 ± 0.00
192	534.10	$C_{24}H_{22}O_{14}$	[M+H]+	Luteolin-7-O-(6″-malonyl)glucoside	Flavonoids	0.02 ± 0.01
193	147.05	$C_5H_9NO_4$	[M-H]-	L-threo-3-Methylaspartate	Amino acids and derivatives	0.02 ± 0.00
194	330.10	$C_{14}H_{18}O_9$	[M-H]-	1-O-Vanilloyl-D-Glucose	Phenolic acids	0.02 ± 0.01
195	200.18	$C_{12}H_{24}O_2$	[M-H]-	Dodecanoic acid (Lauric acid)	Lipids	0.02 ± 0.00
196	272.24	$C_{16}H_{32}O_3$	[M-H]-	2-Hydroxyhexadecanoic acid	Organic acids	0.02 ± 0.01
197	149.07	$C_6H_7N_5$	[M+H]+	1-Methyladenine	Nucleotides and derivatives	0.02 ± 0.01
198	145.05	C_9H_7NO	[M+H]+	Indole-3-carboxaldehyde	Alkaloids	0.02 ± 0.00
199	436.14	$C_{21}H_{24}O_{10}$	[M-H]-	Phloretin-2′-O-glucoside (Phlorizin)	Flavonoids	0.02 ± 0.01
200	696.19	$C_{31}H_{36}O_{18}$	[M-H]-	Syringoylcaffeoylquinic acid-D-glucose	Phenolic acids	0.02 ± 0.00

Table S1 Continued ...

	m/z Q3 (Da)	Formula	Ionization mode	Compound name	Compound class	Peak area ratio (%)
201	242.23	$C_{15}H_{30}O_2$	[M-H]-	13-methylmyristic acid	Lipids	0.02 ± 0.01
202	523.36	$C_{26}H_{54}NO_7P$	[M+H]+	LysoPC 18:0(2n isomer)	Lipids	0.02 ± 0.00
203	219.11	$C_9H_{17}NO_5$	[M-H]-	D-Pantothenic Acid	Others	0.02 ± 0.00
204	165.07	$C_6H_7N_5O$	[M+H]+	6-O-methylguanine	Nucleotides and derivatives	0.02 ± 0.01
205	196.06	$C_6H_{12}O_7$	[M-H]-	Gluconic acid	Others	0.02 ± 0.00
206	518.11	$C_{24}H_{22}O_{13}$	[M+H]+	Apigenin-7-O-(6″-malonyl)glucoside	Flavonoids	0.01 ± 0.00
207	122.07	$C_8H_{10}O$	[M-H2O+H]+	2-Phenylethanol	Phenolic acids	0.01 ± 0.00
208	519.33	$C_{26}H_{50}NO_7P$	[M+H]+	LysoPC 18:2	Lipids	0.01 ± 0.00
209	507.33	$C_{25}H_{50}NO_7P$	[M+H]+	LysoPC 17:1	Lipids	0.01 ± 0.00
210	133.04	$C_4H_7NO_4$	[M-H]-	Iminodiacetic acid	Organic acids	0.01 ± 0.00
211	166.05	$C_5H_{10}O_6$	[M-H]-	D-Xylonic acid	Others	0.01 ± 0.00
212	300.08	$C_{13}H_{16}O_8$	[M-H]-	4-O-Glucosyl-4-hydroxybenzoic acid	Phenolic acids	0.01 ± 0.00
213	224.07	$C_{11}H_{12}O_5$	[M-H]-	Sinapic acid	Phenolic acids	0.01 ± 0.00
214	514.31	$C_{27}H_{46}O_9$	[M+H]+	1-α-Linolenoyl-glycerol-3-O-glucoside	Lipids	0.01 ± 0.01
215	254.06	$C_{15}H_{10}O_4$	[M+H]+	Chrysin	Flavonoids	0.01 ± 0.00
216	491.30	$C_{24}H_{46}NO_7P$	[M+H]+	LysoPC 16:2	Lipids	0.01 ± 0.00
217	785.16	$C_{27}H_{33}N_9O_{15}P_2$	[M-H]-	Riboflavin 5′-Adenosine Diphosphate	Nucleotides and derivatives	0.01 ± 0.00
218	626.15	$C_{27}H_{30}O_{17}$	[M+H]+	Quercetin-3,7-Di-O-glucoside	Flavonoids	0.01 ± 0.00
219	300.09	$C_{13}H_{16}O_8$	[M-H]-	1-O-Salicyloyl-β-D-glucose	Phenolic acids	0.01 ± 0.00
220	562.21	$C_{28}H_{34}O_{12}$	[M-H]-	Pinoresinol-4-O-(6″-acetyl)glucoside	Lignans and Coumarins	0.01 ± 0.00
221	676.37	$C_{33}H_{56}O_{14}$	[M+H]+	1-α-Linolenoyl-glycerol-2,3-di-O-glucoside	Lipids	0.01 ± 0.00