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Efficacy and safety of a novel dietary pyrroloquinoline quinone disodium salt on muscle strength and physical function in healthy volunteers: A randomized, double-blind, placebo-controlled study

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Highlights

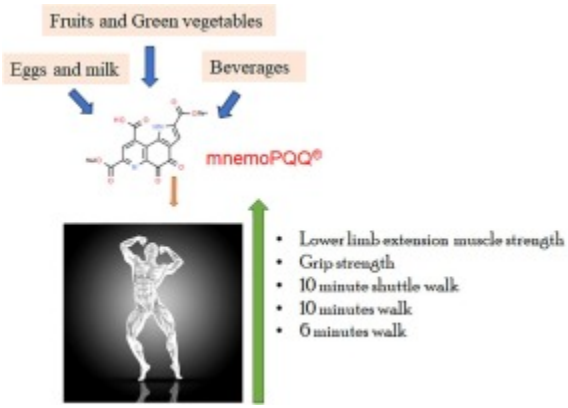
- Evaluated the effects of PQQ disodium salt (mnemoPQQ®) intake on improving muscle strength and physical function in human volunteers.

- A randomized, double-blind, placebo-controlled parallel-group comparative study was conducted in 64 healthy Japanese adult males and female subjects (age = 20- <75 Y) who consumed PQQ disodium salt regularly over a period of 12 consecutive weeks.
- Assessed the efficacy and safety on muscle strength and physical function (motor function) by measuring and evaluating the lower limb extension muscle strength as a primary endpoint; grip strength, the 10-meter shuttle walking (ISWT), the 6-minutes walking (6MWT), and the 10-meter walking test as secondary endpoints; and the Five Times Sit-to-Stand Test (FTSST) and the Timed up and go test (TUG) as exploratory endpoints.
- Adverse event monitoring was strictly enforced.

Abstract

A randomized, double-blind, placebo-controlled study was conducted in 64 healthy Japanese male and female adults over a period of 12 weeks to demonstrate the safety and efficacy of pyrroloquinoline quinone (PQQ) disodium salt (mnemoPQQ®; 21.5 mg/day as PQQ disodium salt) for improving muscle strength and physical function. The subjects were randomly assigned to receive either mnemoPQQ® or placebo. The efficacy on muscle strength and physical function was investigated using lower limb extension muscle strength as the primary outcome (primary endpoint) and grip strength, 10-meter shuttle walking, 6-minutes walking, and 10-meter walking tests as secondary outcomes (secondary endpoints). A total of 62 subjects [placebo=31 (age=54.2±1.2 Y); mnemoPQQ® = 31 (age=54.5±1.0 Y)] completed the study. Significant improvements were observed in lower limb extension muscle strength and grip strength in the mnemoPQQ® group ($p<0.01$). The physical function results of the 10-meter shuttle walking, 6-minutes walking, and 10-meter walking tests were also significantly improved in the mnemoPQQ® group ($p<0.01$). No adverse events were observed. Overall, the present study demonstrates that mnemoPQQ® supplementation improves muscle strength and physical function (motor function) in healthy Japanese male and female volunteers.

Graphical abstract



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Keywords

Pyrroloquinoline quinone disodium salt; Muscle strength; Leg extension muscle strength; Grip strength; Physical function; Motor function; Walking ability

1. Introduction

The aging population is rapidly increasing worldwide, according to the “World Population Prospects 2019” published by the United Nations (United Nations, 2019). The world’s total population reached 7.7 billion in 2019, which was an increase of 1 billion since 2007 and 2 billion since 1994, and it is expected to reach 8.5 billion in 2030 and 9.7 billion in 2050. Furthermore, the proportion of people aged 65 years and over in the population (population aging rate) reached 9.1% in 2019, increasing from 5.1% in 1950. The aging population rate is expected to rise to approximately 12% in 2030 and 16% in 2050. Hence, there is an increasing importance on maintaining the physical function (motor function) of middle-aged and older individuals through nutrition and exercise from the perspective of extending healthy life expectancy and preventing nursing care.

Many middle-aged and older individuals have reduced muscle strength and physical

function compared to that of young individuals (Evans, 1995, Hirasawa et al., 2004). Muscle strength declines with aging, and its progression may interfere with daily life, such as decreased walking speed and increased difficulty bathing or changing clothes. Furthermore, it increases difficulty in balancing the body and increasing the risk of falls and fractures. One of the causes of age-related muscle weakening is a decrease in daily physical exercise, which results in thinner muscle fibers. However, it has been demonstrated that the rate of decline in muscle strength and physical function tend to vary among individuals, depending on their daily nutritional status and degree of daily activities. Therefore, age-related decline in muscle strength and muscle mass (sarcopenia) have become important risk factors for physical dysfunction in middle-aged and older individuals. These aging-induced dysfunctions are strongly associated with nutritional deficiencies, muscle weakness and frailty. Thus, healthy nutritional status, and regular exercise are instrumental for preventing falls and hospitalization.

Improvement in muscle strength is crucial in leading an independent daily life; this is necessary not only for middle-aged and older individuals but also for young individuals to reduce the possibility of developing sarcopenia and frailty (Katayama & Yamasaki, 2017). Thus, while having well-balanced dietary habits and moderate daily physical exercise are essential, it is also vital to consume proper nutrients or functional ingredients that the individual is deficient of. Worldwide, numerous studies have been conducted on the improvement of muscle strength and physical function using nutraceuticals and functional ingredients. Numerous studies have previously demonstrated the efficacy of functional food ingredients in improving muscle strength and physical function (motor function) including pyrroloquinoline quinone (PQQ) disodium salt (Shiojima et al., 2022), undenatured type II collagen (Shiojima et al., 2023), black ginger-derived polymethoxyflavone (Yamana et al., 2019), 3-hydroxy-3-methyl butyrate (HMB) (Berton et al., 2015), HMB calcium (Stahn, Maggioni, Gunga, & Terblanche, 2020), and creatine monohydrate (Pearson, Russel, & Harris, 1999). All these functional food ingredients have been consumed worldwide for many years; these are considered highly safe based on dietary experience. It is important to indicate that PQQ is available in a wide variety of foods that we consume daily; PQQ is available in many vegetables including cabbage, carrot, and tomato, fruits including apple, banana, and kiwi, beverages including green tea, oolong tea, and whiskey, eggs, and milk (Kumazawa et al., 1995, Kumazawa et al., 1993). Particularly, PQQ is abundant in breast milk, which is essential for the growth of infants (Mitchell et al., 1999, Kumazawa et al., 1992). Thus, PQQ disodium salt has attracted growing interest as a functional food ingredient in recent years, and many studies have been conducted on various physiological and

pharmacological aspects of PQQ disodium salt (Akagawa et al, 2016b).

PQQ has been detected in various human organs and breast milk (Kumazawa et al., 1992). When orally consumed, PQQ concentration in the blood peaks approximately two hours after intake (Harris et al., 2013) and absorbed PQQ reaches various organs and tissues, and the majority is then metabolized and excreted approximately 24h after intake (Smidt, Unkefer, Houck, & Rucker, 1991). Numerous studies on the beneficial effect of PQQ have been conducted by various researchers worldwide (Akagawa et al., 2016, Misra et al., 2012). PQQ, which serves as a coenzyme with redox properties along with high antioxidant potency, boosts muscle strength and physical function preventing the decline in the skeletal muscle strength and regeneration of skeletal muscle via activation of mitochondria, as well as suppression of muscle protein degradation and muscle mass decrease *via* the activation of PGC-1α (Kuo et al., 2015, Xu et al., 2018). However, fewer human clinical studies evaluated the benefits of PQQ in humans.

The present study was designed to evaluate the effects of PQQ disodium salt (mnemoPQQ®) intake on improving muscle strength and physical function in human volunteers for the first time. In this randomized, double-blind, placebo-controlled parallel-group comparative study, 64 healthy Japanese adult males and females (age = 20 - < 75 Y) consumed PQQ disodium salt regularly over a period of 12 consecutive weeks. We examined its efficacy and safety on muscle strength and physical function (motor function) by measuring and evaluating the lower limb extension muscle strength as a primary endpoint (primary outcome); grip strength, the 10-meter shuttle walking test (incremental shuttle walking test; ISWT), the 6-minutes walking test (6MWT), and the 10-meter walking test as secondary endpoints (secondary outcomes); and the Five Times Sit-to-Stand Test (FTSST) and the Timed up and go test (TUG) as exploratory endpoints (exploratory outcomes).

2. Materials and methods

2.1. Clinical study approval

A randomized, double-blind, placebo-controlled study was conducted to investigate the efficacy and safety of PQQ disodium salt on muscle strength and physical function in healthy Japanese subjects (age=20 - < 75 Y). The clinical study protocol (protocol number: 2202R) was reviewed and approved by the institutional review board (IRB No. 18000064) of Yamazaki Otolaryngology Clinic Medical Corporation (Hokkaido, Japan)

following the ethical standards set out in the Declaration of Helsinki and the guidelines for epidemiological and clinical studies issued by the Ministry of Health, Labor and Welfare and the Ministry of Education, Culture, Sports, Science, and Technology (approval date: July 1, 2022).

This study was preregistered in the University Hospital Medical Information Network (UMIN) clinical trials registry system (https://www.umin.ac.jp ↗), a public database (UMIN ID: 000048641). Duly signed informed consent was obtained from all participants. The trial was conducted by the contract research organization Kyowa Trial Co., Ltd. (Sapporo, Hokkaido, Japan) at GOZEN Medical Corporation Kita 7-jo Goda Orthopedics (Sapporo, Hokkaido, Japan) from July to December 2022.

The broad-spectrum safety of mnemoPQQ® (21.5 mg/day as PQQ disodium salt) was ascertained by a battery of toxicological studies (Shiojima et al., 2022), clinical investigation (Shiojima et al., 2022), and other earlier studies (Itoh et al., 2016, Harris et al., 2013).

2.2. Participant recruitment and intervention strategy

The study volunteers were recruited through 3H Medi Solution Inc. (Tokyo, Japan) through rigorous screening as per the inclusion and exclusion criteria (Table 1). All recruited subjects duly reviewed, understood, and signed the IRB-approved consent forms.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria:
1) Japanese male and female subjects (age = 20 - < 75 Y at the time of filing the written consent)
2) Healthy individuals who were not currently undergoing treatment for any serious disease
3) Those with a score of 13 or higher in the Activities of Daily Living (ADL) test questionnaire (conducted in advance)
4) Those who were able to visit the designated facility on the scheduled visit date

5) Those who had provided written consent after fully understanding the purpose and content of this study

Exclusion criteria:

1) Those meeting the sarcopenia criteria (*) based on the results of grip strength measurement (higher value was used after the measurements in both hands)

   *Sarcopenia criteria: those whose grip strength was less than 28 kg for males and less than 18 kg for females, with a walking speed of less than 1.0 m/sec (Chen, Woo, & Arai, 2020)

2) Those who exercise regularly at least two days a week

3) Those who had visited the hospital for pain in joints, such as knees and hips, in the last three months

4) Those with a history of major surgery in the gastrointestinal tract, such as gastric resection, gastrointestinal suture, and intestinal resection

5) Those who had difficulty participating in the study due to hepatic/renal/cardiac disease, breathing disorder, endocrine disorder, metabolic disorder, neurological disorder, consciousness disorder, diabetes mellitus (based on the standards set by the Japan Diabetes Society), or other diseases

6) Those with a history of circulatory system disease

7) Those who regularly consume amino acid- or protein-fortified foods or beverages to maintain physical strength, improve motor function, or were dieting

8) Those with allergies associated with the test foods

9) Those who had hepatitis currently or in the past, circulatory system disease, or severe anemia

10) Those who regularly took medicines and/or health foods/supplements that could affect the outcomes of this study (including foods for specified health uses (FOSHU), foods with function claims (FFC), and foods with nutrient function claims (FNFC)) (however, this did not apply to those who could discontinue the intake of such products at the time of providing consent)

11) Those who had experienced feeling unwell or deterioration of physical condition due to blood collection in the past

12) Those who had donated 200 mL or more blood from the earlier month scheduled for the study or have plan to do so during the study period

13) Those who were currently participating in another clinical study or participated in another clinical study within the last four months

14) Excessive alcohol drinkers and heavy smokers

15) Those with highly irregular dietary habits

16) Those working on late-night or irregular shift

17) Those who did not agree with the purpose of this study when it was explained to them earlier

18) Those who thought that the study doctor assigned is not qualified enough to evaluate for this study results

The screening assessment examined age, medical history, overall health conditions, medication status, smoking and drinking habits, daily activity, lifestyle habits, food allergies, and health foods/supplements intake. It also included physical examination [height, weight, body mass index (BMI), body temperature, blood pressure, and pulse], blood test, and urinalysis, ensuring the selection of healthy participants without disease.

Fig. 1 shows the flow diagram of this study starting from subject enrollment to analysis. This study was performed on 130 volunteers who had provided consent to participate in the study, and based on the inclusion and exclusion criteria, a total of 64 subjects who met all criteria were selected, randomized, and assigned into two groups, (i) placebo- and (ii) mnemoPQQ® groups, and 32 subjects were assigned in each group. The mnemoPQQ® group consumed capsule containing PQQ disodium salt (21.5 mg/capsule/day).

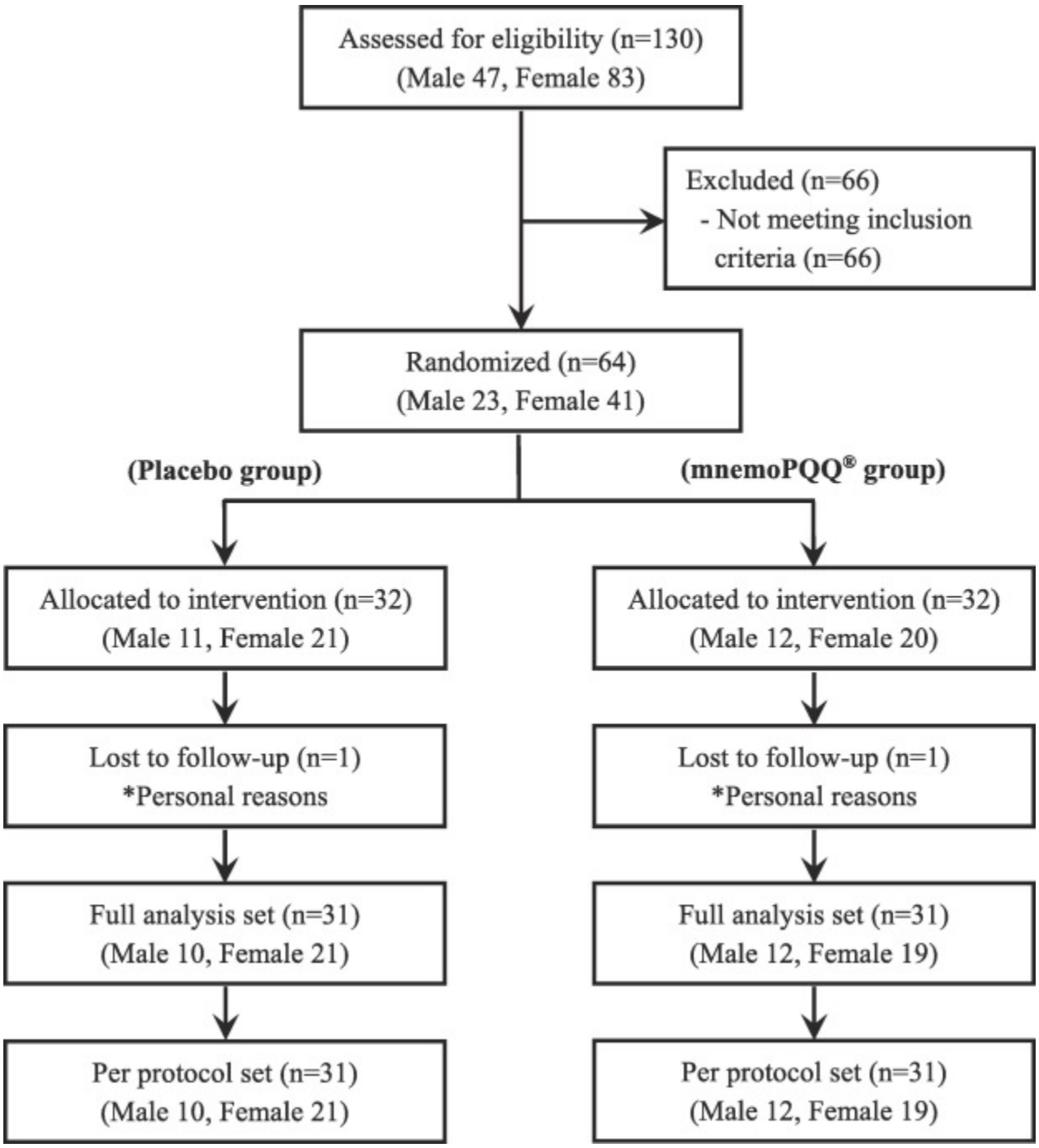

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Fig. 1. Schematic flow diagram of the clinical study.

2.3. Clinical study design

This randomized, double-blind, placebo-controlled study evaluated the efficacy of PQQ disodium salt or placebo. The study period consisted of 4weeks of pre-treatment period (observation) and 12weeks of treatment period, for a total of 16weeks. The sample size of

this study was set based on the effect on lower limb extension muscle strength, which was the study's primary endpoint (primary outcome). No previous study has reported the effect of PQQ intake on lower limb extension muscle strength, and this is the first detailed clinical investigation. We set the sample size based on the data on lower limb extension muscle strength of the general Japanese population as well as in-house data (Katayama and Yamasaki, 2017, Hirasawa et al., 2004).

The average lower limb extension muscle strength of participants before the start of this study was assumed to be approximately 0.75 kgf/kg, and the amount of change in lower limb extension muscle strength due to the intake of the intervention supplement was assumed to be 0.075 kgf/kg, with a standard deviation of 0.1 kgf/kg. Based on these values, the number of individuals required for examination at the significance level (α) of 5% (two-sided) and the power (1 - β) of 80% was calculated as 28 per group. However, in this study, the target number of individuals in one group at the start was 32, considering those who would discontinue or drop out. The participants were randomly allocated to one of the two groups by the allocation manager of a third-party institution not involved in this study (Sapporo University of Health Sciences: Hokkaido, Japan). The allocation groups were referred to as "α" and "β" at this time, and the allocation manager randomly assigned one of the placebo or treatment capsules to the allocation groups.

Here, a random number was assigned to each placebo or treatment group, and the placebo or treatment capsules were assigned to the allocation groups α and β in descending order of the random number. In addition, interviews by doctors, physical examination, blood pressure measurement, blood test, and urinalysis were carried out during the observation period before the start of the placebo or treatment capsule intake (four weeks before the treatment period) and every six weeks during the intake period (weeks 0, 6, and 12).

Muscle strength and function as the primary endpoint were determined by lower limb extension muscle strength during the intake period (weeks 0, 6, and 12). Measurements of grip strength, the ISWT, 6-minutes WT, and 10-meter walking test, which were the secondary endpoints, as well as the FTSST and TUG as the exploratory endpoints, were performed during the intake period (weeks 0, 6, and 12). Adverse events monitoring was enforced.

Also, the subjects were instructed to maintain a regular lifestyle during the study period, maintain the same normal lifestyle habits as maintained before the start of the study to the possible extent, and refrain from overeating, overdrinking, and strenuous physical

exercise without making any major changes to living conditions, such as dietary and exercise habits.

2.4. Dietary pyrroloquinoline quinone disodium salt (PQQ disodium salt)

PQQ disodium salt powder used in this study was mnemoPQQ® (Ryusendo Co., Ltd., Tokyo, Japan), produced by microbial fermentation, fractionated, and purified. Its purity was quantified by high-performance liquid chromatography (HPLC) using a reference standard (≥ 99.0%) from Fujifilm Wako Pure Chemical Corporation (Osaka, Japan). PQQ disodium salt was mixed with maltodextrin and filled into dark brown capsules (hydroxypropyl methylcellulose; HPMC, caramel dye). Each capsule, filled with 21.5 mg of PQQ disodium salt, was individually packaged in an aluminum packet as one dose/day. For the placebo, dark brown capsules were filled with crystalline cellulose (HPMC, caramel dye), and their weight and appearance were matched to affirm that both the placebo and treatment capsules look identical and totally indistinguishable. Also, each placebo capsule was individually packaged in an aluminum packet as one dose/day. Both the intervention and placebo capsules were packaged at a Good Manufacturing Practice (GMP)-certified manufacturer and supplied by Ryusendo Co., Ltd. Both placebo and treatment capsules were instructed to consume one capsule per day with water or lukewarm water within 30 min after breakfast.

2.5. Quantification of PQQ disodium salt

Purity of mnemoPQQ® and the PQQ disodium salt content were evaluated using HPLC (Prominence® HPLC system: Shimadzu Corporation, Kyoto, Japan) using a reference standard (≥99.0%) from Fujifilm Wako Pure Chemical Corporation (Osaka, Japan). HPLC measurement was performed using an ODS column (InertSustain® C18, 150 mm × 4.6 mm, 5 μm: GL Sciences Inc., Tokyo, Japan) equipped with a UV–visible absorption detector (SPD-20AV: Shimadzu Corporation, Kyoto, Japan), set at 259 nm, column oven temperature at 40 °C, and flow rate at 1.0 mL/min. The mobile phase was acetic acid : ammonium acetate solution [0.1 mol/L acetic acid: 0.1 mol/L ammonium acetate = 30 : 70 (v/v), pH 5.1]. In addition, the PQQ disodium salt content per capsule was calculated from the average weight of one capsule. The measurements of PQQ disodium salt were conducted by two institutions: the Faculty of Pharma-Science at Teikyo University (Tokyo, Japan), and the Japan Inspection Association of Food and Food Industry Environment (Tokyo, Japan).

2.6. Measurements of lower limb extension muscle strength and grip strength

The efficacy of PQQ was evaluated through the assessment of muscle strength and function by lower limb extension muscle strength as the primary endpoint. Lower limb extension muscle strength was assessed using a Leg Muscle Dynamometer (Locomo Scan-II®; ALCARE Co., Ltd., Tokyo, Japan) (Kawada et al., 2023, Narumi et al., 2017). Muscle strength and function by grip strength were determined using a digital grip dynamometer (Grip-D; Takei Scientific Instruments Co., Ltd., Niigata, Japan).

2.7. Measurements of physical function

The following evaluations were performed to evaluate physical function (motor function). In the 10-meter shuttle walk test (incremental shuttle walking test; ISWT), the participants continued walking according to the instructed rhythm between the marks placed 10-meter apart on non-slippery flat ground (i.e., continued walking while gradually increasing walking speed). The assessment was completed when the participant failed to keep up with speed. Motor function was evaluated based on the number of shuttles (times) performed between the marks (Yamada, 2020). In the 6-minutes walking test (6MWT), turnaround points were set up at both ends of a 30m straight line on flat ground, and the participant walked back and forth between the points as fast and long as possible for 6-minutes (Satake, Shiotani, Takahashi, & Sugawara, 2019). The exercise tolerability was evaluated based on the walking distance (meter). In the 10-meter walking test, the number of steps and required time (seconds) at normal and fastest walking speeds were measured (Iida & Aoki, 2017). In the stand-up test, a general chair with a seat height of 40cm was used and starting from a sitting position with arms folded in front of the chest, the time required to complete the stand-up motion five times was measured (Makizako et al., 2008). In the Timed up and go test (TUG), a chair, like the one used in the stand-up test, and a 3m walkway were prepared. First, the subjects sat on the chair and placed their hands on their thighs. Then, subjects stood up at the signal to start, walked to a mark 3m ahead, changed direction, walked back, and sat down, and the time required was measured (Shimada et al., 2006). The test was carried out at a normal walking speed.

2.8. Measurements of physical and circulatory parameters

The physical and circulatory parameters were assessed as follows: height: measured using a stadiometer; body weight and BMI: measured using a body composition analyzer

(DC-430; TANITA corporation, Tokyo, Japan); body temperature; measured using an electronic thermometer (ET-C205; Terumo Corporation, Tokyo, Japan); and blood pressure and pulse: measured using an automatic sphygmomanometer (digital sphygmomanometer HEM-1020; OMRON Corporation, Kyoto, Japan). BMI was computed from height and body weight.

2.9. Blood biochemistry and hematological tests

Blood samples were collected during 12 h-fasting in the early morning four weeks before the intake of the study capsules, at the initiation of the treatment period (day 0), week 6, and 12 of treatment. Parameters measured were: total protein (TP), albumin (Alb), AST (SGOT), ALT (SGPT), γ-GT, ALP, total bilirubin (T-Bil), LDH, CK (CPK), creatinine, uric acid (UA), urea nitrogen (UN), total cholesterol (T-CHO), HDL-cholesterol (HLD-CHO), LDL-cholesterol (LDL-CHO), triglycerides (TG), fasting blood glucose (GLU), Na, K, Cl, Ca, Mg, Fe, IP, and amylase (AMY). The hematological test items measured were white blood cell count (WBC), red blood cell count (RBC), hemoglobin content, hematocrit level (Ht), platelet count (PLT), MCV, MCH, and MCHC. Blood samples were collected at GOZEN Medical Corporation Kita 7-jo Goda Orthopedics (Sapporo, Hokkaido, Japan). The measurements were performed using an automatic analyzer (BioMajesty™ JCA-BM8040: JEOL Ltd., Tokyo, Japan) and a multi-item automatic blood cell counter (XN-9000: Sysmex Corporation, Kobe, Hyogo, Japan) at SRL, Inc./SRL Hokkaido Laboratory (Sapporo, Hokkaido, Japan).

2.10. Urinalysis

Urine samples were collected four weeks before the intake of the study capsules, at the initiation of treatment period (day 0), at the completion of week 6 and 12 of treatment. A general urinalysis was performed for specific gravity (USG), pH, protein (PRO: qualitative), glucose (GLU: qualitative), urobilinogen (URO: qualitative), occult blood reaction (BLD: qualitative), bilirubin (BIL: qualitative), and ketone body (KET: qualitative). In addition, the participants' urine samples were collected at GOZEN Medical Corporation Kita 7-jo Goda Orthopedics (Sapporo, Hokkaido, Japan). The measurements were performed using a fully automatic urine analyzer (US-3500: Eiken Chemical Co., Ltd., Tokyo, Japan) at SRL, Inc./SRL Hokkaido Laboratory (Sapporo, Hokkaido, Japan).

2.11. Daily diary of diet and physical activity

The participants were encouraged not to change their regular dietary, exercise, and

lifestyle habits. Consumption of regular diet, physical activity, exercise routine, and intake of placebo/treatment capsules were recorded daily in the participant diary. Furthermore, regular activities were recorded by always wearing an activity meter (Lifecorder GS; Suzuken Co., Ltd., Nagoya, Aichi, Japan) during the study period. Also, to evaluate dietary habits, a nutrition survey was conducted by a trained dietician using a dietary record sheet filled in by each participant for three days before each visit and the participants overall health status were recorded on every visit to the study center. In addition, adverse events, if any, were recorded.

2.12. Statistical analysis

Data are expressed as mean±standard error (SE). For inter-group comparisons, a significant difference was determined using an unpaired *t*-test on the values at each measurement point from week 0 (baseline) to 12 of the treatment periods. For intra-group comparisons, a significant difference was determined using a paired *t*-test on each measured value relative to the value at week 0. For measurement of functionality, observed values and the amount of change (Δ value) from the baseline were expressed as mean±SE. For inter-group comparisons, a significant difference was determined using an unpaired *t*-test from week 0 to 12 of treatment. Similarly, a significant difference was determined using an unpaired *t*-test on weeks 6 and 12 of treatment. For intra-group comparisons, a significant difference was determined using a paired *t*-test on each measured value relative to the value at week 0. In addition, the measured values of the blood biochemistry test and general blood test before and after treatment (weeks 0, 6, and 12) were expressed as mean±SE, and a significant difference was determined similarly as above. The grade and the number of participants in each grade were determined for quantitative analysis of urine samples. A significant difference in inter- and intra-group comparisons was determined using an unpaired *t*-test and a paired *t*-test, respectively.

Regarding quantitative urinalysis values, the Wilcoxon rank-sum test was performed for inter-group comparisons, and the Wilcoxon signed-rank test was performed for intra-group comparisons. Fisher's exact test was performed for the comparisons of adverse events. SAS 9.4 software (SAS Institute Inc., NC, USA) was used for statistical analysis. The level of statistical significance was two-sided and set at 5%, 1%, and 0.1%, and a significant difference was expressed as less than 5% ($p<0.05$), less than 1% ($p<0.01$), and less than 0.1% ($p<0.001$). In addition, no correction for multiplicity was performed for the paired *t*-test.

Regarding the fixation of statistical data and disclosure of allocation, the participants, and data to be analyzed were fixed by the principal investigator based on the exclusion criteria for statistical analysis after completing the study. Subsequently, the allocation manager opened the sealed envelope containing the allocation table and information was disclosed based on the contract of the allocation disclosure report.

3. Results

Based on the rigorous inclusion and exclusion criteria, 64 participants were enrolled, while 2 participants dropped out due to personal reasons. A total of 62 subjects (31 each in the placebo and mnemoPQQ® group) completed the study. The 62 enrolled subjects who started taking placebo or mnemoPQQ® were assigned to Full Analysis Set (FAS).

Table 2 shows the baseline characteristics of the participants, including age (Y), height (cm), body weight (kg), BMI (kg/m^2), body temperature (°C), systolic and diastolic blood pressures (mmHg), and pulse rate (beats/min). For safety analysis, the participants were assigned to the FAS (31 subjects each in the placebo and mnemoPQQ® group), and no serious adverse events were reported.

Table 2. Baseline characteristics of the subjects.

Parameter	Placebo group	mnemoPQQ® group
n (Male/Female)	31 (10/21)	31 (12/19)
Age (years)	54.2 ± 1.2	54.5 ± 1.0
Height (cm)	162.3 ± 7.7	162.8 ± 7.7
Body weight (kg)	55.7 ± 1.4	56.1 ± 1.4
Body mass index (kg/m^2)	21.1 ± 0.3	21.2 ± 0.4
Body temperature (℃)	36.4 ± 0.1	36.3 ± 0.1
Systolic blood pressure (mmHg)	118.5 ± 2.4	121.4 ± 3.0
Diastolic blood pressure (mmHg)	79.5 ± 1.6	83.5 ± 2.3
Pulse (beats/min)	71.3 ± 1.6	72.7 ± 1.6

Values represent the mean±SE.

No significant differences were observed in any parameters between the two groups.

The intake of placebo and mnemoPQQ® was 99.5±1.5% in the placebo and 99.9±0.5% in the mnemoPQQ® group, respectively, with no significant difference. The dietary records and the amount of activity (number of steps) analyzed every six weeks during the study period showed no intra- or inter-group differences in the amount of nutritional intake (proteins, lipids, carbohydrates, and sodium chloride equivalents), including the amount of energy intake.

3.1. PQQ disodium salt content in the mnemoPQQ®

The purity of PQQ disodium salt, the raw material of mnemoPQQ® used to prepare the treatment capsules, was 99.5%. The PQQ disodium salt content in the investigational product (PQQ-containing capsules) was 21.5±0.3 mg/capsule (mnemoPQQ® group), while PQQ disodium salt was not detected in the placebo capsules (placebo group).

3.2. Measurements of lower limb extension muscle strength

Table 3 demonstrates the lower limb extension muscle strength as the primary endpoint

(primary outcome). There was no significant difference in the initial value of the endpoint between the mnemoPQQ® and placebo groups. The mnemoPQQ® group had a significant higher measured value of lower limb extension muscle strength (kgf) at week 12 than that before treatment ($p<0.001$). Moreover, the measured value of lower limb extension muscle strength (kgf) at week 12, there was a significant difference between the two groups ($p<0.05$) (placebo group: 44.59±2.33 vs mnemoPQQ® group: 48.84±2.91). At week 12, the amount of change (change value Δ) in lower limb extension muscle strength was significantly different from that baseline value (before treatment) intake ($p<0.01$) (placebo group: 0.78±1.03 vs mnemoPQQ® group: 4.99±0.76). Furthermore, the mnemoPQQ® group had a significantly higher measured value of lower limb extension muscle strength per weight (kgf/kg) at the completion of week 12 as compared to the baseline value (before treatment) ($p<0.001$). Also, the measured value of lower limb extension muscle strength per weight (kgf/kg) at week 12 was significantly different between the two groups ($p<0.05$) (placebo group: 0.80±0.04 vs mnemoPQQ® group: 0.86±0.04). At week 12, the amount of its change from that before treatment (baseline) was significantly different between two groups ($p<0.01$) (placebo group: 0.02±0.02 vs mnemoPQQ® group: 0.09±0.02), while there was no significant intra-group difference in the placebo group.

Table 3. Results of lower limb extension muscle strength (primary outcome).

Parameter	Group		0week (Before)	6weeks	12weeks
Lower limb extension muscle strength (kgf)	Placebo	Measured value	43.81 ± 2.62	44.97 ± 2.49	44.59 ± 2.33
		Change value Δ		1.16 ± 0.85	0.78 ± 1.03
	mnemoPQQ®	Measured value	43.85 ± 2.90	44.81 ± 2.81	48.84 ± 2.91 ***. #
		Change value Δ		0.96 ± 1.05	4.99 ± 0.76 ##
Lower limb extension muscle strength per	Placebo	Measured value	0.78 ± 0.04	0.80 ± 0.04	0.80 ± 0.04

Parameter	Group		0week (Before)	6weeks	12weeks
body weight (kgf/kg)		Change value Δ		0.02 ± 0.02	0.02 ± 0.02
	mnemoPQQ®	Measured value	0.77 ± 0.04	0.79 ± 0.04	0.86 ± 0.04 ***. #
		Change value Δ		0.02 ± 0.02	0.09 ± 0.02 ##

Values represent the mean±SE. Placebo group (n=31), mnemoPQQ® group (n=31).

*, ***; $p<0.05$, 0.001 vs. before (0w).

#, ##; $p<0.05$, 0.01 vs. placebo group.

No significant differences were observed in any parameters between the two groups at the before ingestion (0week).

3.3. Measurements of grip strength and various walking tests

Table 4 shows the results of grip strength and various walking tests, which were the secondary endpoints. There was no significant difference between the initial values in the mnemoPQQ® and placebo groups. The mnemoPQQ® group had a significantly higher measured value of grip strength at week 12 of treatment as compared to baseline ($p<0.001$). Also, there was a significant difference in the measured value of grip strength at week 12 between the two groups ($p<0.05$). At week 12, the two groups showed a significant difference in the amount of change in grip strength as compared to the baseline ($p<0.01$). Furthermore, the mnemoPQQ® group exhibited a significant improvement in the measured values of the ISWT, 6MWT, and 10-meter walking test (normal, fastest), which evaluated physical function (motor function), at week 12 of treatment as compared to the baseline ($p<0.001$, $p<0.01$, or $p<0.05$). There was also a significant difference in the measured values of ISWT, 6MWT, and the 10-meter walking test (normal speed, seconds) at week 12 of treatment between the placebo and mnemoPQQ® groups ($p<0.05$). At week 12, the two groups demonstrated a significant difference in the amount of change in each endpoint as compared to the baseline ($p<0.001$ or $p<0.01$).

Table 4. Results of grip strength and various walking tests (secondary outcomes).

Parameter	Group		0week (Before)	6weeks	12weeks
Grip strength (kg)	Placebo	Measured value	28.9 ± 1.8	29.0 ± 1.8	28.6 ± 1.7
		Change value Δ		0.2 ± 0.5	−0.3 ± 0.5
	mnemoPQQ®	Measured value	28.5 ± 1.6	29.1 ± 1.6 *	29.7 ± 1.2 ***. #
		Change value Δ		0.6 ± 0.2	1.2 ± 0.3 ##
10-meter shuttle walking test (times)	Placebo	Measured value	46.52 ± 1.87	47.90 ± 1.80 *	47.58 ± 1.88
		Change value Δ		1.39 ± 0.56	1.07 ± 0.87
	mnemoPQQ®	Measured value	44.77 ± 1.72	47.19 ± 1.46 *	51.16 ± 1.82 ***. #
		Change value Δ		2.42 ± 0.90	6.39 ± 1.11 ###
6-minute walking test (m)	Placebo	Measured value	477.42 ± 9.85	480.48 ± 10.12	469.19 ± 9.92
		Change value Δ		3.06 ± 7.34	−8.23 ± 11.05
	mnemoPQQ®	Measured value	470.81 ± 8.80	483.06 ± 8.57 ***	487.34 ± 12.74 **. #
		Change value Δ		12.26 ± 5.36 #	16.53 ± 9.23 ##

Parameter	Group		0week (Before)	6weeks	12weeks
10-meter walking test -normal speed (sec)	Placebo	Measured value	6.63 ± 0.15	6.54 ± 0.12	6.75 ± 0.15
		Change value Δ		−0.09 ± 0.09	0.13 ± 0.10
	mnemoPQQ®	Measured value	6.87 ± 0.14	6.57 ± 0.14 ***	6.37 ± 0.12 ***. #
		Change value Δ		−0.30 ± 0.05 #	−0.50 ± 0.08 ###
10-meter walking test -normal speed (steps)	Placebo	Measured value	13.81 ± 0.28	13.73 ± 0.22	13.98 ± 0.27
		Change value Δ		−0.08 ± 0.11	0.18 ± 0.11
	mnemoPQQ®	Measured value	14.16 ± 0.24	13.74 ± 0.24 ***	13.45 ± 0.21 ***
		Change value Δ		−0.42 ± 0.11 #	−0.71 ± 0.10 ###
10-meter walking test -fastest speed (sec)	Placebo	Measured value	5.03 ± 0.12	5.10 ± 0.11	5.24 ± 0.13 *
		Change value Δ		0.07 ± 0.06	0.21 ± 0.08
	mnemoPQQ®	Measured value	5.25 ± 0.13	5.05 ± 0.12 ***	4.94 ± 0.12 ***
		Change value Δ		−0.21 ± 0.03 ###	−0.31 ± 0.04 ###

Parameter	Group		0week (Before)	6weeks	12weeks
10-meter walking test -fastest speed (steps)	Placebo	Measured value	12.60 ± 0.24	12.53 ± 0.25	12.73 ± 0.26
		Change value Δ		−0.06 ± 0.14	0.13 ± 0.10
	mnemoPQQ®	Measured value	12.85 ± 0.26	12.68 ± 0.26	12.55 ± 0.24 *
		Change value Δ		−0.18 ± 0.13	−0.31 ± 0.12 ##

Values represent the mean±SE. Placebo group (n=31), mnemoPQQ® group (n=31).

*, **, ***; $p<0.05$, 0.01, 0.001 vs. before (0w).

#, ##, ###; $p<0.05$, 0.01, 0.001 vs. placebo group.

No significant differences were observed in any parameters between the two groups at the before ingestion (0week).

3.4. Measurements of the FTSST and TUG

Table 5 shows the results of the FTSST and TUG, which were the exploratory endpoints. There was no significant difference in the initial values between the mnemoPQQ® and placebo groups. The mnemoPQQ® group had significantly lower measured values of FTSST and TUG (normal, fastest) at week 6 ($p<0.01$ or $p<0.05$) and week 12 ($p<0.001$) as compared to the baseline. Also, there was a significant difference in the measured value of TUG (normal) at week 12 between the placebo and mnemoPQQ® groups ($p<0.05$). At week 12, the placebo and mnemoPQQ® groups showed a significant difference in the amount of change in each endpoint as compared to the baseline ($p<0.001$ or $p<0.01$).

Table 5. Results of five times sit to stand test and timed up and go test (exploratory outcomes).

Parameter	Group		0week (Before)	6weeks	12weeks

Parameter	Group		0week (Before)	6weeks	12weeks
Five times sit to stand test (sec)	Placebo	Measured value	8.08 ± 0.29	7.35 ± 0.30 *	7.27 ± 0.28 ***
		Change value Δ		−0.33 ± 0.20	−0.41 ± 0.13
	mnemoPQQ®	Measured value	8.28 ± 0.31	7.85 ± 0.30 ***	7.08 ± 0.27 ***
		Change value Δ		−0.42 ± 0.14	−1.20 ± 0.15 ###
Timed up and go test -normal speed (sec)	Placebo	Measured value	7.57 ± 0.16	7.43 ± 0.17	7.72 ± 0.21
		Change value Δ		−0.14 ± 0.10	0.15 ± 0.13
	mnemoPQQ®	Measured value	7.70 ± 0.16	7.32 ± 0.15 ***	7.12 ± 0.15 ***. #
		Change value Δ		−0.38 ± 0.09	−0.58 ± 0.11 ###
Timed up and go test -fastest speed (sec)	Placebo	Measured value	5.84 ± 0.13	5.56 ± 0.12 ***	5.78 ± 0.15
		Change value Δ		−0.20 ± 0.07	−0.06 ± 0.05
	mnemoPQQ®	Measured value	5.88 ± 0.13	5.69 ± 0.13 **	5.59 ± 0.12 ***
		Change value Δ		−0.20 ± 0.07	−0.29 ± 0.05 ##

Values represent the mean±SE. Placebo group (n=31), mnemoPQQ® group (n=31).

*, **, ***; $p<0.05$, 0.01, 0.001 vs. before (0w).

#, ##, ###; $p<0.05$, 0.01, 0.001 vs. placebo group.

No significant differences were observed in any parameters between the two groups at the before ingestion (0week).

3.5. Safety measurements

Table 6, Table 7 show the results of blood biochemistry tests, hematological tests, and urinalysis. The two groups showed no significant difference in these parameters at the initiation and completion of the treatment. In addition, although certain values exhibited significant fluctuations, all values remained within the reference range and have no clinical issues.

Table 6. Results of blood biochemical parameter, hematological parameter, urinary USG and pH.

Parameter	Unit	Reference range	Group	0week (Before)	6weeks	12weeks
TP	(g/dL)	6.7–8.3	Placebo	7.22 ± 0.06	7.18 ± 0.04	7.33 ± 0.06
			mnemoPQQ®	7.20 ± 0.05	7.24 ± 0.06	7.30 ± 0.06
Alb	(g/dL)	3.8–5.2	Placebo	4.33 ± 0.04	4.33 ± 0.04	4.46 ± 0.05 **
			mnemoPQQ®	4.32 ± 0.06	4.37 ± 0.07	4.34 ± 0.04
AST (SGOT)	(U/L)	8–38	Placebo	20.8 ± 0.9	20.1 ± 0.7	20.7 ± 0.7
			mnemoPQQ®	20.6 ± 0.8	21.7 ± 0.8 *	21.7 ± 0.7
ALT (SGPT)	(U/L)	4–44	Placebo	17.9 ± 1.2	19.0 ± 1.8	18.5 ± 1.3
			mnemoPQQ®	16.9 ± 1.2	18.9 ± 1.6 **	18.1 ± 1.2
γ-GT	(U/L)	M: ≦80 F: ≦30	Placebo	29.2 ± 3.2	29.3 ± 3.5	30.1 ± 3.4
			mnemoPQQ®	24.3 ± 3.3	25.8 ± 3.7 *	23.5 ± 2.7
ALP	(U/L)	38–113	Placebo	71.0 ± 3.7	71.6 ± 3.9	72.8 ± 4.1
			mnemoPQQ®	70.9 ± 4.2	73.3 ± 4.7 *	73.6 ± 4.5 *

Parameter	Unit	Reference range	Group	0week (Before)	6weeks	12weeks
T-Bil	(mg/dL)	0.2–1.1	Placebo	0.79 ± 0.08	0.73 ± 0.07	0.79 ± 0.08
			mnemoPQQ®	0.80 ± 0.06	0.81 ± 0.06	0.80 ± 0.06
LDH	(U/L)	120–245	Placebo	176.3 ± 4.2	166.3 ± 4.6 **	175.4 ± 4.4
			mnemoPQQ®	180.2 ± 4.8	173.5 ± 3.9 **	181.6 ± 5.3
CK (CPK)	(U/L)	M: 50–220 F: 40–170	Placebo	97.3 ± 11.0	102.2 ± 9.4	106.8 ± 9.0
			mnemoPQQ®	100.5 ± 10.4	98.4 ± 6.8	110.1 ± 14.7
Cr	(mg/dL)	M: 0.66–1.11 F: 0.50–0.86	Placebo	0.74 ± 0.02	0.75 ± 0.03	0.75 ± 0.02
			mnemoPQQ®	0.77 ± 0.03	0.77 ± 0.03	0.78 ± 0.03
UA	(mg/dL)	2.0–7.0	Placebo	4.8 ± 0.2	4.8 ± 0.2	4.7 ± 0.2
			mnemoPQQ®	5.0 ± 0.2	5.1 ± 0.2	4.9 ± 0.2
UN	(mg/dL)	8.0–22.0	Placebo	12.0 ± 0.5	12.0 ± 0.4	12.2 ± 0.3
			mnemoPQQ®	12.3 ± 0.5	12.1 ± 0.5	12.2 ± 0.5
T-CHO	(mg/dL)	130–220	Placebo	216.5 ± 5.1	220.8 ± 5.8	222.3 ± 6.4
			mnemoPQQ®	220.7 ± 6.1	225.5 ± 5.3	217.9 ± 6.6
HDL-CHO	(mg/dL)	M: 40–90 F: 40–100	Placebo	67.6 ± 2.1	71.9 ± 2.3 **	71.5 ± 2.4 **
			mnemoPQQ®	70.4 ± 2.8	74.1 ± 3.0 **	75.4 ± 3.2 **
LDL-CHO	(mg/dL)	70–139	Placebo	125.6 ± 4.7	127.3 ± 5.5	130.7 ± 6.2
			mnemoPQQ®	130.5 ± 4.8	132.3 ± 4.0	134.3 ± 4.7
TG	(mg/dL)	50–149	Placebo	116.4 ± 10.21	108.03 ± 11.09	110.48 ± 10.69
			mnemoPQQ®	99.1 ± 6.89	95.55 ± 6.76	96.19 ± 6.60
GLU	(mg/dL)	70–109	Placebo	87.4 ± 1.57	88.35 ± 1.58	90.03 ± 1.28
			mnemoPQQ®	86.5 ± 0.89	87.26 ± 1.15	91.58 ± 2.18 *
Na	(mEq/	137–147	Placebo	141.5 ± 0.2	140.8 ± 0.2 **	141.7 ± 0.3

Parameter	Unit	Reference range	Group	0week (Before)	6weeks	12weeks
	L)		mnemoPQQ®	141.4 ± 0.4	141.2 ± 0.3	141.5 ± 141.4
K	(mEq/L)	3.5–5.0	Placebo	4.04 ± 0.06	4.18 ± 0.05	4.27 ± 0.05 **
			mnemoPQQ®	4.07 ± 0.06	4.12 ± 0.06 **	4.33 ± 0.06 **
Cl	(mEq/L)	98–108	Placebo	103.5 ± 0.4	102.7 ± 0.3 *	102.8 ± 0.3
			mnemoPQQ®	103.6 ± 0.5	102.4 ± 0.4 **	102.8 ± 0.4 *
Ca	(mg/dL)	8.4–10.2	Placebo	8.91 ± 0.05	8.95 ± 0.05	9.02 ± 0.05
			mnemoPQQ®	8.89 ± 0.06	9.04 ± 0.06 *	9.01 ± 0.05 *
Mg	(mg/dL)	1.8–2.4	Placebo	2.07 ± 0.03	2.01 ± 0.03 **	2.09 ± 0.03
			mnemoPQQ®	2.05 ± 0.03	2.01 ± 0.03	2.03 ± 0.03
Fe	(μg/dL)	M: 60–200 F: 50–160	Placebo	122.7 ± 7.6	121.9 ± 8.2	123.2 ± 8.6
			mnemoPQQ®	123.3 ± 6.1	127.1 ± 5.5	130.2 ± 6.0
IP	(mg/dL)	2.5–4.5	Placebo	3.44 ± 0.08	3.43 ± 0.08	3.44 ± 0.10
			mnemoPQQ®	3.34 ± 0.08	3.34 ± 0.07	3.31 ± 0.08
AMY	(U/dL)	37–125	Placebo	81.6 ± 5.3	82.5 ± 5.3	83.8 ± 5.1
			mnemoPQQ®	77.9 ± 3.8	80.1 ± 4.1	79.9 ± 3.8
WBC	($\times 10^3$/μL)	M: 3.5–8.7 F: 3.2–8.6	Placebo	5.6 ± 0.3	5.7 ± 0.3	5.3 ± 0.2
			mnemoPQQ®	5.1 ± 0.2	5.1 ± 0.3	4.9 ± 0.2
RBC	($\times 10^6$/μL)	M: 4.35–5.55 F: 3.86–4.92	Placebo	4.60 ± 0.07	4.61 ± 0.07	4.67 ± 0.08
			mnemoPQQ®	4.53 ± 0.06	4.61 ± 0.07 *	4.61 ± 0.06 *
Hb	(g/dL)	M: 13.7–16.8	Placebo	13.7 ± 0.2	13.7 ± 0.2	14.0 ± 0.2 *

Parameter	Unit	Reference range	Group	0week (Before)	6weeks	12weeks
		F: 11.6–14.8	mnemoPQQ®	13.7 ± 0.2	13.9 ± 0.2 *	13.9 ± 0.2 *
Ht	(%)	M: 40.7–50.1	Placebo	42.3 ± 0.6	42.4 ± 0.5	43.1 ± 0.6 *
		F: 35.1–44.4	mnemoPQQ®	42.0 ± 0.5	42.6 ± 0.6	42.9 ± 0.5 *
PLT	($\times 10^3$/μL)	M: 157–346	Placebo	268.3 ± 8.9	266.2 ± 9.4	269.5 ± 9.8
		F: 160–353	mnemoPQQ®	274.9 ± 18.8	281.4 ± 19.3	287.9 ± 18.7 **
MCV	(fL)	M: 85–98 F: 84–97	Placebo	92.23 ± 0.91	92.35 ± 0.78	92.68 ± 0.87
			mnemoPQQ®	92.77 ± 0.73	92.42 ± 0.63	93.16 ± 0.67
MCH	(pg)	M: 28.3–33.4	Placebo	29.92 ± 0.31	29.87 ± 0.31	30.07 ± 0.30
		F: 26.9–32.9	mnemoPQQ®	30.20 ± 0.27	30.21 ± 0.28	30.17 ± 30.20
MCHC	(%)	M: 32.0–35.4	Placebo	32.44 ± 0.16	32.35 ± 0.17	32.48 ± 0.15
		F: 31.5–35.0	mnemoPQQ®	32.56 ± 0.13	32.66 ± 0.16	32.41 ± 0.14
USG		1.006–1.030	Placebo	1.017 ± 0.001	1.015 ± 0.001	1.017 ± 0.001
			mnemoPQQ®	1.016 ± 0.001	1.015 ± 0.001	1.017 ± 0.001
pH		5.0–7.5	Placebo	6.3 ± 0.1	6.2 ± 0.1	6.2 ± 0.1
			mnemoPQQ®	6.2 ± 0.1	6.2 ± 0.1	6.2 ± 0.1

M=Male, F=Female. Values represent the mean±SE. Placebo group (n=31), mnemoPQQ® group (n=31).

* and ** indicate $p<0.05$ and 0.01, respectively, vs. before (0weeks).

No significant differences were observed in any parameters between the two groups.

Table 7. Results of urinary parameters.

Parameter	Reference range	Group	0week (Before)			6weeks			12weeks		
			-	±	+	-	±	+	-	±	+
PRO	–	Placebo	31	0	0	27	2	2	26	4	1
		mnemoPQQ®	30	1	0	28	3	0	29	2	0
GLU	–	Placebo	30	0	1	31	0	0	31	0	0
		mnemoPQQ®	31	0	0	31	0	0	31	0	0
URO	±	Placebo	0	31	0	0	31	0	0	31	0
		mnemoPQQ®	0	31	0	0	31	0	0	30	1
BLD	–	Placebo	26	4	1	24	2	5	25	4	2
		mnemoPQQ®	27	2	2	23	5	3	26	3	2
BIL	–	Placebo	31	0	0	31	0	0	31	0	0
		mnemoPQQ®	31	0	0	31	0	0	31	0	0
KET	–	Placebo	31	0	0	31	0	0	31	0	0
		mnemoPQQ®	31	0	0	31	0	0	31	0	0

Placebo group (n=31), mnemoPQQ® group (n=31).

No significant differences within each group or between the placebo group and the mnemoPQQ® group.

3.6. Adverse events

During the study period, the placebo group (n=31) had 14 adverse events in 8 participants (headache: 3 cases, malaise: 2 cases, sore throat: 2 cases, throat discomfort: 1 case, chill: 1 case, diarrhea: 1 case, abdominal pain: 1 case, fatigue: 1 case, cough: 1 case, and runny nose: 1 case), and the mnemoPQQ® group (n=31) had 23 adverse events in 7 participants (headache: 5 cases, fatigue: 2 cases, sore throat: 2 cases, cough: 2 cases, runny nose: 2 cases, abdominal pain: 2 cases, malaise: 1 case, dizziness: 1 case, diarrhea: 1 case, swollen gums: 1 case, heartburn: 1 case, nausea: 1 case, slight fever: 1 case, and stomach discomfort: 1 case). However, no serious adverse event was reported in either

group.

4. Discussion

Muscle strength and physical function are important in extending healthy life expectancy and preventing sarcopenia is crucial. Muscle strength and muscle mass, which decrease with aging, are thought to lead to a decline in physical function. However, very few studies have examined factors affecting the Japanese population's muscle strength and physical function. The present study is designed for a clinical investigation to evaluate the efficacy and safety of a 12-weeks of supplementation of PQQ disodium salt in capsules on muscle strength and physical function (motor function) in healthy Japanese male and female volunteers (age=20 - < 75 Y).

The muscle strength of mnemoPQQ® treatment was evaluated on three parameters: lower limb extension muscle strength (kgf), lower limb extension muscle strength/body weight (kgf/kg), and grip strength (kg). Results indicated a significant improvement in muscle strength in all measured values at week 12 of supplementation as compared to baseline ($p<0.001$). The actual measured values of these three evaluation items in the mnemoPQQ® group were significantly different from placebo group at week 12 ($p<0.05$). Furthermore, for each evaluation item, there was a significant difference in the amount of change between the two groups at week 12 of supplementation as compared to before treatment ($p<0.01$). While in the placebo group, no significant differences were observed at 12 weeks of treatment. These results demonstrate that supplementation of PQQ disodium salt over a period of 12 weeks improved muscle strength in healthy subjects.

The physical function (motor function) in the mnemoPQQ® group was evaluated using measurements of ISWT, 6MWT, the 10-meter walking test (normal and fastest speed), FTSST, and TUG (normal and fastest speed). Results exhibited significant improvement in physical function in all measured values at week 12 of supplementation as compared to the baseline. In the mnemoPQQ® supplementation group, the ISWT, 6MWT, and 10-meter walking test (normal speed), and TUG (normal speed) in the mnemoPQQ® group demonstrated significant differences as compared to the placebo group at week 12 of treatment ($p<0.05$). Additionally, there was a significant difference in the amount of change observed in each parameter between the mnemoPQQ® supplemented and the placebo groups at week 12 of treatment ($p<0.001$ or $p<0.01$). This suggests that continuous intake of PQQ disodium salt over a period of 12 weeks improved physical function in healthy subjects. Furthermore, it was observed that the improvement in muscle strength was due to PQQ disodium salt supplementation, which also had a

pronounced effect on the improvement of physical functions in various walking tests, FTSST, and TUG. Fig. 2 provides a conceptual diagram of this clinical investigation.

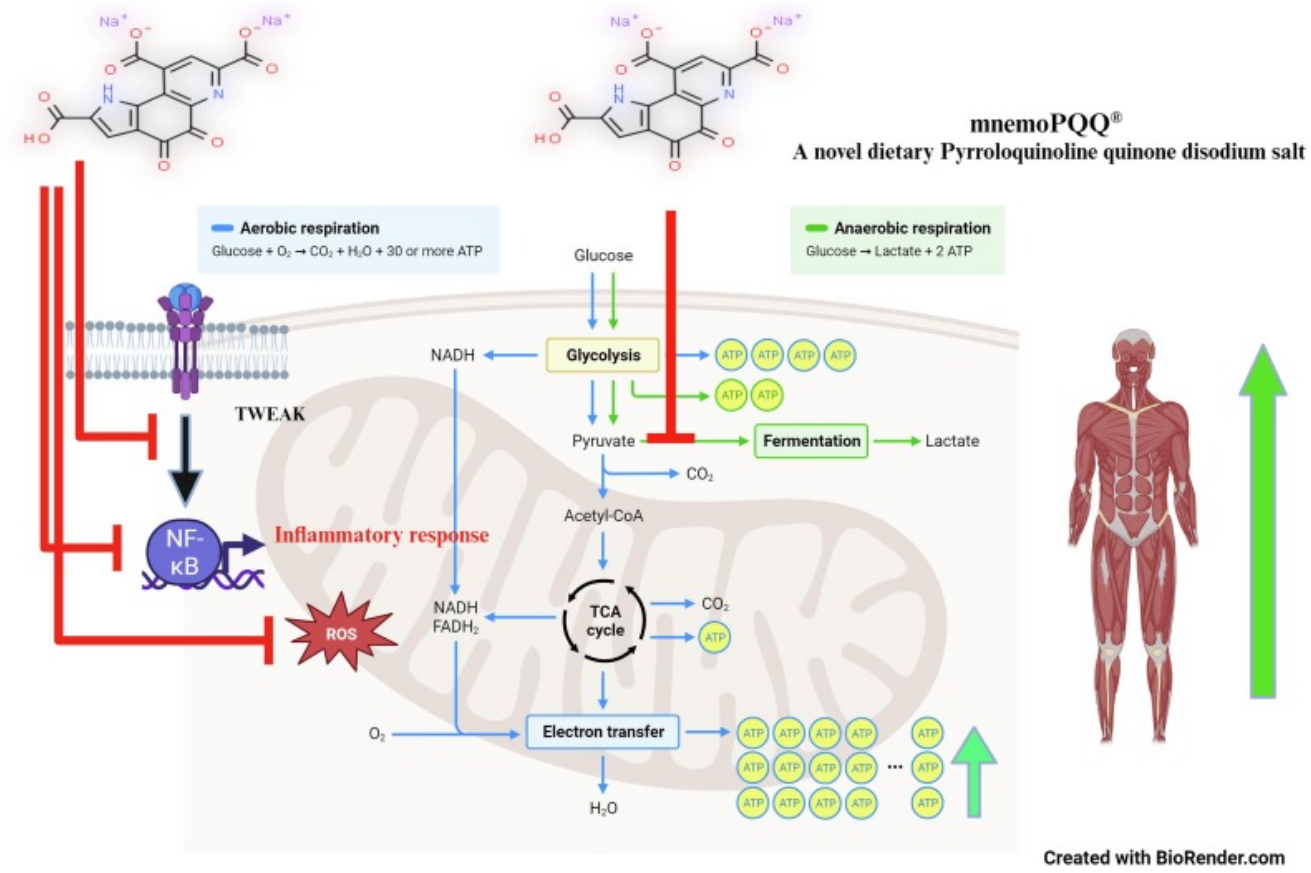

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Fig. 2. Mechanistic insight into the effect ofpyrroloquinoline quinone (PQQ) disodium salt [mnemoPQQ®]. The compound archivesincrease in musclemass and strength by several mechanisms including, 1) Inhibition of Anaerobic metabolism and ATP production through TCA cycle; 2) Inhibition of TWEAK mediated activation of NF-κB pathway and corresponding damage to the muscle cells by inflammatory response; 3) Prevention of oxidative damage by scavenging free radicals.

Earlier studies have demonstrated a correlation between muscle mass and muscle strength (Sugimoto and Miyagi, 2018). Decline in physical functions is largely dependent on reduced muscle mass and strength (Evans, 1995). It is known that muscle strength decreases with age, while independent walking as a physical function becomes difficult when knee extension muscle strength per kg body weight falls below 0.25 kgf/kg (Katayama and Yamasaki, 2017, Hirasawa et al., 2004). Several clinical studies have also shown that there is a relationship between advancing age and reduced physical function

(Sakata et al., 2019, Ota et al., 2015, Berton et al., 2015, Yamana et al., 2019, Yamamoto et al., 2021). It is also known that decreased lower extremity muscle strength significantly prolongs the time required for TUG (Inaoka et al., 2014). The present study evaluated multiple parameters which have shown that there is also a correlation between muscle strength and physical function (motor function).

Animal and cell culture experiments have demonstrated till date that PQQ is effective in maintaining muscle strength (muscle mass) (Kuo et al., 2015, Akagawa et al., 2016). The decrease in muscle mass, which is strongly associated with muscle strength, is related to mitochondrial activity (Kuo et al., 2015). Earlier studies in mice with sciatic nerve resection confirmed that the absence of PQQ decreases gastrocnemius and soleus muscle mass and adversely affects mitochondrial activity, while in the presence of PQQ, increases in muscle mass as well as mitochondrial activity were observed. In addition, peroxisome proliferators-activated receptor-gamma co-activator-1α (PGC-1α) and electron transport chain (ETC) complex protein levels were also increased by PQQ administration. Addition of PQQ to cultured mouse NIH/3T3 fibroblast cells results in its binding with lactate dehydrogenase (LDH) to oxidize NADH to generate NAD^+, which significantly facilitates the conversion of lactate to pyruvate (Akagawa et al., 2016, Akagawa et al., 2016,b).

PQQ increases intracellular ATP levels in NIH/3T3 fibroblasts by decreasing intracellular lactate levels and increasing pyruvate, indicating that PQQ promotes energy production via the TCA cycle and oxidative phosphorylation. Moreover, PQQ increases NAD^+levels in a concentration-dependent manner without changing the total levels of intracellular $NAD^+$and NADH (Saihara, Kamikubo, Ikemoto, Uchida, & Akagawa, 2017). The increase in $NAD^+$by PQQ enhances sirtuin 1 (SIRT1) activity, which is an NAD^+dependent deacetylase, and promotes mitochondrial production through deacetylation of PGC-1α. This mitochondrial production and activation by PQQ are effective in maintaining muscle strength and muscle mass, accompanied by the activation of PGC-1α. The present study revealed a significant increase in lower limb extension muscle strength and grip strength in the mnemoPQQ® group as compared to the placebo group.

Activation of PGC-1α has been reported to suppress muscle atrophy induced by the inflammatory cytokine TNF-like weak inducer of apoptosis (TWEAK) in skeletal muscle (Hindi et al., 2014, Sato et al., 2014). TWEAK activates protein degradation pathways such as NF-κB signaling pathway, the ubiquitin–proteasome system (UPS), and ALS, inducing muscle protein degradation. Furthermore, NF-κB downregulates PGC-1α. In other words, it is concluded that the activation of PGC-1α in skeletal muscle by PQQ suppresses such

mechanisms and suppresses protein degradation in muscle, which in turn maintains muscle strength and physical function.

Earlier studies reported that PQQ scavenges reactive oxygen species (ROS) in skeletal muscle and suppresses muscle atrophy (Xu et al., 2018). C2Cl2, a mouse-derived myoblast cell line, demonstrated that enhanced generation of ROS was enhanced in a TNF-α (tumor necrosis factor-α)-induced myotube atrophy model, while PQQ suppressed the atrophy of C2C12 myotubes induced by TNF-α (Takada et al., 2012). Furthermore, an increase in ROS in muscles upregulates skeletal muscle atrophy factors, such as muscle RING-finger protein-1 (MuRF-1) and muscle atrophy F-box (MAFbx), which are included in the ubiquitin–proteasome system (UPS), the key regulator of protein degradation in skeletal muscle (Fang et al., 2017, Rodney et al., 2016).

The results showed that protein degradation occurred by ROS, while MAFbx and MuRF-1 levels were suppressed by PQQ. Alternatively, it is inferred that PQQ suppresses the increase in skeletal muscle atrophy factors, thereby reducing ROS production, which further enhances muscle strength and physical function.

In another study, C2C12 cells were subjected to oxidative stress using hydrogen peroxide, which demonstrated oxidative stress suppresses the proliferation of C2C12 cells and inhibits their differentiation into myotubes (Fukunaga & Murakami, 2019). This result suggests that oxidative stress suppresses the expression of the myosin heavy chain, thereby affecting the induction of myotube differentiation. Furthermore, an excessive amount of ROS has various deleterious effects on living organisms. Oxidative stress has also been suggested to be involved in the pathology of age-related sarcopenia (Garcia-Prat et al., 2013, Hansen et al., 2007). As for example, the differentiation of satellite cells into myoblasts and myotube cells are inhibited by oxidative stress. Thus, strong antioxidant property of PQQ reduces oxidative stress in skeletal muscles and promotes the differentiation of myoblasts into myotube cells, which enhances muscle strength and physical function.

Multiple mechanistic pathways are involved to demonstrate the functional benefits of PQQ for muscle strength and physical function (motor function) including (i) mitochondrial production and activation; (ii) suppression of protein degradation by activation of PGC-1 in skeletal muscle; (iii) suppression of the production of ROS, which in turn can promote skeletal muscle degradation, and (iv) increase in the differentiation of myoblasts into myotube cells. The present study demonstrates PQQ can maintain or inhibit the decline of muscle strength and physical function (motor function) in healthy

adult male and female volunteers. Moreover, the functional benefits of PQQ doesn't differ with age or sex.

No serious adverse events were reported in our earlier clinical studies following supplementation of PQQ disodium salt (mnemoPQQ®) (Shiojima et al., 2022). The present study also evaluated the safety of mnemoPQQ® in addition to enhancing muscle strength and physical function. The safety of mnemoPQQ® was also reconfirmed by the principal investigator during interview with the subjects. Therefore, the study confirmed that there were no safety issues with the 12-weeks of supplementation of mnemoPQQ® (21.5 mg/day as PQQ disodium salt).

5. Conclusion

The present study investigated the efficacy and safety of 12-weeks continuous supplementation of PQQ disodium salt capsules on muscle strength and physical function (motor function) in healthy Japanese male and female subjects (age = 20 - < 75 Y). The results showed a significant improvement in lower limb extension muscle strength at week 12, the primary endpoint, in the mnemoPQQ® group. Moreover, the mnemoPQQ® group showed significant improvements in grip strength, ISWT, 6MWT, and the 10-meter walking test (normal speed) as the secondary endpoints, as well as the FTSST and TUG as the exploratory endpoints. At week 12, a significant difference between the mnemoPQQ® and placebo groups was observed in the measured value of grip strength, ISWT, 6MWT, the 10-meter walking test (normal speed), and TUG (normal speed) as compared to the placebo group. No adverse effects due to PQQ supplementation were observed. Overall, it was demonstrated that continuous intake of PQQ disodium salt (21.5 mg/day) improved muscle strength and physical function (motor function) in healthy Japanese adult male and female volunteers. The present study affirms that PQQ disodium salt is a functional nutrient, which can be safely consumed in daily life. Regular consumption of mnemoPQQ® can safely maintain muscle strength and physical function and prevent sarcopenia, frailty, and other degenerative conditions in young and older population.

6. Author's contributions.

YS, MT, RT, HM, DB, MB, IK, TS, and TG contributed to the conception and the design of the study, acquisition of data, or analysis and interpretation of data. YS, MT, and RT drafted the manuscript for important intellectual content. All authors approved the

version of the manuscript to be submitted.

7. Disclosure statement

YS, MT, RT, and HM are employees of Ryusendo Co., Ltd., the study sponsor. DB and MB served as independent consultants. TS and TG are the resident investigator. Ryusendo provided the research funds to Kyowa Trial Co., Ltd. TS and TG received a research grant from Kyowa Trial and have no conflicts of interest to declare. YS, MT, RT, HM, DB, MB, and IK were not involved in the interpretation of results and did not influence the outcomes at any stage of the clinical study. All authors have declared that they have no other conflict of interest.

8. Funding

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9. Ethics statement

A randomized, double-blind, placebo-controlled study was conducted to investigate the efficacy and safety of PQQ disodium salt on muscle strength and physical function in healthy Japanese subjects (age = 20 - < 75 Y). The clinical study protocol (protocol number: 2202R) was reviewed and approved by the institutional review board (IRB No. 18000064) of Yamazaki Otolaryngology Clinic Medical Corporation (Hokkaido, Japan) following the ethical standards set out in the Declaration of Helsinki and the guidelines for epidemiological and clinical studies issued by the Ministry of Health, Labor and Welfare and the Ministry of Education, Culture, Sports, Science, and Technology (approval date: July 1, 2022).

This study was preregistered in the University Hospital Medical Information Network (UMIN) clinical trials registry system (http://www.umin.ac.jp), a public database (UMIN ID: 000048641). Duly signed informed consent was obtained from all participants. The trial was conducted by the contract research organization Kyowa Trial Co., Ltd. (Sapporo, Hokkaido, Japan) at GOZEN Medical Corporation Kita 7-jo Goda Orthopedics (Sapporo, Hokkaido, Japan) from July to December 2022.

CRediT authorship contribution statement

Yoshiaki Shiojima: Writing – review & editing, Original dradt, Validation, Supervision,

Formal analysis, Data curation, Conceptualization, Project administration, Methodology, Investigation. **Megumi Takahashi:** Writing – original draft, Supervision, Resources, Project administration, Formal analysis. **Ryohei Takahashi:** Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. **Hiroyoshi Moriyama:** Writing – original draft, Validation, Supervision, Software, Methodology, Investigation, Conceptualization. **Manashi Bagchi:** Writing – original draft, Validation, Methodology, Formal analysis, Conceptualization. **Isao Kanbayashi:** Writing – original draft, Supervision, Resources, Methodology, Formal analysis. **Takuro Sasaki:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Taketoshi Goda:** Writing – original draft, Visualization, Resources, Project administration, Methodology, Formal analysis. **Debasis Bagchi:** Writing – review & editing, Original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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