**Supplementary Material**

**Effect of Chlorogenic Acids on Cognitive Function in Mild Cognitive Impairment: A Randomized Controlled Crossover Trial**

**Supplementary Table 1.** Medications of the participants

|  |  |  |
| --- | --- | --- |
|  | Number | (%) |
| No medication | 4 | 11.8% |
| Taking medication | 30 | 88.2% |
| Medicine types |  |  |
| Agents affecting digestive organs | 15 | 50.0% |
| Antihypertensive agents | 20 | 66.7% |
| Lipid-lowering agents | 11 | 36.7% |
| Sedative hypnotic agents | 12 | 40.0% |
| Hematologic agents | 13 | 43.3% |
| Bone metabolism improving agents | 4 | 13.3% |
| Antidiabetic drugs | 3 | 10.0% |
| Others | 3 | 10.0% |

**Supplementary Table 2**. Characteristics of the participants

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | PPS (n=28) | | |  | Dropouts and exclusion (n=6) | | |  | p |
| Number | 28 (Female 14) | | |  | 6 (Female 5) | | |  |  |
| Age (y) | 73.5 | ± | 6.0 |  | 74.5 | ± | 6.5 |  | 0.747 |
| Height (cm) | 158.5 | ± | 9.0 |  | 151.8 | ± | 3.8 |  | 0.008 |
| Body weight (kg) | 58.5 | ± | 9.5 |  | 47.8 | ± | 3.2 |  | 0.000 |
| BMI (kg/m2) | 23.2 | ± | 3.0 |  | 20.8 | ± | 1.6 |  | 0.013 |
| SBP (mmHg) | 137.6 | ± | 14.9 |  | 142.5 | ± | 9.1 |  | 0.312 |
| DBP (mmHg) | 76.5 | ± | 7.5 |  | 74.7 | ± | 14.4 |  | 0.773 |
|  |  |  |  |  |  |  |  |  |  |
| GDS | 1.5 | ± | 1.4 |  | 2.3 | ± | 1.2 |  | 0.193 |
| MMSE | 27.0 | ± | 2.5 |  | 26.3 | ± | 4.3 |  | 0.728 |
| ADAS-cog | 5.0 | ± | 3.4 |  | 6.5 | ± | 4.5 |  | 0.465 |
| TMT-A |  |  |  |  |  |  |  |  |  |
| Time (s) | 54.4 | ± | 20.9 |  | 71.5 | ± | 56.5 |  | 0.497 |
| Errors | 0.0 | ± | 0.0 |  | 0.2 | ± | 0.4 |  | 0.363 |
| TMT-B |  |  |  |  |  |  |  |  |  |
| Time (s) | 141.9 | ± | 69.9 |  | 174.0 | ± | 97.3 |  | 0.472 |
| Errors | 1.1 | ± | 1.6 |  | 2.7 | ± | 2.8 |  | 0.229 |

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GDS, Japanese version of Geriatric Depression Scale – Short Version; MMSE, Japanese version of Mini-Mental State Examination; ADAS-cog, Japanese version of Alzheimer's Disease Assessment Scale-cognitive component; TMT-A, Japanese version of the Trail Making Test A; TMT-B, Japanese version of the Trail Making Test B. The p-value represents the significance level of the difference between the PPS and Dropouts/exclusion (t-test).

**Supplementary Table 3.** Concentrations of CGAs in human plasma

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Concentration in plasma (ng/ml) | | | | | | | | | |
|  | Baseline | | |  | Active | | | p |
| 3-caffeoylquinic acid | 0.5 | ± | 1.4 |  | 0.6 | ± | 1.4 | 0.691 |
| 4-caffeoylquinic acid | 0.7 | ± | 1.9 |  | 0.9 | ± | 2.1 | 0.386 |
| 5-caffeoylquinic acid | 1.0 | ± | 2.6 |  | 1.6 | ± | 3.1 | 0.150 |
| 3-feruloylquinic acid | 2.6 | ± | 4.7 |  | 3.0 | ± | 6.5 | 0.705 |
| 4-feruloylquinic acid | 2.1 | ± | 3.9 |  | 1.9 | ± | 3.6 | 0.827 |
| 5-feruloylquinic acid | 1.0 | ± | 1.6 |  | 1.5 | ± | 2.3 | 0.264 |

Values are expressed as the mean ± SD (N = 28).

Dicaffeoylquinic acids were not detected in plasma of both samples. The p-value represents the significance level of the difference between the baseline and active beverage conditions (paired t-test).

**Supplementary Table 4.** List of adverse events

|  |  |  |  |
| --- | --- | --- | --- |
| **Events** | **Placebo (n=34)** | **Active (n=31)** | **p** |
|  | **n (%)** | **n (%)** |  |
| Total number of AEs | 23 | 31 | 0.354 |
| AEs by number of participants | 17 (50.0%) | 17(54.8%) | 1.000 |
| Any severe AEs | 1 (2.9%) | 3 (9.7%) | 0.357 |
|  |  |  |  |
| Infections and infestations |  |  |  |
| Phlebitis infective | 4 (11.8%) | 7 (22.6%) | 0.516 |
| Shingles | 1 (2.9%) | 0 (0%) | 1.000 |
| Bladder infection | 0 (0%) | 1 (3.2%) | 0.485 |
| Gastrointestinal disorders |  |  |  |
| Stomach discomfort | 1 (2.9%) | 0 (0%) | 1.000 |
| Abdominal pain | 1 (2.9%) | 0 (0%) | 1.000 |
| Constipation | 1 (2.9%) | 0 (0%) | 1.000 |
| Hemorrhoidal hemorrhage | 1 (2.9%) | 0 (0%) | 1.000 |
| Dry mouth | 1 (2.9%) | 0 (0%) | 1.000 |
| Excess belching | 0 (0%) | 2 (6.5%) | 0.239 |
| Nausea | 0 (0%) | 2 (6.5%) | 0.239 |
| Diarrhea | 0 (0%) | 2 (6.5%) | 0.239 |
| Mucositis oral | 0 (0%) | 1 (3.2%) | 0.485 |
| Toothache | 0 (0%) | 1 (3.2%) | 0.485 |
| Tooth extraction | 0 (0%) | 1 (3.2%) |  |
| Gingivitis | 0 (0%) | 2 (6.5%) | 0.239 |
| Injury, poisoning and procedural complications | |  |  |
| Trauma capitis | 1 (2.9%) | 0 (0%) | 1.000 |
| Fracture | 1 (2.9%) | 2 (6.5%) | 0.608 |
| Musculoskeletal and connective tissue disorders | |  |  |
| Pain in the hands and feet | 1 (2.9%) | 0 (0%) | 1.000 |
| Knee bruise | 1 (2.9%) | 0 (0%) | 1.000 |
| Skin laceration | 1 (2.9%) | 0 (0%) | 1.000 |
| Back pain | 0 (0%) | 1 (3.2%) | 0.485 |
| Arthralgia | 0 (0%) | 2 (6.5%) | 0.239 |
| Nervous system disorders |  |  |  |
| Muscle cramp | 1 (2.9%) | 0 (0%) | 1.000 |
| Headache | 0 (0%) | 1 (3.2%) | 0.485 |
| Ear and labyrinth disorders |  |  |  |
| Tinnitus | 1 (2.9%) | 0 (0%) | 1.000 |
| Eye disorders |  |  |  |
| Eye pain | 1 (2.9%) | 0 (0%) | 1.000 |
| Macular hole | 0 (0%) | 1 (3.2%) | 0.485 |
| Respiratory, thoracic and mediastinal disorders | |  |  |
| Pharyngeal fistula | 0 (0%) | 1 (3.2%) | 0.485 |
| Skin and subcutaneous tissue disorders | |  |  |
| Pruritus | 1 (2.9%) | 0 (0%) | 1.000 |
| Scalp of rash | 1 (2.9%) | 0 (0%) | 1.000 |
| Eczema | 0 (0%) | 2 (6.5%) | 0.239 |
| Renal and urinary disorders |  |  |  |
| Nocturia | 0 (0%) | 1 (3.2%) | 0.485 |
| General disorders and administration site conditions | |  |  |
| Fatigue | 1 (2.9%) | 0 (0%) | 1.000 |
| Immune system disorders |  |  |  |
| Seasonal allergy | 1 (2.9%) | 0 (0%) | 1.000 |
| Investigations |  |  |  |
| CRP | 1 (2.9%) | 1(3.2%) | 1.000 |

AEs, adverse events; CRP, C-reactive protein. The p-value represents the significance level of the difference between the placebo and active beverage conditions (Fisher’s exact test).