THE EFFECTS OF COSMOS CAUDATUS SUPPLEMENTATION ON NEURODEGENERATIVE PREVENTION AMONG OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT

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INTRODUCTION
Introduction

30.8 % (Aging adults) [1]  
 Household Income (<RM 3,000 or USD 715) [1]  
 Low Flavonoids Intake [2]  

Cognitive impairment

RATIONALE OF THE STUDY

1. **Prevalence of MCI**
   - Worldwide: 5.0-36.7\% [3]
   - Malaysia: 16\% [4]

2. **Medicinal plants**
   - Secondary metabolites improve cognition
   - i.e. *Centella asiatica*, *Gingko biloba*, *Polygonum minus* [6-8]

3. **Cosmos caudatus**
   - High antioxidants and polyphenols [5]

4. **Novelty**
   - 1. Human clinical trial
   - 2. Preventive effects
   - 3. Using neuroimaging

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Cosmos caudatus

Ulam raja

**Characteristic**

*Ulam raja* widely distributed in Malaysia [5]

**Nutrient**

Rich in flavonoids and antioxidants [5]

**Medicinal properties**

Antidiabetic, anti-inflammatory, antihypertensive, anticancer, antimicrobial [9,10]

**Toxicity & in-vivo study**

Safe to consume up to 500 mg/kg and exhibit antioxidant properties in animal model [11,12]

GENERAL OBJECTIVE

To develop *Cosmos caudatus* supplement that can improve cognitive, mood, biochemical changes as well as brain activation among older adults with mild cognitive impairment.

1. To develop and determine the nutrient composition of *Cosmos caudatus* supplement using standard food analytical procedures.

2. To determine the efficacy of *Cosmos caudatus* supplementation on its ability to improve cognitive function and mood status using neuropsychological batteries and POMS.

3. To determine the efficacy of *Cosmos caudatus* supplementation on its ability to improve brain activation using fMRI among older adults with MCI.

4. To determine the efficacy of *Cosmos caudatus* supplementation on its ability to improve health parameters and biomarkers among older adults with MCI.
METHODOLOGY
TWO PHASES OF STUDY

1. Development of *Cosmos caudatus* supplement and placebo and nutrient analysis.

2. Effects of *Cosmos caudatus* supplement in improving cognitive status, mood status, biomarkers and health parameters in H-CARE & UKMMC, UKM.

- Ethic approval & informed consent
- RCT registration: ISRCTN16793907
Objective 1:
To develop and determine the nutrient composition of *Cosmos caudatus* supplement using standard food analytical procedures.
Phase 1: Development of *Cosmos caudatus* supplement and determination of its nutrient composition

95 g or approximately 3 cups of *Cosmos caudatus* fresh leaves could yield 500 mg preparation powder.
Table 1: Comparison of nutrient composition of CC supplement with placebo, P. minus, CC plant wet basis and RNI 2017

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Cosmos caudatus supplement (Dry basis)</th>
<th>Placebo</th>
<th>Polygonum minus aqueous extract (Dry basis)</th>
<th>Cosmos caudatus plant (wet basis)</th>
<th>Recommended nutrient intake Malaysia 2017 (%) met</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macronutrients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy (kcal)</td>
<td>284 ± 4</td>
<td>376 ± 3</td>
<td>305</td>
<td>18</td>
<td>1800 (15.8)</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>47.35 ± 0.92</td>
<td>94.05 ± 0.64</td>
<td>67.6</td>
<td>0.6</td>
<td>NA</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>20.30 ± 0.42</td>
<td>0</td>
<td>8.6</td>
<td>2.9</td>
<td>50-58 (81-94)</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>1.40 ± 0.14</td>
<td>0</td>
<td>0</td>
<td>0.4</td>
<td>NA</td>
</tr>
<tr>
<td>Total Dietary Fiber (g)</td>
<td>7.80 ± 2.97</td>
<td>1.8 ± 0.14</td>
<td>1.6</td>
<td>20-30 (26-39)</td>
<td></td>
</tr>
<tr>
<td><strong>Micronutrients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A Retinol (µg)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>100.50 ± 2.12</td>
<td>0</td>
<td>27.0</td>
<td>64.6</td>
<td>70 (144)</td>
</tr>
<tr>
<td>Vitamin E Alpha-Tocopherol (mg)</td>
<td>2.10 ± 0.42</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>7.5-10 (21-28)</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>2255.00 ± 7.07</td>
<td>9.06 ± 0.54</td>
<td>38.5</td>
<td>270</td>
<td>1000 (226)</td>
</tr>
<tr>
<td>Selenium (mg)</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>7.69 ± 0.16</td>
<td>0.62 ± 0.13</td>
<td>-</td>
<td>4.6</td>
<td>11-14 (55-70)</td>
</tr>
<tr>
<td>Potassium (mg)</td>
<td>9610 ± 466.69</td>
<td>15.00 ± 0.71</td>
<td>-</td>
<td>426</td>
<td>4700 (204)</td>
</tr>
<tr>
<td>Sodium (mg)</td>
<td>71.60 ± 5.52</td>
<td>69.15 ± 2.62</td>
<td>-</td>
<td>4</td>
<td>1500 (5)</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>2.77 ± 0.52</td>
<td>0.70 ± 0.14</td>
<td>-</td>
<td>-</td>
<td>4.3-6.3 (44-64)</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total phenolic content (mg Gallic acid equivalent)</td>
<td>1482 ± 101</td>
<td>3.56 ± 0.10</td>
<td>-</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>DPPH (mmol Trolox equivalent)</td>
<td>330.86 ± 9.48</td>
<td>4.57 ± 2.01</td>
<td>-</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>FRAP (mmol Trolox equivalent)</td>
<td>393.57 ± 9.78</td>
<td>1.45 ± 1.17</td>
<td>-</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>Ash content (g)</td>
<td>26.70 ± 1.27</td>
<td>0.05 ± 0.07</td>
<td>-</td>
<td>1.4</td>
<td>NA</td>
</tr>
<tr>
<td>Moisture content (%)</td>
<td>4.25 ± 0.49</td>
<td>5.85 ± 0.50</td>
<td>-</td>
<td>93.1</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Bioactive content (% w/w)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quercetin</td>
<td>0.9</td>
<td>NA</td>
<td>0.4</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>Quercitrin</td>
<td>1.0</td>
<td>NA</td>
<td>0.1</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>Recommended nutrient intake Malaysia 2017 (%) met</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Randomised based on gender using block randomisation.

Below toxicity level and exceed the antioxidant effect dosage in animal model [11,12]

Determination of dosage

Compliance checking
- Regularly remind subjects using phone calls and text messages.
- Report adverse events and compliance.

Study product

Cosmos caudatus supplement and placebo labelled as A or B by repacker.
**Phase 2:**
**Effects of Cosmos caudatus supplement in improving cognitive status, mood status, biomarkers and brain activation**

**Older adult is/with:**
- Malaysian older adults age between 60-75 years at the time of informed consent.
- Older adults with mild cognitive impairment based on Petersen et al. (2014).
  - Currently not receiving any clinical judgements on dementia.
  - Have no or very minimal limitations in instrumental activities of daily livings (IADL) with a score of ≤ 1.5 SD from mean norm.
  - Essentially preserved general cognitive functioning by scoring ≥ 19 in Mini Mental State Examination (MMSE).
  - Objective memory impairment with a score of at least 1.5 SD below the mean average in one or more cognitive test (Vanoh et al. 2017).
  - Subjective memory complaints.
- Older adults with BMI= 20-30kg/m².

**Older adult is/with:**
- Alcohol and/or substance dependence.
- Smoker.
- Neurodegenerative diseases (i.e. Parkinson disease, dementia, etc).
- Diagnosis of a depressive disorder, schizophrenia or score > 5 in Geriatric Depression Scale (GDS).
- Uncontrolled diabetes, chronic heart disease, cancer and kidney, liver or renal failure.
- Attention Deficit Hyperactivity Disorder (ADHD).
- Regular consumers of traditional herbs, vitamin and mineral supplementation for the past 6 months.
- Female older adults with ongoing Hormone Replacement Therapy.
- On medications (i.e. warfarin).
- Metallic implant, such as prostheses, shrapnel or aneurysm clips, or electronic implants, such as cardiac pacemakers.
- Claustrophobic.
Phase 2 outcomes

<table>
<thead>
<tr>
<th>Task</th>
<th>Neuropsychological assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-mental state examination (MMSE)</td>
<td>Global cognitive function</td>
</tr>
<tr>
<td>Digit Span</td>
<td>Attention and working memory</td>
</tr>
<tr>
<td>RAVLT (immediate &amp; delayed recall)</td>
<td>Verbal immediate memory</td>
</tr>
<tr>
<td>Visual Reproduction (immediate &amp; delayed recall)</td>
<td>Visuo-spatial function</td>
</tr>
<tr>
<td>Digit symbol substitution</td>
<td>Psychomotor speed</td>
</tr>
<tr>
<td>Profile of mood state (POMS)</td>
<td>Tension, depression, anger, fatigue, esteem-related effect, vigour and confusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarkers</td>
<td>BDNF, MDA, iNOS, COX-2, SOD, GSH</td>
</tr>
<tr>
<td>Biochemical profiles</td>
<td>Liver function test, renal function test, full blood count</td>
</tr>
<tr>
<td>fMRI</td>
<td>Brain activation</td>
</tr>
</tbody>
</table>
Phase 2: Task-based Functional Magnetic Resonance Imaging

Region of Interest (ROI) : DLPFC

Frontal Pole ($BA_{10}$)

Broca's Area ($BA_{44,45}$)

DLPEC ($BA_{9,46}$)

Side View (Left)

Anatomical Region

0-back

1-back

4 blocks

15 trials per block
RESULTS
Objective 2:
To determine the efficacy of Cosmos caudatus supplementation on its ability to improve cognitive function and mood status using neuropsychological batteries and POMS.
Baseline Sociodemographic Information (N=48)

Age: 65.1 ± 4.1 years old

Percentage of subjects (%)

- Female: 66.7%
- Malay: 60.4%
- Secondary school: 62.5%
- Married: 77.1%
- Hypertension: 35.4%
- Diabetes: 22.9%
- Hyperlipidaemia: 31.3%
- 1-2 times physically active: 39.6%
Table 2: Main effect of group by time interaction of cognitive tests from baseline to 12th week

CC supplement contains high **quercetin** and **quercitrin** levels which involved in cognitive pathway (Figueira et al. 2017) •

**Quercetin** acts as adenosine antagonist to improve cognitive functioning and reduce cognitive fatigue (Bigelman et al. 2011) •

**Quercitrin** was found to be involved in the dilution of oxidative stress, clampdown of inflammation and the improvement of neurotransmitter dysfunction (Costa et al. 2016; Ma et al. 2016) •

CC supplement also contains other flavonoids (catechin, proanthocyanidin, epicatechin) which could exert synergistic effect in cognitive pathway (Moshawih et al. 2017; Youdim et al. 2005) •

*Significant at p < 0.05 using independent t-test analysis
Table 3: Main effect of group by time interaction of mood states from baseline to 12th week

**Quercetin** was reported to have an impact on gamma-aminobutyric acid (GABA) receptors that produce sedation, anxiolytic and anti-convulsive effects (Jager & Saaby 2011)

**Quercetin** also act as phosphodiesterase-5 inhibitors, has been proven to be effective in neutralizing reactive oxygen species for the treatment of anxiety-related disorders (Kinrys et al. 2009)

Presence of synergistic impact between the combination of polyphenols and antioxidants in natural plant could exert anti-anxiety effect (Xu et al. 2014)
Objective 3:
To determine the efficacy of Cosmos caudatus supplementation on its ability to improve cognitive brain activation using fMRI among older adults with MCI.
Table 4: Main effect of group by time interaction of brain activation from baseline to 12\textsuperscript{th} week

<table>
<thead>
<tr>
<th>Parameters (N = 20)</th>
<th>Partial Eta Square</th>
<th>Power</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-back Right DLPFC</td>
<td>0.147</td>
<td>0.262</td>
<td>0.177</td>
</tr>
<tr>
<td>0-back Left DLPFC</td>
<td>0.008</td>
<td>0.059</td>
<td>0.764</td>
</tr>
</tbody>
</table>

Flavonoids of CC supplement might have potential to pass across blood brain barrier and protect against the reduction of cerebral blood flow \cite{Figueira2017}.

Right DLPFC is responsible for manipulating information in spatial reasoning such as 1-back task \cite{Barbey2013}.

![Graph showing percentage mean difference over time for CC supplement and Placebo groups.](image)

**Significant at p < 0.01 using independent t-test analysis**
Brain activations during brain memory tasks on a volume rendered brain (Placebo)

Baseline

Middle frontal gyrus
Precentral gyrus

12th week

Middle frontal gyrus
Precentral gyrus

1-back in MFG
1-back in Precentral gyrus

p<0.05, FWE corrected
Brain activations during brain memory tasks on a volume rendered brain
(CC supplement)

- 1-back in MFG
- 1-back in Precentral gyrus

Baseline

Middle frontal gyrus
Precentral gyrus

12th week

Middle frontal gyrus
Precentral gyrus

p<0.05, FWE corrected
Objective 4:
To determine the efficacy of *Cosmos caudatus* supplementation on its ability to improve blood biomarkers among older adults with MCI.
Table 5: Main effect of group by time interaction of cognitive-related biomarkers from baseline to 12\textsuperscript{th} week

<table>
<thead>
<tr>
<th>Parameters (N = 47)</th>
<th>Partial Eta Square</th>
<th>Power</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain-derived neurotrophic factor (pg/ml)</td>
<td>0.001</td>
<td>0.052</td>
<td>0.884</td>
</tr>
<tr>
<td>Inducible nitric oxide synthase (pg/ml)</td>
<td>0.000</td>
<td>0.050</td>
<td>0.994</td>
</tr>
</tbody>
</table>

Flavonoids of CC supplement might have potential to avert DNA oxidative damage, reduce lipid peroxidation and rummage ROS (Garcia-Blanco et al. 2017).

The role of flavonoids in CC might assist the increment of serum glutathione levels but the bioavailability of glutathione from CC in human body is remained unknown (Winterbourn 2016).

*Significant at \( p < 0.05 \) using independent \( t \)-test analysis
1. This study successfully developed *Cosmos caudatus* (CC) supplement with high flavonoids content with 0.9% of quercetin and 1.0% of quercitrin.

2. CC supplement has potential to reduce lipid peroxidation and increase serum glutathione and it would lead to the improvement in DLPFC activation and cognitive function.

3. CC supplement has potential to reduce tension and total mood disturbance.

4. 43.5% of subjects from CC supplement group were reversed to normal cognition and no serious adverse events was reported.
POSSIBLE MECHANISM
Strengths

The use of neuroimaging approach that compliments with the neuropsychological batteries.

The use of a randomised, double-blinded placebo controlled study design.

Recruited older adults with mild cognitive impairment who are at high risk in getting irreversible neurodegenerative diseases.

Limitations

Same sets of neuropsychological batteries were used throughout the study. Learning effect might be occurred.

Mood status was assessed using self-reported questionnaire which is less sensitive for MCI individuals.
IMPACT OF STUDY

Landmark for future trials

Healthy lifestyle

Reduced risk of contracting neurodegenerative diseases

Knowledge-economy
Acknowledgement

- Dana Padanan Kolaborasi (DPK), UKM
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- Zamalah Yayasan Canselor, CRIM UKM
- Researchers/Enumerators and staffs helped in this study
- Subjects who joined this study
- Research team (Supervisors)
References


thank you