A Clinical Research of The Effect of Ferulic Acid and Angelica Archangelica Extract on Amyloid Beta Deposition in Mild Cognitive Impairment Patients.

(MCI患者に対するフェルラ酸とガーデンアンゼリカの有効性の研究）

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1. Background
The number of elderly is increasing in Japan.

The ratio of elderly over 65 years old is 27.3% in Japan.
The number of dementia patients is also increasing.

- There are estimated 4.62 million dementia patients and over four million mild cognitive impairment (MCI) elderly.
- The number of dementia patients will be seven million in 2025. This is one out of five in Japanese elderly.
The most common cause of dementia is Alzheimer’s disease (AD).
Amyloid cascade hypothesis

Age

50  60  70  80 

Clinical Symptom

MCI  Dementia

Neuron damage

neurofibrillary tangle formation

Amyloid Beta Deposition

neurofibrillary tangle formation
Ferulic acid and Angelica archangelica

• Ferulic acid (FA) is a kind of polyphenol. Some researchers say it has antioxidant and anti-inflammatory potential and it may decreases Amyloid beta in the brain.

• Angelica archangelica (AA) is a kind of herb. Some researchers say it regenerates neuron and reduces the activity of acetylcholinesterase.
Ferulic acid and Angelica archangelica

Using a supplement containing ferulic acid and angelica archangelica extract (FA: 200mg per day, AA: 40mg per day), we will be able to assess the effect of ferulic acid and angelica archangelica on amyloid beta deposition in the human brain.
Previous studies of Ferulic acid and Angelica archangelica

Ferulic acid

- decreases amyloid beta in the brain of AD-model mice
- inhibits beta-secretase
- destabilizes amyloid beta fibrils
- has antioxidant and anti-inflammatory potential

Angelica archangelica

- reduces the activity of acetylcholinesterase

Previous studies of supplement of FA and AA

- ADAS–Jcog score of 28 MCI elderly improved after taking the supplement for 96 weeks\(^1\).
- It inhibited the reduction of ADAS–J cog score of 143 AD patients after taking the supplement for nine months \(^2\).
- Behavioral and psychological symptoms of frontotemporal lobar degeneration and dementia with Lewy bodies was improved after taking the supplement for four weeks\(^3\).

Amyloid PET (positron emission tomography)

- We used amyloid PET to assess the amyloid deposition in the brain.
- Injected [11C]PiB binds amyloid beta and it is detected by PET.
- [11C]PiB bindings is expressed by SUV (Standardized Uptake Value). SUV of each brain region is divided by SUV of cerebellum and this SUVR (SUV ratio) is used as an assessment value. The cutoff is SUVR > 1.5 in many reports.
VSRAD (Voxel-based specific regional analysis system for Alzheimer’s disease)

- VSRAD is a voxel-based morphometry of brain magnetic resonance imaging (MRI).
- It is used to assess the brain atrophy, and is a biomarker of progression of Alzheimer’s disease.
- There are four indicators:

1. **Severity of VOI atrophy**
   - VOI内萎縮度: *Severity of VOI atrophy*
   - [ Reads ] 被選択した VOI の平均スコアを示す指標です。
   - (参考) 0-1: 被選択した VOI の萎縮はほとんど見られない
   - 2-3: 被選択した VOI の萎縮がやや見られる
   - 3+: 被選択した VOI の萎縮が強い
   - 1.76

2. **Extent of GM atrophy**
   - 全脳萎縮領域の割合: *Extent of GM atrophy*
   - [ Reads ] 全脳内の萎縮を示す指標です。
   - (参考) 10%: 全脳の萎縮が強いか
   - 11.18%

3. **Extent of VOI atrophy**
   - VOI内萎縮領域の割合: *Extent of VOI atrophy*
   - [ Reads ] 被選択した VOI の萎縮を示す指標です。
   - (参考) 30%: 被選択した VOI の萎縮が弱いか
   - 34.76%

4. **Ratio of VOI/GM atrophy**
   - 萎縮比 (VOI内 / 全脳): *Ratio of VOI/GM atrophy*
   - [ Reads ] 被選択した VOI の萎縮を示す指標です。
   - (参考) 5%: 被選択した VOI の萎縮が強いか
   - 3.11倍
2. Objective and Method
Objective of the research

The objective is to assess the effect of ferulic acid and angelica archangelica on amyloid beta deposition in MCI patients’ brain and to examine their clinical benefit.

• Primary outcome
  The time-depending change of [11C]PiB amyloid positron emission tomography tracer bindings in MCI patients’ brain at baseline, 48 weeks, and 96 weeks after taking the supplement.

• Secondary outcomes
  1. The time-depending change of magnetic resonance imaging of the brain at baseline, 48 weeks, and 96 weeks after taking the supplement.
  2. The time-depending change of psychological test score with time, at baseline, 24 weeks, 48 weeks, 72 weeks and 96 weeks after taking the supplement.
Design of the research

• This is a open-label interventional multi-institutional joint research of Kobe University and Institute of Biomedical Research and Innovation (IBRI).

• Research Period
  Recruitment: from August 2014 to March 2017
  Total research period: from August 2014 to March 2020

• Subjects
  Twenty patients diagnosed as MCI
    Intervention group (taking the supplement) : 10 patients
    Control group (not taking the supplement) : 10 patients

Each subject decides which group he joins according to his will.
Amyloid negative subject in the screening test is ineligible.
<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>24 weeks</th>
<th>48 weeks</th>
<th>72 weeks</th>
<th>96 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>amyloid PET</td>
<td>○</td>
<td></td>
<td>○</td>
<td></td>
<td>○</td>
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<tr>
<td>brain MRI</td>
<td>○</td>
<td>○</td>
<td></td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>psychological test (MMSE, ADAS, FAB, WMS–R logical memory IA, II A)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>ApoE gene</td>
<td>○</td>
<td></td>
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<td></td>
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</tbody>
</table>
3. Result (midterm report)
Progress

- Ten intervention group subjects and seven control group subjects were recruited by March 2017.
- All subjects finished 72 week test.
- Six intervention group subjects and three control group subjects finished 96 week test.
Statistical analysis

- Amyloid deposition (SUVR) and brain atrophy (VSRAD four indicators): We compare baseline (BL), 48 week, and 96 week data between intervention and control group.

- Psychological test (MMSE, ADAS, FAB, WMS-R logical memory I A, II A): We compare BL, 24 week, 48 week, and 72 week data between intervention and control group.

- We used t-test except VSRAD analysis which used Wilcoxon test.

- Significant level is 0.007 for SUVR, 0.013 for VSRAD, and 0.01 for psychological test, respectively followed by Bonferroni’s correction.
## Baseline data

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>p-value</th>
<th>test</th>
</tr>
</thead>
<tbody>
<tr>
<td>sample size</td>
<td>10</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>74.6±2.2</td>
<td>75.7±1.8</td>
<td>0.72</td>
<td>t</td>
</tr>
<tr>
<td>gender (male:female)</td>
<td>3 : 7</td>
<td>2 : 5</td>
<td>1</td>
<td>Fisher</td>
</tr>
<tr>
<td>ApoE ε4 (positive:negative)</td>
<td>5 : 5</td>
<td>4 : 3</td>
<td>1</td>
<td>Fisher</td>
</tr>
<tr>
<td>MMSE</td>
<td>26.4±0.7</td>
<td>26.0±0.6</td>
<td>0.68</td>
<td>t</td>
</tr>
<tr>
<td>ADAS</td>
<td>9.7±0.8</td>
<td>9.1±1.6</td>
<td>0.74</td>
<td>t</td>
</tr>
<tr>
<td>FAB</td>
<td>11.4±0.5</td>
<td>10.7±0.8</td>
<td>0.44</td>
<td>t</td>
</tr>
<tr>
<td>LM1A</td>
<td>4.5±0.7</td>
<td>5.6±1.2</td>
<td>0.42</td>
<td>t</td>
</tr>
<tr>
<td>LM2A</td>
<td>0.8±0.4</td>
<td>0.1±0.1</td>
<td>0.19</td>
<td>t</td>
</tr>
<tr>
<td>severity of atrophy</td>
<td>2.04±0.23</td>
<td>2.28±0.33</td>
<td>0.55</td>
<td>t</td>
</tr>
<tr>
<td>global SUVR</td>
<td>2.19±0.10</td>
<td>2.23±0.20</td>
<td>0.86</td>
<td>t</td>
</tr>
</tbody>
</table>

There is no significant difference between groups.
There is no significant difference between groups.

\[
\begin{align*}
\text{Intervention} & \\
48\text{w}-\text{BL}: & 0.119 \pm 0.026 \ (N=10) \\
96\text{w}-\text{BL}: & 0.169 \pm 0.041 \ (N=6) \\
\text{Control} & \\
48\text{w}-\text{BL}: & 0.061 \pm 0.020 \ (N=7) \\
96\text{w}-\text{BL}: & 0.119 \pm 0.075 \ (N=3) \\
\end{align*}
\]

\[48\text{w}-\text{BL}: p=0.13 > 0.007 \quad 96\text{w}-\text{BL}: p=0.54 > 0.007\]
PiB posterior cingulum SUVR change (48w–BL, 96w–BL)

There is no significant difference between groups.

48w–BL: 0.129 ± 0.035 (N=10)  
96w–BL: 0.184 ± 0.035 (N=6)  

48w–BL: 0.053 ± 0.073 (N=7)  
96w–BL: 0.082 ± 0.082 (N=3)

48w–BL: p=0.13 > 0.007  
96w–BL: p=0.21 > 0.007
## PiB SUVR change of other region

<table>
<thead>
<tr>
<th></th>
<th>frontal lobe</th>
<th>lateral temporal lobe</th>
<th>lateral parietal lobe</th>
<th>posterior lobe</th>
<th>striatum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>48w-BL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>0.137 ± 0.027</td>
<td>0.110 ± 0.025</td>
<td>0.102 ± 0.023</td>
<td>0.071 ± 0.028</td>
<td>0.084 ± 0.025</td>
</tr>
<tr>
<td>Control</td>
<td>0.046 ± 0.020</td>
<td>0.037 ± 0.022</td>
<td>0.054 ± 0.026</td>
<td>0.029 ± 0.028</td>
<td>0.022 ± 0.026</td>
</tr>
<tr>
<td>p-value</td>
<td>0.05</td>
<td>0.08</td>
<td>0.22</td>
<td>0.36</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>96w-BL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>0.198 ± 0.050</td>
<td>0.167 ± 0.042</td>
<td>0.125 ± 0.050</td>
<td>0.089 ± 0.046</td>
<td>0.102 ± 0.044</td>
</tr>
<tr>
<td>Control</td>
<td>0.125 ± 0.057</td>
<td>0.127 ± 0.070</td>
<td>0.142 ± 0.093</td>
<td>0.134 ± 0.066</td>
<td>0.080 ± 0.043</td>
</tr>
<tr>
<td>p-value</td>
<td>0.40</td>
<td>0.61</td>
<td>0.87</td>
<td>0.59</td>
<td>0.77</td>
</tr>
</tbody>
</table>

There is no significant difference between groups.
VSRAD severity of atrophy in the medial temporal lobe (48w-BL, 96w-BL)

There is no significant difference between groups.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>48w-BL</td>
<td>0.268±0.082</td>
<td>0.014±0.061</td>
</tr>
<tr>
<td>96w-BL</td>
<td>0.343±0.092</td>
<td>-0.020±0.114</td>
</tr>
</tbody>
</table>

48w-BL: p=0.03>0.013  96w-BL: p=0.07>0.013
<table>
<thead>
<tr>
<th></th>
<th>extent of GM atrophy</th>
<th>extent of VOI atrophy</th>
<th>ratio of GM/VOI atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>48w-BL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>0.228±0.242</td>
<td>7.97±3.23</td>
<td>0.849±0.484</td>
</tr>
<tr>
<td>Control</td>
<td>−0.360±0.249</td>
<td>−0.49±2.57</td>
<td>0.162±0.328</td>
</tr>
<tr>
<td>p-value</td>
<td>0.15</td>
<td>0.11</td>
<td>0.37</td>
</tr>
<tr>
<td>96w-BL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>0.813±0.435</td>
<td>11.67±3.07</td>
<td>0.942±0.423</td>
</tr>
<tr>
<td>Control</td>
<td>0.003±0.399</td>
<td>−5.41±2.87</td>
<td>−0.760±0.210</td>
</tr>
<tr>
<td>p-value</td>
<td>0.25</td>
<td>0.03</td>
<td>0.03</td>
</tr>
</tbody>
</table>

There is no significant difference between groups. (significant level = 0.013)
MMSE, ADAS score change (24w-BL, 48w-BL, 72w-BL)

There is no significant difference between groups.

p-value 0.34 0.86 0.55

Red: Intervention  Blue: control
FAB, LMⅠA, LMⅡA score change (24w–BL, 48w–BL, 72w–BL)

FAB

LMⅠA

LMⅡA

Red: Intervention  Blue: control

There is no significant difference between groups.
Discussion

• There are no significant difference between two groups on the 48 week change of amyloid beta deposition, brain atrophy.

• Ninety-six week data can’t be assessed correctly because of its small sample size.

• There are also no significant difference between two groups on the 24 week, 48 week, and 72 week change of psychological test score.
Limitation

• This research is a open-label study, not double blind randomized trial.
• There may be selective bias. Patients who progress to dementia faster may tend to join the intervention group.
• Sample size is small.
• We need more samples to assess the difference of psychological test.
• Sample size of the previous studies is 28\textsuperscript{1) and 143\textsuperscript{2).}

Disclosure of Conflict of Interest

- Research founding: Glovia Co., Ltd.