Role of Ginkgo biloba extract as an adjunctive treatment of elderly patients with depression and on the expression of serum S100B

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Abstract
Objective: To explore the effect of ginkgo biloba extract (EGb) as an adjunctive treatment of elderly patients with depression and the effect on the expression of serum S100B.

Methods: 136 elderly patients with depression were divided into EGb + citalopram (Cit) group and Cit group equally. Efficacy was evaluated by Hamilton Depression Rating Scale (HAMD), Wisconsin Card Classification Test (WCST) was used to evaluate cognitive function. Serum S100B expression was measured with ELISA. The relationship of S100B with HAMD, Hamilton Anxiety Scale (HAMA) score, and WCST results was evaluated subsequently.

Results: The time of onset of efficacy was significantly shorter in EGb + Cit group. There were significant differences in HAMD and HAMA scores after treatment than before treatment between groups (all P < .05). After treatment, total number of WCST test, the number of continuous errors and non-persistent errors in both groups were less than those before treatment. The correct number and classifications number were increased than before treatment. In EGb + Cit group, correct numbers and classifications were increased, and the number of persistent errors was decreased. After treatment, S100B level was decreased, and S100B levels change in EGb + Cit group was greater than in Cit group. Serum S100B level was positively correlated with HAMD and HAMA scores before treatment and positively correlated with persistent errors number in WCST.

Conclusion: EGb, as an adjunctive treatment, can effectively improve depressive symptoms and reduce expression of serum S100B, which is a marker of brain injury, suggesting that EGb restores neurologic function during the treatment of depression in elderly patients and S100B participates in the therapeutic mechanism. EGb combined with depressive drugs plays synergistic role, and the time of onset of efficacy is faster than single antidepressants.

Abbreviations: 5-HT = 5-hydroxytryptamine, Cit = citalopram, EGb = ginkgo biloba extract, HAMD = Hamilton Depression Rating Scale, PAF = platelet activating factor, SSRIs = selective serotonin reuptake inhibitors, WCST = Wisconsin Card Classification Test.

Keywords: depression, effect, elderly, ginkgo biloba extract, HAMA, HAMD, serum S100B, WCST

1. Introduction
Depression is a common and chronic disease.[1] It is a group of mood disorders or affective disorders caused by various causes.[2] Depression is primarily characterized by persistent low mood, loss of interest and pleasure, slow thinking, reduced willingness to act, serious suicidal thoughts and behaviors, as well as illusions and delusions in some patients.[3,4] The disease has a tendency to relapse, but the etiology and pathogenesis are still unclear so far.[5,6] The abnormal activation of microglia causes astrocyte glutamatergic dysfunction, contributing to vulnerability to stress; whereas the microglial antagonist could lower inflammatory process and restore the synaptic plasticity in the hippocampal CA1 region.[7,8] Traditional tricyclic antidepressants are now being replaced by the new selective serotonin reuptake inhibitors (SSRIs), the most commonly administered antidepressants for the treatment of depression which have minimal psychomotor and anticholinergic effects.[9–11] Citalopram (Cit) together with fluoxetine, fluvoxamine, paroxetine and sertraline belong to SSRIs.[12] Cit is effective in the treatment of major depression with a substantially better tolerability profile and the absence of anticholinergic adverse effects or cardiotoxic effects.[11,13] Serotonin-norepinephrine reuptake inhibitor (SNRI), such as duloxetine, is a potent inhibitor of the inactivation by neuronal reuptake of both serotonin and norepinephrine and shows good efficacy in major depressive disorder.[14] Recent studies have demonstrated the advantages of adjunctive use of Chinese herbal medicine in the treatment of depression without causing any serious adverse effects.[15,16]

The main active ingredients of ginkgo biloba extract (EGb) are flavonoids and terpene lactone.[17] The main pharmacological action of EGb for the central nervous system is to inhibit platelet activating factor (PAF), promote blood circulation, increase blood flow, improve hemorheological changes, resist free
radicals, increase tolerance to hypoxia, prevent brain edema induced by trauma and toxin, and protect nerves. Recent studies have shown that EGB can improve the cognitive function of attention and memory in patients with mild to moderate Alzheimer’s disease, and its curative effect is similar to that of Donepezil (cholinesterase inhibitor).

S100B is mainly distributed in the astrocytes and oligodendroglia cells in the central nervous system and the peripheral nervous system in mammals, and some of the neurons. S100B is also known as a glial-derived protein. As an intracellular calcium receptor protein, S100B protein has extensive biological activities, such as intercellular connection, growth, cell structure, energy metabolism, movement and conduction and intracellular signal. Moreover, S100B has been reported to be implicated in regulating inflammation, learning and memory ability, and neural plasticity. Interestingly, antidepressants can reduce the concentration of S100B with the improvement of depressive symptoms. In both animal models and patients of depression, serum S100B levels were observed to be decreased. S100B is a neurotrophic factor that is involved in neuroplasticity, which is disrupted in depression; whereas, antidepressants can restore enhanced neuroplasticity in response to high serum S100B levels.

Accordingly, the present study was carried out to explore the efficacy and adverse effects of EGB as an adjunctive treatment of elderly patients with depression and the effect on the expression of serum S100B. We hypothesized that EGB combined with Cit, as an SSRI, was superior to conventional SSRIs in the treatment of elderly patients with depression, and EGB may increase cognitive function in patients with late-onset depression.

2. Materials and methods

2.1. Study subjects

A total of 136 elderly patients with depression were selected in the Department of Psychiatry in our hospital in March 2015~March 2017. Among the 136 cases, there were 3 male and 72 female, with a mean age of (67.3 ± 4.8) years. Inclusion criteria:

1) Age range: ≥60 years old;
2) In accordance with the diagnostic criteria for depressive episodes mentioned by Diagnostic and Statistical Manual of Mental Disorders issued by American Psychiatric Association (DSM-V); Hamilton depression scale ≥21 points; 3) Patients who did not take plenty of medicines or alcohol within 2 weeks, or wasn’t addicted to alcohol or medicines (including lifelong addicts to alcohol or substance addicts or substance abusers);
3) No organic somatic diseases in the brain or, somatic diseases (including severe cardiovascular diseases, kidney diseases, liver diseases, endocrine diseases or blood diseases);
4) No schizophrenia, mania, bipolar disorder and other psychiatric disorders;
5) Patients with no allergy to EGB and Cit. If there was a history of psychotropic drugs administration, the patient needed to withdraw the drugs for 2 weeks as a cleaning period. 7) Non-illiterate patients.

2.2. Therapeutic method

Patients in Cit group were treated with Cit. Concrete measures: Oral administration of Cit for patients in this group, 20mg per day, and 1 time a day. On the basis of Cit group, EGb + Cit group was treated with EGB Tablets (Harbin HaoBo Pharmaceutical Co., Ltd.) for treatment, 19.2mg per time, and 3 times a day. Two groups of patients were allowed to use a small amount of benzodiazepines to control insomnia and other symptoms when necessary.

2.3. Observation indexes and evaluation of curative effect

Before treatment and after treatment, 5 mL of fasting venous blood was collected from the 2 groups of patients at 6:30 to 8:00 in the morning. Then the blood sample was then placed at room temperature for 30 minutes, followed by centrifugation at 2500 r/min for 15 min. After this, the sample was stored at −80°C for further usage after the separation of serum. The serum S100B levels were measured according to the instructions of the human S100B ELISA Kit (Nanjing JianCheng Biotechnology Co., Ltd., Nanjing, Jiangsu, China). Furthermore, 2 trained psychiatrists (Kappa=0.92) evaluated the efficacy of the subjects at the beginning of treatment and at the 2, 4, 6, 8, and 12 weekends after the treatment regularly. The curative effect was evaluated by the Hamilton Depression Rating Scale (HAMD) and the Hamilton Anxiety Scale (HAMAI), and the adverse effects in the treatment were evaluated by the Treatment Emergent Symptoms Scale (TESS). The Wisconsin Card Classification Test (WCST) with unified guidance was used to evaluate the cognitive function of the patients with depression. Examinations of routine blood test, routine urine test, liver function, renal function and electrocardiogram were performed once a week during the treatment.

2.4. Statistical analysis

SPSS21.0 (SPSS, Inc, Chicago, IL) software package was used to analyze all the data. The categorical data were expressed as the rate, percentage or the constituent ratio, and chi-square test was used for statistical analysis. The measurement data were expressed as mean ± standard deviation. Analysis of variance (ANOVA) analysis was used in comparison among multiple groups, and t test was used in comparison between 2 groups. Correlation analysis was performed with Pearson correlation analysis. P < .05 means that the difference was statistically significant.

3. Results

3.1. General data comparison

The 136 included subjects were divided into 2 groups of EGb + Cit group (68 cases) and Cit group (68 cases). In the 68 cases in the Cit group, there were 31 males and 37 females, with an average age of (66.8 ± 2.3) years. Meanwhile, in the 68 cases of EGb + Cit group, there were 33 males and 35 females, with an mean age of (66.4 ± 2.4) years. There was no obvious statistical difference in the gender (male/female), age, body weight, body mass index (BMI), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and course of disease (P > .05), which was shown in Table 1. The above results suggested the 2 groups were comparable.
3.2. Comparison of the time of onset of efficacy between groups

The time of onset of efficacy of EGb+Cit group and Cit group was recorded, and the results showed that the time of onset of efficacy of EGb+Cit group was 4−15d, with a mean time of (6.2±1.8)d; besides, the time of onset of efficacy of Cit group was 10−25d, with a mean time of (13.9±3.7)d. The difference between the two groups was significant regarding the time of onset of efficacy (P<.05) (Fig. 1), as shown in Table 2. The results indicated that the effect of EGb group was faster than Cit group.

3.3. HAMD and HAMA scores comparison between groups before and after treatment

The results of HAMD and HAMA scores in EGb+Cit group and Cit group were compared before and after treatment. The results of comparative analysis showed that there was no significant difference in HAMD and HAMA scores between the 2 groups before treatment (P>.05). The scores of HAMD and HAMA were gradually reduced during the period of treatment, besides, there were significant differences between the two groups of HAMD and HAMA scores at the end of 2, 4, 6, 8, and 12 weeks of the treatment (P<.01). HAMD and HAMA scores were significantly different at the end of 2 weeks in the two groups (P<.05), and significant differences were found following 4, 6, 8, and 12 weeks of treatment (P<.01). The results suggested that the EGb+Cit group had more obvious effect, and the antidepressant and anti-anxiety effect was better than that of the Cit group.

3.4. Comparison of curative effect between groups

Evaluation of clinical curative effect was achieved by the current four-level assessment standard in China. HAMD reduction rate > 75%, complete recovery; ≥ 50%, basic recovery; ≥ 25%, improvement; < 25%, ineffective. In the 2 week treatment, the effective rate was 44.12% and 80.88% in EGb+Cit group and Cit group (P<.05). In the 4, 6, 8, and 12 weeks of treatment, the effective rate of Cit group was 77.94%, 85.29%, 89.70%, and 94.12%, respectively, and it was 82.35%, 88.23%, 92.65%, and

Table 1

|                  | Cit group | EGb + Cit group | χ²/ t        | P       |
|------------------|-----------|-----------------|--------------|---------|
| Gender (Male/Female) | 31/37     | 33/35           | 0.118        | .731    |
| Age, Year        | 66.82±3.35| 66.48±4.12      | 0.528        | .598    |
| Weight, kg       | 66.31±7.13| 65.86±7.86      | 0.350        | .727    |
| BMI, kg/m²       | 20.18±1.26| 20.27±1.25      | 0.418        | .676    |
| HR, beat/min     | 73.54±2.24| 74.11±2.01      | 1.562        | .121    |
| SBP, mmHg        | 132.12±12.18| 133.05±11.68  | 0.454        | .690    |
| DBP, mmHg        | 87.24±6.06  | 86.63±5.92      | 0.594        | .553    |
| Course of disease, Month | 3.8±2.7     | 3.8±3.0         | 0.409        | .668    |

BMI = body mass index; Cit = citalopram; DBP = diastolic blood pressure; EGb = ginkgo biloba extract; HR = heart rate; SBP = systolic blood pressure.

Figure 1. Comparison of the time of onset of efficacy between groups.
There was no significant difference in the comparison between groups (P > .05), which was shown in Table 3.

### 3.5. Adverse effect comparison between groups

During the treatment, the adverse effect of the 2 groups was recorded according to the TESS (Table 4). The adverse effects of the 2 groups were compared. The results showed that 19 cases had adverse effects in Cit group, the occurrence of which was 27.94%. In EGb + Cit group, 14 cases had adverse effects, the occurrence of which was 20.59%. There was no significant difference in the occurrence of adverse effects between the two groups (χ² = 0.610, P = .435). The results showed that the combination of EGb and Cit did not increase adverse effects.

### Table 2

Comparison of the results of HAMD and HAMA scores between the 2 groups before and after treatment.

| Scales      | Cit group | EGb + Cit group | t     | P     |
|-------------|-----------|-----------------|-------|-------|
| HAMD        |           |                 |       |       |
| Before treatment | 31.04 ± 7.26 | 31.03 ± 7.24  | 0.008 | .994  |
| 2 weeks of treatment | 24.01 ± 5.68* | 21.87 ± 5.24*  | 2.284 | .024  |
| 4 weeks of treatment | 20.65 ± 5.24* | 17.52 ± 4.42*  | 3.765 | <.001 |
| 6 weeks of treatment | 18.76 ± 4.89* | 15.24 ± 3.84*  | 4.669 | <.001 |
| 8 weeks of treatment | 16.39 ± 4.62* | 12.99 ± 3.02*  | 5.080 | <.001 |
| 12 weeks of treatment | 11.36 ± 5.24* | 8.68 ± 5.23*   | 5.376 | <.001 |
| HAMA        |           |                 |       |       |
| Before treatment | 23.25 ± 5.45 | 23.12 ± 5.23  | 0.142 | .887  |
| 2 weeks of treatment | 16.78 ± 4.45* | 15.09 ± 4.42*  | 2.199 | .030  |
| 4 weeks of treatment | 14.78 ± 4.01* | 12.23 ± 3.68*  | 3.864 | <.001 |
| 6 weeks of treatment | 13.45 ± 3.25* | 11.35 ± 2.89*  | 3.982 | <.001 |
| 8 weeks of treatment | 12.21 ± 2.34* | 10.24 ± 2.66*  | 4.585 | <.001 |
| 12 weeks of treatment | 10.67 ± 2.12* | 8.26 ± 2.12*   | 6.338 | <.001 |

Cit = citalopram, HAMA = Hamilton Anxiety Scale, HAMD = Hamilton Depression Rating Scale.

### Table 3

Comparison of clinical effects of 2 groups.

| Groups      | Cure | Significant improvement | Improvement | Invalid | Effective rate |
|-------------|------|-------------------------|-------------|---------|----------------|
| Cit group   |      |                         |             |         |                |
| 2 weeks of treatment | 7    | 10                      | 13          | 38      | 44.12%         |
| 4 weeks of treatment | 14   | 19                      | 20          | 15      | 77.94%         |
| 6 weeks of treatment | 21   | 20                      | 17          | 10      | 85.29%         |
| 8 weeks of treatment | 30   | 17                      | 14          | 7       | 89.70%         |
| 12 weeks of treatment | 40   | 13                      | 11          | 4       | 94.12%         |
| EGb + Cit group | 15   | 18                      | 22          | 13      | 88.88%*        |
| 2 weeks of treatment | 22   | 19                      | 16          | 11      | 83.82%         |
| 4 weeks of treatment | 12   | 10                      | 15          | 8       | 88.23%         |
| 6 weeks of treatment | 29   | 16                      | 15          | 8       | 88.23%         |
| 8 weeks of treatment | 38   | 14                      | 11          | 5       | 92.65%         |
| 12 weeks of treatment | 46   | 12                      | 8           | 2       | 97.06%         |

EGb = ginkgo biloba extract.

### Table 4

Comparison of adverse reaction between groups.

| Adverse reaction                  | Cit group | EGb + Cit group |
|-----------------------------------|-----------|-----------------|
| Increased appetite                | 0         | 0               |
| Anorexia                          | 10        | 14.7            |
| Constipation                      | 6         | 8.82            |
| Gain weight                       | 0         | 0.00            |
| Dizziness and weakness            | 8         | 11.76           |
| Dry mouth                         | 13        | 19.11           |
| Dreaminess                        | 19        | 27.94           |
| Insomnia                          | 14        | 20.59           |
| Nausea and vomiting               | 9         | 13.24           |
| Elevation of glutamic pyruvic transaminase | 0         | 0.00            |
| Irritability and excitement       | 8         | 11.76           |
| Excessive stabilization           | 0         | 0.00            |
| Tachycardia                       | 3         | 4.41            |

Cit = citalopram, EGb = ginkgo biloba extract.
3.6. Comparison of WCST results before and after treatment in two groups

WCST was used to evaluate cognitive function in elderly patients with depression. Corresponding results revealed that there were no statistical differences of the total number of WCST, the correct number, the number of persistent errors, the number of non-persistent errors, and the number of classifications before treatment of the 2 groups (\( P > .05 \)). After 12 weeks of treatment, the total number of WCST, the number of persistent errors, and the number of non-persistent errors were less in the two groups than those before the treatment (\( P < .05 \)), while the correct number and the number of classifications were increased before the treatment (\( P < .05 \)). The number of correct and classification in Egb+Cit group was higher than that in Cit group, and the difference was statistically significant (\( P < .05 \)). Detailed information was shown in Table 5.

3.7. Detection and analysis of the level of S100B protein before and after treatment in two groups

Serum S100B protein level in two groups of elderly patients with depression was detected by enzyme-linked immunosorbent assay before and after treatment. It was found that (Fig. 2) before treatment, there was no significant difference in the content of S100B protein between the Egb+Cit group and the Cit group (\( P > .05 \)). After treatment, S100B level was decreased significantly in the 2 groups (\( P < .05 \)), the change of the level of S100B in Egb+Cit group was significantly higher than that in Cit group (\( P < .05 \)).

3.8. Relationship of HAMD and HAMA scores, and WCST results with serum S100B protein level

The relationship between serum S100B protein level and HAMD, HAMA, and WCST results (total number of tests, correct number, the number of persistent errors, the number of non-persistent errors, and number of classifications) was evaluated in elderly depressive patients by Pearson correlation analysis before treatment. Correlation analysis results (Table 6) showed that the level of serum S100B protein before treatment was positively correlated with the HAMD and HAMA scores (\( r = 0.558, P < .001 \); \( r = 0.582, P < .001 \)), and was positively correlated with the number of persistent errors in WCST (\( r = 0.543, P < .001 \)). However, there was no correlation between serum S100B level before treatment and the results of WCST (total number of tests, correct number, the number of persistent errors, the number of non-persistent errors, number of classifications) (\( P > .05 \)).

4. Discussion

Egb, as a natural medicine, contains flavonoids, lactone, polyisoenol, and other active ingredients.\(^{38}\) It has mild property, few toxic and adverse effects, and definite curative

### Table 5

**Comparison of WCST results before and after treatment in the 2 groups.**

| Items                  | Cit group | Egb+Cit group |
|------------------------|-----------|---------------|
|                        | Before treatment | After treatment | Before treatment | After treatment |
| Total number           | 47.02 ± 1.02 | 43.54 ± 3.46* | 46.89 ± 1.65 | 42.96 ± 3.02* |
| Correct number         | 31.10 ± 6.12 | 34.43 ± 5.02* | 30.99 ± 5.86 | 36.55 ± 6.17* |
| Preservative error number | 5.64 ± 2.5 | 2.45 ± 1.06* | 5.56 ± 2.44 | 2.07 ± 1.01* |
| Non-preservative error number | 10.89 ± 4.65 | 5.21 ± 3.02* | 11.12 ± 5.03 | 4.97 ± 2.56* |
| Classification number  | 4.59 ± 1.32 | 5.59 ± 1.12* | 4.32 ± 1.36 | 6.13 ± 1.20* |

* Comparison with that before treatment, \( P < .05 \).
† Comparison with Cit group, \( P < .05 \).

\( \text{Cit} = \text{citalopram, Egb} = \text{ginkgo biloba extract, WCST} = \text{Wisconsin Card Classification Test.} \)

\( P < 0.001 \)

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![Figure 2](https://via.placeholder.com/150)

**Figure 2.** Detection and analysis of the level of S100B protein before and after treatment in 2 groups.
et al pointed out that patients with major depressive disorders have a small number of non-neural tissues, such as melanocytes, and has many biological functions. In mammals, S100B is a small molecular weight, which is widely distributed in various tissues. It can easily pass through blood-brain barrier and brain injury. In addition, it also exists in most important treatment for geriatric depression. For a long time, the dysfunction of the central 5-hydroxytryptamine (5-HT) system is considered to play a key role in the process of depression. 5-HT can also promote platelet aggregation and vasoconstriction in addition to the release of platelets in the periphery of the center as a neurotransmitter. Because of the dual role of 5-HT dysfunction in promoting depression and promoting thrombosis, 5-HT mediated platelet activation may be a common pathophysiological basis for depression and vascular diseases. Ginkgolide in Egb is a highly exclusive PAF receptor blocker and can antagonize abnormal platelet aggregation and thrombosis caused by PAF. It is thus suggested that Egb may be workable by inhibiting platelet activation in antidepressant therapy. On the other hand, the executive dysfunction associated with depression often leads to the slow, low and unstable antidepressant effects. Since Egb has neuroprotective effect and can improve the cognitive function such as attention and memory, it may also promote the improvement of depressive symptoms.

In addition, there was no significant difference in the occurrence of adverse effects between the 2 groups. It indicates that Egb combined with Cit is well tolerated, safe and suitable for elderly patients with depression. Simultaneously, after treatment, the WCST test, the number of continuous errors and the number of non-persistent errors in the 2 groups were less than those before the treatment. The correct number and the number of classifications were increased compared with those before the treatment. In Egb + Cit group, the number of correct numbers and the number of classifications were increased, and the number of persistent errors was decreased. After treatment, S100B level was decreased significantly in the 2 groups, the change of the level of S100B in Egb + Cit group was significantly greater than that in Cit group. The level of serum S100B was positively correlated with HAMD and HAMA scores before treatment, and a positive correlation was found with the number of persistent errors in WCST.

In conclusion, Egb was an effective adjunctive treatment in improving depressive symptoms and reducing the expression of S100B in serum in the treatment of elderly patients with depression. It played a synergistic role with the combination of Cit, in which the time of onset of efficacy was faster than the single use of antidepressants. Egb may be used in adjunctive therapy to increase cognitive functions in elderly patients with depression. However, there are still limitations in this study. The sample sizes were relatively small and extended investigations should be performed in the future to validate the findings. Also, long-term follow-up observation for the efficacy and adverse effects is needed. Furthermore, future studies are needed to clarify the specific molecular mechanisms associated with the function of Egb.

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