RESEARCH ARTICLE

Ginko Biloba Leaves Extract for the Treatment of Anxiety, Stress, and Depression

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Abstract

Anxiety, stress and depression are exceedingly comorbid psychological illnesses that the predominance will expand to the second most important risk of morbidity and sociodemographic burden. Due to several side-effects of chemical drugs, numerous specialists and patients prefer complementary herbal therapies like *Ginkgo Biloba* Extracts (GBE) to medicate the illnesses. In this review, we summarized the antidepressant, anxiolytic and antistress properties of GBE. We perceived that GBE could be beneficial for treatment of these disorders. Although experience of repeated studies on models and humans have proved reliability of antidepressant properties of GBE, further clinical trials are still required to validate the anti-stress and anti-anxiety effects of GBE on humans. *ASEAN Journal of Psychiatry, Vol. 23(4): April 2022:1-7.*

Keywords: *Ginko Biloba*, Antidepressant, Anxiolytic, Antistress, Herbal Medicine

Introduction

Anxiety and depression are universal brain disorders approximately 7.3% and 7% prevalence. These disorders are characterized by stress-linked mood problems and may cause early death [1,2]. Surprisingly, the prevalence of depression is 3 times higher in young people and women are 1.5 times to 2 times more susceptible to anxiety and depression [3,4]. Sleep disorder, weight loss or gain, retardation, fatigue, concentration and decision-making challenges, and even tenderness of suicide are the most reported depression symptoms [5]. Furthermore, these complications caused a significant number of years of life lost to disability in multiple countries [6]. Therefore, controlling mental health challenges became an important aim for many researchers [7]. Scientists have long been aware of the close relationship between anxiety and depression [8]; moreover, notable comorbidities of these patients cause several difficulties in treatment [9]. For several years, diazepam, defined as Ben Zo Diazepine (BZD), has long been a routine treatment for depression. Over time, specialists replaced diazepam with alprazolam due to its lesser sedation [10]. Despite the proper efficiency of these treatments, all these therapies have considerable adverse effects as well [11].

Herbal therapies have been used for a long time to treat depression. For many years, scientists carried

out many trials to target monoamine transmission systems of the brain, such as Norepin Ephrine (NE), 5-Hydroxytryptamine (5-HT), and dopamine. 20(S)-protopanaxadiol, extracted from ginseng, developing NE and 5-HT in the mice brain and decrease depression pathogenesis. Moreover, paeonia lactiflora pall is another traditional Chinese treatment that restricts depression symptoms. The root extract of this blessed species diminishes monoamine oxidase activity. Albizia julibrissin, Perilla frutescens and several components of Rhodiola rosea are the other ancient candidates for depression treatment. To date, the herbal treatments for anxiety have been emphasized on repairing dysregulated brain mechanisms, such as noradrenergic, glutamatergic, and serotonergic pathways. For example, Bacopa monnieri restricts anxiety by enhancing 5-HT2C receptors. Studies on other species, like valeriana officinalis, centalla asiatica, humulus lupulus, and matricaria recutita showed detectable anti-anxiety properties, based on inhibiting glutamate receptors. *Ginkgo Biloba* Extract (GBE) is another promising herbal treatment for several mental disorders such as dementia and anxiety. Besides, GBE downregulates 5-HT, domapin and NE uptake through an unclear mechanism. Herein, we review the different aspects of GBE effects on depression, anxiety, and stress.

Methods

This study reviews the data about *Ginko biloba* leaves extract for the treatment of anxiety, stress, and depression. English articles were searched up to December 2020 through various databases including ISI Web of Science, SID, Google Scholar, PubMed, Scopus, and Science Direct. The searched keywords included *Ginko biloba*, Antidepressant, Anxiolytic, and Antistress. The references of the relevant studies were also searched manually.

Anti- stress effects of GBE

In 1994 to evaluate the anti-stress properties of *Ginkgo biloba (G. biloba*) leaves among young and old rodent models. The extract of these leaves showed a detectable development of plasma hormones such as norepinephrine, corticosterone, and epinephrine; moreover, despite noxious environmental influences, GBE ameliorates cognitive impairment, especially in old rats. Although the next study on *Ginkgo* showed relatively encouraging treatments for memory and aging-related cognitive disorders but started a new quarrel about anti-stress uses of GBE. Further, Rai et al. carried out another experimental trial on herbal treatments against Chronic Stress (CS) and Acute Stress (AS) to measure anti-stress effects of GBE and Panax ginseng. This study demonstrated that GBE has better success in treating acute stress and Panax ginseng for the latter.

In the following, scientists tried lipophilic extracts of *Ginkgo* leaves (LEG). This study introduced intact carboxylic acid, one of the LEG bioactive components, as a promising anti-depressant and anti-stress agent. Supporting previous results, another trial on mice treated with GBE showed significant anti-stress effects; furthermore, analyzing cortex and hippocampus samples demonstrated no detectable immunoreactivity effect on Cyclic-AMP response element-binding protein. Recently, introduced GBE as a protecting treatment. GBE successfully preserved rodent models against chronic unpredictable mild stress. Therefore, future trials on humans are required to prove the clinical function of this blessed species in controlling stress (Table 1).

Table 1. Summarizes the data of the studies on the anti-stress effects of GBE

Author/year	***In-vivo* studies**	**Outcomes**

Rapin et al./ 1994	In first stage, Mice were allowed to adapt environment for 15 days. Models were divided to different groups based on age 4 months and 20 months and administration placebo, 50 or 100mg/kg GBE). Daily inoculation occurred half an hour before exams continued for 3 weeks.	GBE repaired stress symptoms in both ages. These results proved *G. biloba* leaves as a promising therapy for stress.
Jezova et al./ 2002	The study was designed as a double blind, randomized, parallel, placebo-controlled trial among 70 participants. A single p.o dose of 120mg of *G. biloba*, 40mg/ml GBE or placebo were administered.	GBE decreases blood pressure that may influence effect of stress stimuli on cortisol release.
Rai D et al./ 2003	Daily 100mg/kg *P.ginseng* and 30mg/kg GBE inoculated to male rats.	*G. biloba* is more efficient in acute stress, while *P.ginseng* is proper for chronic stress
Kalkunte et al./ 2007	Rodent models charles foster rats were adapted to the environment a week before the exams. Rats were divided into various groups based on inoculation 1.50mg/kg Ginkocer and GBE, 2.50 or 100 mg/kg LEG. Oral administration was done 1 hour before tests.	LEG successfully restricted stress and significantly improved behavioral status.
Ward et al./ 2002	6 male mice got 100 mg/kg/day GBE for 20 month and were examined by the Morris water maze and elevated plus-maze. At last, tissue samples from hippocampus and cortex were analyzed.	Notable difference (F=4.98 in Morris water maze and no significant result in elevated plus-maze) proved anti-stress effects of GBE. This product had no significant involvement in immunoreactivity to CREB.
Yuan-Qing et al./2017	Study evaluated the function of GBE in rats with unpredictable chronic mild stress.	Marked difference between GBE treatment and Saline treatment. Oral administration of GBE prevents CUMS.

Anti-depressant effects of GBE

Many articles have proved that GBE has significant effects on mental disorders. The first study on a chronic depression cases, treated with an unstable regimen of bupropion plus *Ginkgo*, showed promising results. The mental situation of patients continued to become better even while using GBE without bupropion. Moreover, successful experience of administrating GBE to treat unipolar depression, introduced this product as a reliable therapy.

Experimental studies on the anti-depressant effects of GBE developed notable results. For the first experimental attempts, this agent improved the immobility time of rats in the forced swimming test and tail suspension test. Additionally, Inoculating GBE to male rodent models, treated with lipopolysaccharide, showed a significant elevation of dopamine and appetite level. On the other hand, further studies suggested that decreasing lipid peroxidation and superoxide radical production may be responsible for the anti-depressant activities of GBE. At last, current studies showed that water-soluble polysaccharides of GBE ameliorate anxiety symptoms, in addition to depression, through increasing serotonin and dopamine levels. Therefore, based on several experimental trials, BGE demonstrated promising effects on depression among rodent models.

Studies on GBE anti-depressant effects faced several contrasts. Hemmeter et al. designed an innovative open non-randomized trial to evaluate the anti-depressant effect of *Ginkgo*. Results of this trial showed that GBE improves depression and increases non-rapid eye movement stages among participants. In contrast, previous randomized attempts found no reliable GBE effects on winter depression symptoms. On the other hand, combining venlafaxine with GBE showed valuable results in treating depression symptoms. Moreover, while adding GBE, we can decrease venlafaxine in the treatment regimen to achieve the same efficacy with lower adverse effects. Debates between scientists continued until 2017. To put an endpoint to these controversies, Nikfarjam et al. carried out a trial to appraise the effects of *G. biloba* tablets on major depression and cognitive cases, previously received electroconvulsive therapy. This study suggests that GBEs, such as flavonoids, can significantly restrict cognitive and depression problems. Recent study on combination of GBE with citalopram develops depression symptoms through regulating inflammatory glial-derived proteins (Table 2).

Table 2. Studies addressing the anti-depressant properties of *Ginko biloba*

Author/year	*In-vivo* studies/clinical trials	Outcomes
R. Sealey et al./ 1996	A young patient with unipolar depression received five or six doses of GBE about 135mg/day.	GBE activated NMDA-type glutamate receptor and diminished neurotransmitter uptake, such as norepinephrine, serotonin, acetylcholine and dopamine.
sakakibara et al./ 2006	1) FST: 35 rats were divided into 5 groups and orally treated with: 15mg/kg imipramine (1 group), 5mg/kg, 10mg/kg, and 50 mg/kg (3 groups), DW (1 group). 2) TST: 50 rats were divided into 5 groups and orally treated with: 30mg/kg imipramine (1 group), 10mg/kg, 50mg/kg and 100mg/kg (3 groups), DW (1 group).	GBE improved both FST and TST in experimental models. This result showed that GBE has reliable anti-depressant effect on mice.
Yeh et al./ 2015	8-week-old Male Wistar rats were divided into 2 groups (1.50mg/kg GBE, 2.DW). The treatment continued for 1 week. After inoculation Escherichia coli LPS (100μg/kw), further tests performed: Food consumption, sucrose preference test, and dopamine level.	GBE restricted depressive-like disorders through increasing appetite consumption of food and sucrose and elevating dopamine level.
Rojas et al./ 2011	The study contains 2 control groups (1.Saline without FST/2.Saline with FST) and 2 intervention groups (A.15mg/kg imipramine with FST and B.40mg/kg, 20mg/kg, 10mg/kg or 5mg/kg GBE with FST). After 17 days of implementing FST following injection, analysis of brain tissue and hormone levels performed.	GBE resulted in 39% decrease in immobility of models in FST.

Chen et al./ 2019	The experimental models divided into 2 groups: 1) 300mg/kg GPS 2) 30mg/kg paroxetine. Treatment continued for 4 weeks and 3 days experimentation in the following.	Both GPS and paroxetine showed equal antidepressant properties and diminished immobility time in all tests.
Hemmeter U et al/ 2001	16 patients participated in an open non-randomized study to investigate effects of GBE on sleep situation and cognitive performance. The first group received 200mg/d trimipramine-monotherapy for 6 weeks and the latter group got 240mg/d GBE therapy for 4 weeks.	In this study GBE ameliorated sleep regulation and increased non-REM sleep through diminishing tonic CRH-activity.
Lingaerde O et al./1999	27 SAD cases, suffering from WD, participated in this study to investigate anti-depression effects of tablets, containing GBE (for 10 weeks).	The result showed no significant difference between groups and resulted in an unsuccessful administration of GBE.
Qin XS et al./ 2005	Depression rats, treated with combination of venlafaxine and GBE. Detection of BDNF and measuring behavioral changes performed to investigate anti-depressant effects of this regimen.	Adding GBE to venlafaxine showed promising results in treating depression models.
Liang Z-H et al./ 2019	Scientists inoculated GBE for 80 PSD patients to evaluate whether they can decrease venlafaxine doses in PSD treatment.	While adding GBE, the researchers successfully decreased venlafaxine and achieved the same efficacy with lower adverse effects.
Nikfarjam et al. /2012	81 patients were divided into 2 group: 1) 3 times ECT in a week with a placebo. 2) 3 times ECT in a week with a capsule containing GBE. After intervention, Hamilton questionnaire and MMSE was taken.	Both exams showed that GBE provides significant development in depression and cognitive disorders. Therefore, GBE would be a good adjuvant treatment alongside ECT.
Dai et al./ 2018	136 patients suffering from depression were divided into 2 groups: 1) GBE + Cit 2) Cit	GBE significantly controlled depressive symptoms through decreasing S100B and had synergistic effects in combination with Cit.

Hence, we require designing novel extended trials among human subjects to light more aspects of GBE and its combinations with other therapies in controlling depression.

Anxiolytic effects of GBE

From the first studies, GBE showed unique anti-anxiety effects. In an experimental trial, flumazenil significantly neutralized traditional therapies diazepam but showed no obstruction on GBE activities. Surprisingly, low and high doses of GBE showed reliable efficiency and safety in controlling anxiety. Furthermore, combining GBE regimen with traditional therapies improved anxiety, fatigue and tiredness through enhancing cerebrovascular perfusion and strong antioxidant activities. Despite GBE provides reliable treatments with and without other drugs for anxiety, further studies are still required to

discover all aspects of this merciful herbal treatment.

Conclusion

Extract of *G. biloba* leaves showed promising efficiency and safety in several studies. The different components of *G. biloba* control mental disorders through regulating neurobiological mechanisms such as dopamine, serotonin and inflammatory glial-derived proteins. Despite the long history of repeated studies on rats and humans, that proved GBE as a reliable anti-depressant treatment, we require further clinical trials to evaluate the anxiolytic and anti-stress effects of GBE on humans.

Abbreviation

GBE: Gingko Biloba Extract; g Biloba: ginkgo Biloba; po: per os; p. Ginseng: panax Ginseng; leg: lipophilic extracts of ginkgo leaves; creb: cyclic-amp response element binding; cums: chronic unpredictable mild stress; nmda receptor: n-methyl-d-aspartate receptor; fst: forced swimming test; dw: deionized water; tst: tail suspension test; lps: lipopolysaccharides; gps: ginkgo biloba leaves; non-rem: non rapid eye movement; crh: corticotropin releasing hormone; sad: seasonal affective disorders; wd: winter depression; bdnf: brain-derived neurotrophic factor; psd: post-stroke depression; ect: electroconvulsive therapy; mmse: mini mental state exam; cit: citalopram; s100b: s100 calcium-binding protein b; hama: hamilton rating scale for anxiety depression inventory ii:bdi-ii

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