Antidepressive effect of *Gastrodia elata* Bl. on the forced-swimming test in rats

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**Abbreviations Used:** CSF, cerebrospinal fluid; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; FST, forced-swimming test; GE, *Gastrodia elata* Bl. extract; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin, 5-hydroxytryptophan; HVA, homovanillic acid; MDD, Major depression disorder

**Running title:** Antidepressive effect of *Gastrodia elata* Bl.
Abstract

Depression is one of the most common psychiatric disorders, with substantial high morbidity and mortality. The efficacy of pharmacotherapy is not desirable in clinical use. Thus, looking for the alternative treatments, such as a traditional herb with antidepressant effect and minimal side effect is important. The aim of this study is to test the antidepressant effect of *Gastrodia elata* Bl. extract (GE) using forced-swimming test (FST), a widely used animal model for depression in rodents.

Eighteen Spraque-Dawley rats were randomly assigned to three groups: control, GE, and Fluoxetine groups, treated with 1 ml water, 1 g/kg bw of GE, and 15 mg/kg bw of fluoxetine, respectively. Those samples were administered by gavage to rats 23.5, 4.5, and 1 h prior to the test session of FST. After FST, the animals were sacrificed and their brains were collected for the analysis of the monoamines related to depression, 5-HT, 5-HIAA, DA, DOPAC, and HVA, using HPLC-ECD. The results revealed that the duration of immobility was significantly decreased in GE group compared with control ($p < 0.05$). The concentration of 5-HT, 5-HIAA, and the ratio of 5-HT/5-HIAA in frontal cortex, amygdala, and hippocampus were not significantly different between GE and control groups. But administration of GE increased the DA concentration ($p < 0.05$) and decreased the concentration of DOPAC ($p < 0.01$) and the ratio of DOPAC/DA ($p < 0.05$) in striatum significantly compared to that of the control. The
results of this study support that *Gastrodia elata* Bl. extract modulates the turnover of DA and its metabolites in rats, and thus probably possesses the antidepressive effect in rats.

**Keywords:** *Gastrodia elata* Bl.; Antidepresson; Forced-swimming test; Serotonin; Dopamine
1. Introduction

Major depressive disorder (MDD) is among the most prevalent psychiatric disorders. The World Health Organization (WHO) estimates that major depression is the second greatest single cause of disability worldwide (Murray and Lopez, 1997). The lifetime prevalence of depression is greater than 10% (Kessler et al., 1994). About 2/3 of patients with depressive disorder have suicidal attempts, and suicide is estimated to be the cause of death in up to 15% of individuals with depression (Jamison and Goodwin, 1999, Druss et al., 2000). Depression affects the patients either physical or mental conditions seriously, but only less than 20% patients with depression receive psychiatry therapy and less than 10% patients take suitable medication. (Lepine et al., 1997, Parikh et al., 1999). The reasons that depression is rarely diagnosed and treated are complex, such as patients with depression are unwilling to take medicine, side effects occurred during treatment, poor compliance and poor therapeutic effect (Demyttenaere, 2003). The effects of clinical therapies in depression are not desirable. Less than 2/3 patients respond to psychiatric treatments (i.e. medication or psychotherapy) in 8 weeks; the others need to spend more time or try other therapies. In addition, about 1/3 patients have poor compliance to their antidepressant treatments. Stop taking medication is common in clinical treatment (Anderson and Tomenson, 1995, Pampallona et al., 2002). It is crucial to look for the alternative treatments with balanced effect between the effects and side effects. Thus, determining the antidepressant effects of traditional medicine by scientific
method, and finding the effective ingredients of antidepressant from botanicals with low side effects are expected.

The forced-swimming test (FST), developed by Porsolt et al (Porsolt et al., 1977, Porsolt et al., 1978), has been widely used to predict the clinical efficacy of antidepressant drugs. The rat FST is usually conducted with two sessions, which are a 15-minute pretest session on day 1 and a 5-minute test session on day 2. The “behavioral despair” is defined as an animal’s reaction to the inability to escape from a stressful environment. The pretest forced swimming stress decreases the latency to the induction of behavioral immobility from the second test exposure. Administration of antidepressant agents before the first session or between the first and second session effectively decrease the immobility time and increase the active behaviors; this is consistent with a therapeutic effect of increasing escape-directed activities (Page et al., 2003). The effects of antidepressants has made the FST a valid animal model for depression (Detke et al., 1995, Lucki, 1997).

Major depressive disorders have traditionally been considered a neurochemical disorder etiologically (Kandel, 2000). Assessments of cerebrospinal fluid (CSF) chemistry, neuroendocrine responses to pharmacological challenge, and neuroreceptor and transporter binding have demonstrated the abnormalities in the serotonergic, noradrenergic and dopaminergic systems in patients with major depressive disorders (Manji et al., 2001). Previous studies demonstrated that monoamine concentration in rodents’ brain was
significantly changed after FST. After the 5-min test session of FST, DOPAC and HVA were significantly increased in rats’ striatum, and the ratio of 5-HIAA/5-HT was increased significantly in frontal cortex and amygdala (Connor et al., 1997). Dialysate content of 5-HT and 5-HIAA in different brain regions were modulated by FST (Kirby et al., 1995).

Gastrodiae rhizoma, the dry tuber of *Gastrodia elata* Bl. known as Tianma in Chinese, is one of the traditional Chinese medicines. Gastrodin, vanillyl alcohol, p-hydroxybenzylaldehyde, vanillin and p-hydroxybenzyl alcohol are the major active components of *Gastrodia elata* Bl. (Zhao et al., 1999, Cao et al., 2001). Recent studies have shown that *Gastrodia elata* Bl. gives anticonvulsive (Hsieh et al., 1999, Hsieh et al., 2000, Hsieh et al., 2001), antioxidative and free radical scavenging (Liu and Mori, 1992, Liu and Mori, 1993, Ha et al., 2000, Hsieh et al., 2001), learning improvement (Wu et al., 1996), memory consolidation and retrieval (Hsieh et al., 1997) and anti-fungal effects (Xu et al., 1998, Wang et al., 2001).

The objectives of the present investigation were to examine the antidepressant effects of *Gastrodia elata* Bl. extract using the animal behavioral model FST, and to analyze the neurotransmitter concentration in brain regions related to depression for determining the possible antidepressant mechanism of *Gastrodia elata* Bl.

2. Materials and methods
2.1. Materials and Chemicals

Extract of *Gastrodia elata* Bl. (GE) was obtained from the Koda Pharmaceutical Com. Ltd. (Taoyuan, Taiwan). Five kilograms of crude GE was extracted twice with 35 and 25 liters of water for boiling 1 hour and 50 min, respectively. The extract was filtered and freeze-dried. The total yield was 944.2 g (18.9%). The freeze-dried GE extract was authenticated by the high performance liquid chromatography (HPLC) system (Hitachi Instruments Service Co., Ltd., Interface D-700, Pump L-7100, UV-Vis Detector L-7420, Ibaraki-ken, Japan) using vanillyl alcohol as a standard in the Koda Pharmaceutical Co., Ltd. Fluoxetine was provided by Eli Lilly and Company, Taiwan. Ascorbic acid (Ultra, purity 99%), pargyline and isoproterenol were purchased from Sigma (St. Louis, MO, USA). EDTA (ethylenediamine tetraacetic acid) was purchased from Riedel-de Haen (Seelze, Germany). SOS (1-octanesulfonic acid, sodium salt) was purchased from J. T. Backer Inc. (phillipsburg, NJ, USA). TEA (triethylamine) was purchased from Tedia (Fairfield, OH, USA). And NaH$_2$PO$_4$ (sodium dihydrogen phosphate) was purchased from Merck KGaA (Darmstadt, Germany).

2.2. Animals

Six weeks old, male, Sprague-Dawley rats (National Laboratory Animal Center, Taipei, Taiwan) weighted 316.5 ± 0.5 g were subjects. Rats were housed at the animal room with a 12 hr light : dark cycle and the temperature were controlled at 23 ± 2 °C. They were housed two rats of each cage with food (PMI Feed, St. Louis, MO, USA) and deionized water provided *ad*
libitum.

2.3. Forced-swimming test

Experimental procedures were held as rats at 7 to 8 weeks old. Animals were randomly assigned into three groups: control group, treatment (GE) group, and positive control (fluoxetine) group. Deionized water 1ml, Gastrodia elata Bl. extract (GE) 1g/kg bw, and fluoxetine 15 mg/kg bw were administered by gavage in control, GE, and Fluoxetine group, respectively. The samples were given three times following the 15-min pretest, at 23.5, 4.5, and 1 h prior to the swim test. The test session was videotaped. Activity was defined as the swimming, diving, jumping, or strongly moving all four limbs breaking the surface of the water or scratching the walls. Immobility was defined when no additional activity was observed other than that necessary to keep the rat’s head above the water.

The apparatus of the test is a glass cylinder (20 cm in diameter) filled with water about 30-cm depth at room temperature so that the rat could not touch the bottom with his hind paws. Animals were exposed to a pretest for 15 min and after 24 h they were exposed to a 5-min test. Rats were placed into the cylinder in the pretest and test sessions. After pretest, the rats were removed from the water, dried and placed into original cages.

2.4. Quantification of monoamines

Immediately following the 5-min swim exposure, rats were sacrificed by decapitation. Brains
were removed and the frontal cortex, striatum, hippocampus, and amygdala were rapidly dissected according to Glowinski method (Glowinsk and Iversen, 1966) on ice-cold plate. Concentrations of serotonin (5-hydroxytryptophan, 5-HT), 5-hydroxyindoleacetic acid (5-HIAA), dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were measured by high performance liquid chromatography (HPLC, BSA, West Lafayette, IN, USA) coupled with electrochemical detector (ECD, BSA, West Lafayette, IN, USA).

Four sections of brain tissue were stored at -80°C for future use. All tissues were homogenized in 5 ml extract solution according to the method of Cheng et al. (Cheng et al., 1993) with modification. The tissue of amygdala was tiny, so the amygdala of two rats were gathered and then homogenized together, and the other parts of sections (frontal cortex, striatum and hippocampus) were homogenized alone, respectively. The extract solution was 0.1N HCl contained 0.1 μM ascorbic acid, 1.5mg/100ml pargyline and 50 pg/μl isoproterenol. Homogenates were centrifuged at 10000 × g for 20 min at 4°C. After filtered (0.22 μm), the supernatant was injected onto the column (BAS MF-6213, 3 μm, 3.2 × 100 mm). The mobile phase contained 20.5 g NaH₂PO₄, EDTA 185 mg, SOS 130 mg, methanol 75 mL, TEA 1 mL/L, and was adjusted to pH 3.0 using 85% phosphoric acid. The flow rate was 500 μL/min. Electrochemical detector (Amperometric Detector LC-4C, Range 10 nA, Filter 0.1 Hz, AppE cell 0.750V) was coupled to the HPLC with autosampler (CMA 200 Refrigerated...
Microsampler, Stockholm, Sweden).

2.5. Data analysis

Results were expressed as mean±SD. Data were analyzed by unpaired Student’s t-test. Data were considered significantly different when $p < 0.05$.

3. Results

3.1. Animal behaviors in forced swimming test

In the forced-swimming test, the immobility time of control, GE, and Fluoxetine group was 125.3, 90.3 and 130.8 sec respectively. As shown in Fig. 1, administration of GE 1g/kg bw 3 times prior to the test session can diminished the duration of immobility compared with control group ($p < 0.01$); and the activity time was relative longer in GE group. The activity time was 174.7, 209.7 and 169.2 sec in control, GE and Fluoxetine groups respectively. But the immobility time was not significant different between the control and positive group (treated with 15 mg/kg bw fluoxetine).

3.2. Serotonin, dopamine, and their metabolites in brain

The concentration of 5-HT in frontal cortex was significantly increased in Fluoxetine group, administered with 15 mg/kg bw fluoxetine 3 times in 24 h, compared with the controls (shown in Table 1). But the concentrations of 5-HT and 5-HIAA in frontal cortex,
hippocampus and amygdala were not significantly different between GE and control groups (Table 1). The ratio of 5-HT/5-HIAA (data not shown), i.e. the turnover of serotonin, was not affected in Fluoxetine and GE groups.

The concentrations of DA and its metabolite DOPAC and HVA in striatum are shown in Table 2. The concentration of DA was increased in GE group compared with control ($p < 0.05$), but not significantly different between Fluoxetine and control groups. The concentration of DOPAC was significantly decreased in GE and Fluoxetine group compared with control ($p < 0.01$). The turnover of DA in striatum is shown in Fig. 2. $(\text{DOPAC} + \text{HVA}) / \text{DA}$ was decreased significantly in GE and Fluoxetine groups by unpaired Student’s t-test compared with controls ($p < 0.05$ and $0.01$ in GE and Fluoxetine groups, respectively). The results of the concentration of monoamines in brains were consistent with the results of behavioral test in FST; that is, the extract of *Gastrodia elata* Bl. may act as an antidepressant via affecting the turnover of dopamine.

4. Discussion

Forced-swimming test is a behavioral test which predicts the efficacy of antidepressant treatments. It is a quick, reliable and sensitive animal model (Porsolt et al., 1977). When rodents are exposed to the FST procedure, they show an immobility position, which reflect the “behavioral despair” state (learned helplessness) on the assumption (Porsolt et al., 1978).
Therefore, in terms of the duration of immobility can reflect the extent of depressive affection; the longer the immobility time, the stronger the depressive (despaired) affection.

Fluoxetine, the widely used serotonin selective reuptake inhibitor (SSRI) in clinical, was selected as positive control in this study. But the results of FST showed that fluoxetine had no significant effects on antidepression in acute model. However, administration of GE revealed significant antidepressive effects in acute animal model: the activity time was increased and the immobility time was decreased significantly compared with the control group. That is, treatment with the extract of *Gastrodia elata* Bl. can improve the depressive (despaired) affection induced by pretest procedure.

The dosage of fluoxetine in present study (15 mg/kg bw by gavage) was calculated from the suggested dose in clinical (≦ 80 mg). In previous studies, the immobility time was decreased in the forced-swimming test for SD rats treated with fluoxetine subcutaneously 10 mg/kg bw (Page et al., 1999, Reneric et al., 2002) or 20 mg/kg bw (Kirby and Lucki, 1997). Dulawa and his collaborators found that BALB/c mice treated with fluoxetine 18 mg/kg/day (delivered in the drinking water) showed increases in swimming and decreases in immobility relative to control in chronic study (21 days) but no significant different in behavior with control in subchronic study (6 days) (Dulawa et al., 2004). As the results, the reasons that fluoxetine administration had no significant antidepressant effects in the present study may be the difference in route of administration, the insufficiency of the dosage, or the inadequacy of
the experimental exposure periods.

It was found that serotonin (5-HT) is related to the affections (Kandel, 2000). It was found that the concentration of 5-HT in brain and the concentration of 5-HIAA, i.e. the metabolites of 5-HT, in cerebrospinal fluid (CSF) was lower in patients with depressive disorder compared with subjects without depression. The concentration of 5-HIAA and 5-HT in CSF may be related to the symptoms of depression (Asberg et al., 1976, Roy et al., 1989).

Besides serotonin, dopamine is also related to depression. Electroconvulsive therapy (ECT) is one of the methods to treat depression. ECT can improve the symptoms of depression (Strober et al., 1998), and the concentrations of DA and its metabolites and 5-HIAA were significantly altered after ECT treatment (Yoshida et al., 1997, Yoshida et al., 1998).

Gobert and his collaborators collected the CSF via dialysis from Wistar rats treated with 10 mg/kg fluoxetine subcutaneously for 1 h. They found that the dialysate level of 5-HT and DA was increased (Gobert et al., 1997). R-fluoxetine, S-fluoxetine, or RS-fluoxetine were administered sequentially i.p. at 3, 10, and 20 mg/kg for 90 min apart. The three compounds significantly increased the extracellular concentration of 5-HT and DA in CSF collected from frontal cortex via microdialysis (Koch et al., 2002). There was no significant effect of paroxetine administered 7.5 mg/kg/day i.p. for 24 days on the 5-HT in frontal cortex and amygdala, but the 5-HIAA and 5-HIAA/5-HT were significantly decreased (Connor et al.,
In the animal models described above, administration of antidepressant significantly modified the concentrations of neurotransmitters in brain. In other words, the symptoms of the depression can be improved via the modification of neurotransmitters. Thus the reasons that the extract of *Gastrodia elata* Bl. diminished the immobility time may be due to the modification of the concentration or the turnover of DA and its metabolites.

**5. Conclusion**

In conclusion, administration of the extract of *Gastrodia elata* Bl. in forced swimming test showed significant antidepressive effects in acute animal model. Extract of *Gastrodia elata* Bl. had no effect on the concentrations of 5-HT, 5-HIAA and the ratio of 5-HIAA/5-HT, but it significantly elevated the concentration of DA (*p* < 0.05), and attenuated the concentration of DOPAC in striatum (*p* < 0.01), and also diminished the ratio of (DOPAC + HVA)/DA (*p* < 0.01). Therefore, *Gastrodia elata* Bl. may be a potential antidepressant via regulating the concentrations of dopamine and its metabolites.

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Table 1. Concentrations of 5-HT and 5-HIAA in frontal cortex, hippocampus and amygdala

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<th>Groups</th>
<th>N</th>
<th>5-HT</th>
<th>5-HIAA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ng/g brain tissue</td>
<td></td>
</tr>
<tr>
<td><strong>Frontal cortex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>255.0 ± 37.6</td>
<td>261.4 ± 18.8</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>237.7 ± 73.7</td>
<td>251.6 ± 42.1</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>6</td>
<td>323.7 ± 39.5 *</td>
<td>309.8 ± 54.0</td>
</tr>
<tr>
<td><strong>Hippocampus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>ND</td>
<td>464.1 ± 36.7</td>
</tr>
<tr>
<td>GE</td>
<td>6</td>
<td>ND</td>
<td>448.9 ± 50.6</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>6</td>
<td>ND</td>
<td>449.0 ± 27.9</td>
</tr>
<tr>
<td><strong>Amygdala</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>ND</td>
<td>481.6 ± 74.6</td>
</tr>
<tr>
<td>GE</td>
<td>3</td>
<td>ND</td>
<td>564.0 ± 91.9</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>3</td>
<td>ND</td>
<td>634.6 ± 123.2</td>
</tr>
</tbody>
</table>

Data represented as mean ± SD

All samples were administered for three times by gavage with the dosage: Control, 1 ml deionized water; GE, extract of *Gastrodia elata* Bl. 1 g/kg bw; Fluoxetine, fluoxetine 15 mg/kg bw.

5-HIAA: 5-hydroxyindoleacetic acid; 5-HT: serotonin, 5-hydroxytryptophan

** p < 0.01 compared with control group by unpaired Student’s t-test

ND: not detected
Table 2. Concentrations of DA, DOPAC and HVA in striatum

<table>
<thead>
<tr>
<th>Groups</th>
<th>DA</th>
<th>DOPAC</th>
<th>HVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ng/g striatum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4098.1 ± 852.8</td>
<td>1470.8 ± 215.4</td>
<td>394.3 ± 105.8</td>
</tr>
<tr>
<td>GE</td>
<td>5155.7 ± 1546.7 *</td>
<td>782.3 ± 292.4 **</td>
<td>451.0 ± 305.9</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>4161.6 ± 856.1</td>
<td>733.5 ± 131.2 **</td>
<td>347.4 ± 182.6</td>
</tr>
</tbody>
</table>

Data represented as mean ±SD (n=6)

All samples were administered for three times by gavage with the dosage: Control, 1 ml deionized water; GE, extract of Gastrodia elata Bl. 1 g/kg bw; Fluoxetine, fluoxetine 15 mg/kg bw.

DA: dopamine; DOPAC: 3,4-dihydroxyphenylacetic acid; HVA: homovanillic acid

* p < 0.05, ** p < 0.01 compared with control group by unpaired Student’s t-test
**Fig. 1.** Immobility and activity time of rats in forced-swimming test

Data represented as mean ±SD (n=6)

All samples were administered for three times by gavage with the dosage: Control, 1 ml deionized water; GE, extract of *Gastrodia elata* Bl. 1 g/kg bw; Fluoxetine, fluoxetine 15 mg/kg bw.

**p < 0.01** compared with control group by unpaired Student’s t-test

**Fig. 2.** The ratio of (DOPAC + HVA) / DA in striatum

Data represented as mean ±SD (n=6)

All samples were administered for three times by gavage with the dosage: Control, 1 ml deionized water; GE, extract of *Gastrodia elata* Bl. 1 g/kg bw; Fluoxetine, fluoxetine 15 mg/kg bw.

DA: dopamine; DOPAC: 3,4-dihydroxyphenylacetic acid; HVA: homovanillic acid

* p < 0.05, ** p < 0.01 compared with control group by unpaired Student’s t-test
Fig. 1
Fig. 2