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ANTIDEPRESSENT ACTIVITY OF *CUMINUM CYMINUM.L.* BY CHRONIC MILD STRESS INDUCED RAT MODEL

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ABSTRACT

Cuminum cyminum (Apiaceae) a herb collected from the Chirala region, A.P. India. Phytochemical studies of *Cuminum cyminum*, ethanolic fraction subjected to column chromatography and estimation of total flavanoid content and to evaluate antidepressant activity of methanolic extract of *Cuminum cyminum*. The plant powder was subjected to continuous hot extraction in Soxhlet Apparatus & extracted successively with methanol as solvent. The extracts prepared were tested for the type of chemical constituents present by known qualitative tests. Total chemical content of methanolic extract of *Cuminum cyminum* were done. In vivo Antidepressant activity of methanolic extract was evaluated using Tail suspension method(TST), Forced swimming test (FST) methods in physically depressed rats. Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by the Tukey's test for multiple comparisons.

KEYWORDS: *Cuminum cyminum*; Anti-depression activity, Tail suspension test, Forced swimming test.

1). INTRODUCTION[1]

Depression is a state of mental illness. It is characterized by deep, long lasting feelings of sadness or despair. Depression can change an individual's thinking or feelings and also affects his/her social behaviour and sense of physical well-being.

1.1. Types of Depression and Disorders[2,3]

There are several forms of depression, each one with its own constellation of symptoms.

1. Major Depression: Major depression is a serious illness that affects a person's family personal relationships, work or school life, sleeping eating habits and general health. It's impact on functioning and well-being has been equated to that of chronic medical conditions such as diabetes. These observable changes occur nearly every day over at least a two week period of time and represent a change from the person's previous level of functioning. A Major Depressive Disorder (MDD) is characterized by episodes of more persistent and pervasive disturbances in mood and accompanying features. It is formally diagnosed by the presence of at least five out of the nine symptoms including depressed mood and loss of interest. Over time, the person may also withdraw from social contact and show impairment in performing usual social roles. MDD is generally categorized into bipolar and unipolar subtypes. A distinction is made based on the different courses of the disorders and indicating different approaches to treatment.

2. Minor Depression: It is also called as "subclinical" or "subsyndromal" depression because it does not meet the full criteria for major depression. For example, the person has 4 of 5 symptoms. Like major depression, minor depression is associated with disability, reduced quality of life and responds well to the same treatments that are used with major depression.

3. Dysthymic Disorder: It is a chronic but less severe form of depression that includes depressed mood and at least two additional symptoms that persist for at least two years. People with dysthymia may also develop major depression.

4. Bipolar Disorder: Bipolar disorder is characterized by episodes of depression which may alternate with mania, which is indicated by elevated mood or irritability and other symptoms. Bipolar disorder requires different treatments from major depression; professional diagnosis and treatment is essential. Depression can be classified into two

opposite poles:

- Melancholic or somatic syndrome and
- Atypical syndrome.

a) Melancholic syndrome

Melancholic depression includes major depressive disorder, dysthymia and sub-syndromal depression.

b) Atypical syndrome

The atypical syndrome can be characterized by reverse symptoms such as increased appetite, weight gain, hypersomnia, extreme fatigue and interpersonal rejection sensitivity.

5. Unipolar disorders: Unipolar disorder represents a larger residual group of disorders where an individual experiences depressive episodes only.

6. Postnatal depression: It describes the expression of depression associated with childbirth and post-partum mood disorder. These include brief episodes of depressed mood, MDD and post-partum psychosis in which psychosis symtoms are also present.

1.2. Causes of depression[4]

There are a number of factors that may increase the chance of depression, including the following:

- **Abuse.** Past physical, sexual, or emotional abuse can increase the vulnerability to clinical depression later in life.
- **Certain medications.** Some drugs, such as isotretinoin (used to treat acne), the antiviral drug interferon-alpha, and corticosteroids, can increase your risk of depression.
- **Conflict.** Depression in someone who has the biological vulnerability to develop depression may result from personal conflicts or disputes with family members or friends.
- **Death or a loss.** Sadness or grief from the death or loss of a loved one, though natural, may increase the risk of depression.
- **Genetics.** A family history of depression may increase the risk. It's thought that depression is a complex trait, meaning that there are probably many different genes that each exert small effects, rather than a single gene that contributes to disease risk. The genetics of depression, like most psychiatric disorders, are not as simple or straightforward as in *purely* genetic

diseases such as Huntington's chorea or cysticfibrosis.

- **Major events.** Even good events such as starting a new job, graduating, or getting married can lead to depression. So can moving, losing a job or income, getting divorced, or retiring. However, the syndrome of clinical depression is never just a "normal" response to stressful life events.
- **Other personal problems.** Problems such as social isolation due to other mental illnesses or being cast out of a family or social group can contribute to the risk of developing clinical depression.
- **Serious illnesses.** Sometimes depression co-exists with a major illness or may be triggered by another medical condition.
- **Substance abuse.** Nearly 30% of people with substance abuse problems also have major or clinical depression. Even if drugs or alcohol temporarily make you feel better, they ultimately will aggravate depression.

1.3. Signs and Symtoms[5]

Major depressive disorder is characterized by a heterogeneous group of behavioral, psychological and physiological symptoms, which include:

1.3.1: Emotional

- Sadness caused by any kind of change in life or any type of loss of family members or friends and may be by divorce or breakups.
- Anxiety is present in individual, guilt or feelings of worthlessness. The person gets angry and mood swings occur.
- A feeling of helplessness and lack of confidence in himself found which was not present earlier.
- Loss of interest in family,friends and favorites by becoming frustrated easily by anything.

1.3.2: Behavioural

- The affected individual isolate himself from friends, family and society.
- A typical crying behavior develops and the person is unable to concentrate in things of his intrest.
- Major change in personality occur; the person may attempt to harm himself as suicidal thoughts developed in case of depression.
- The person may become irresponsible. There is a chance that affected individually may

become a drug abuser.

1.3.3: Physical

It includes persistent pain and aches all the time without any explanation.

- The person always feel tired and have lack of energy.
- There may be a chance in appetite, which cause either weight loss or weight gain.
- The person either sleep too much than normal or not at all.
- The person may feel problems related to sex.

1.3.4: Thoughts

- In severe cases of depression delusional thoughts and hallucinations may develops.
- Self-criticism, self-worthlessness, failure thoughts generate.
- The person develops suicidal thinking and was unable to decide in anything or remember.

2). PATHOPHYSIOLOGY OF DEPRESSION[6-13]

The monoamine hypothesis of depression came into the picture after the s first serendipitous discovery of the first antidepressant drugs that were otherwise developed for other medical conditions. These clinical observations have contributed greatly to the understanding of the pathophysiological changes that take place in the brains of depressed individuals. The drugs were proposed to increase the amount of monoamine neurotransmitters in the brain either by blocking a monoamine degrading enzyme monoamine oxidase inhibitor (MAOI) or by blocking the reuptake of the neurotransmitters into the presynaptic neuron.

i) The Serotonin hypothesis: Serotonin is a monoamine neurotransmitter with a wide range distribution throughout the central nervous system. It is involved in physiologic activities such as pain sensation, appetite regulation, aggression and mood. Dysfunction in serotonergic system has been implicated in mood and anxiety disorders. The basis for this hypothesis is the fact that the first antidepressant drugs worked by reviving the diminished monoamine activity in the brain. And later SSRIs alone were found to be sufficient to treat symptoms of depression effectively. This fact further strengthened the involvement of 5-HT in the pathogenesis of the disease.

Subset of depressed patients have been reported to have a lowered level of 5-hydroxyindoleacetic acid (5-HIAA) a metabolite of 5-HT in the cerebrospinal fluid (CSF), which has been related to aggressive behavior and increased suicidal intent and impulsivity.

The plasma level of the amino acid precursor (tryptophan) of 5- HT decreased and depressive symptoms can be induced in patients who are susceptible to depression by depleting this amino acid. Moreover, positron emission tomography (PET) imaging studies have reported a decrease in density of 5-HT1A receptor subtype on depressed patients in different regions of the brain. There is also a decreased availability of 5-HTT in midbrain and brainstem regions. But this serotonergic dysfunction associated in depression is debated whether it is an etiologic factor or increases susceptibility.

ii) The catecholamine hypothesis: The catecholamine hypothesis of depression emerged in the 1960s after the observation that reserpine; an antihypertensive drug depletes central and peripheral amine storage in the nervous system, induced depression.

However, there are no consistent findings on the alteration in the levels of NE metabolites in the CSF of depressed individuals. In subsequent years, the "supersensitivity hypothesis" was proposed which links depression to supersensitive presynaptic α2-R which is also supported by an increased density of these receptor types in post mortem studies, leading to an impaired NE activity.

Additionally, some symptoms of depression including anhedonia and psychomotor retardation are better explained by a derangement in the brain DA systems. These systems include the substantia nigra -basal ganglia motor system and the reward circuitry involving the NAc and VTA. There is a diminished DA activity in the NA specifically which corresponds to the inability to experience pleasure which is one of the hallmarks of depression. The concentration of the dopamine metabolite homovanillic acid (HVA) in CSF is reported to be lower in depressed patients as well.

3). PATHOLOGY OF *CUMINUM CYMINUM.L.*[14,15]

The World Health Organization (WHO) estimates that 4 billion people, 80% of the world population, presently use herbal medicine for some aspect of primary health care.

Nomenclature[16-19]

The plant is known by different vernacular names e.g. Safaid jeera (Bengali), Jeeru (Gujarati), Jira or Safed jira or Zeera (Hindi), Jeerkam (Malayalam), Jire (Marathi), Jeera (Oriya), Zeera (Punjabi), Zirgaum (Tamil), Jikaka (Telugu), Amla (Urdu) and Cumin (English), etc.

Cultivation, Collection and Storage[20-22]

It is drought-tolerant, and is mostly grown in Mediterranean climates. Cumin cultivated in semi-arid areas with moderate winter and light rain. It is grown from seed, sown in spring, and needs fertile, well-drained soil. The crop can be grown when the atmosphere is humid. The seed are sown during April-May and for each crop, sowing is done between middle November and December, they are transplanted. Cultivation of cumin requires a hot summer of 3 to 4 months, with daytime temperatures around 30°C. The total vegetative period of cumin is 100 to 110 days.

Seeds are usually collected and threshed by hand or cut by sickle. Seeds are ready 120 days after planting for harvesting when the seed become hard and the fruit change color. The plants are pulled out along with roots and dried in the Sun light. The seeds are separated by beating the plants with light slicks and cleaned by winnowing. The seeds should be dried in Sun before storage in gunny bags.

Chemical Constituents[17]

The characteristic odour of cumin is attributed to the presence of "cuminaldehyde", 1, 3-p-menthadien7al, 1-4-p-menthadien-7-al, 14 free amino acids, 18% protein, flavonoid glycosides, including apigenin-7-glucoside, luteolin-7-glucoside and luteolin-7-glcuronosyl glucoside, tannin, resin, gum. The other constituents are moisture, fat, crude fiber, carbohydrate, mineral matter, calcium, phosphorus, sodium, potassium, iron, vitamin A, B1, B2 & C, etc.

Medicinal Properties[23,24]

Cumin seeds stimulant, antispasmodic, diuretic, aphrodisiac, emmenagogue, carminative, stomachic, astringent and useful in diarrhea, colic & dyspepsia, particularly in veterinary medicine. It is considered also very cooling, prescribed for whooping cough, the spitting up of blood, spasmodic cough and enters into most of the prescriptions for gonorrhoea. It is used in as a lactagogue. Cumin seed prescribed for snake-bite and scorpion–sting.

Pharmacological Activities[25]

Cumin helps in digesting food properly. It is one of the best herbs for digestive sluggishness; it also helps in the cure of digestion related problems. It is due to cuminaldehyde, that our salivary glands stimulate and this enables the primary digestion of food. Thymol is another compound present in cumin that stimulates the glands

secreting digestive acids to bring about complete digestion of food.Moreover, it relieves for gas troubles, bloating and gurgling.

The essential oils present in cumin have anti fungal and disinfecting properties which prevent fungal and microbial infections from harming, the skin, it has also antibacterial properties and its decoction protects against hookworm infections too.

The essential oils present in cumin also play an important role in strengthening the immunity. Cumin seed and oil is a great source of vitamins such as vitamin A, B, C, E and iron, its prevent the deficiency of iron.

PhytoChemical Testing

The extracts of the drug were tested for presence of different organic groups and results are presented in Table.

Table 1: Phtochamical evaluation ethanolic extract of *Cuminumcyminum.L.*

S.No	Phytoconstituents & Name of the Test		Results
1	Alkaloids	Hager's test	+
2	Amino acids	Ninhydrine test	+
3	Carbohydrates	Molish's test	+
4	Volatile oils	Filter paper test	+
5	Flavanoids	Shinoda test	+
6	Proteins	Biuret test	-
7	Steroids	Salkowski reaction	-
8	Tannins & Phenolic compounds	a) Lead acetate solution	+
		b) Diluted HNO3	+
		c) 5% Fecl3	+
9	Glycosides	a) Keller-killiani test	+
		b) Legal test	+

(-) Negative ; (+) Positive

Physico-Chemical Constants Analytical Values

The analytical values in respect of physico-chemical constant of drug were established and results are reported in Table-2.

Table 2: Analytical Values of Physico-chemical Constants.

Physico-Chemical Constants	Analytical Values
Moisture Content, %w/w	8.0
pH	7.3
Total Ash, %w/w	7.5
Acid Insoluble Ash, %w/w	1.0

Alcool Soluble Extract, %w/w	6.5
Water Soluble Extract, %w/w	13.0
Essential Oil, %v/w	_

Pathophysiology[26-29]

The Cuminum cyminum is having the main chemical constituent known as "Cuminaldehyde". Where as it is having the tyrosinase inhibitory property. Therefore upon oxidation it prevents the release of DOPA into the synapse and blocks the dendride. While the DOPA is inhibited it leads to the increase in the release of transmittors from the neurotransmission and leads to reduce the depression as shown in the figure below with the main monoamine transmitter.

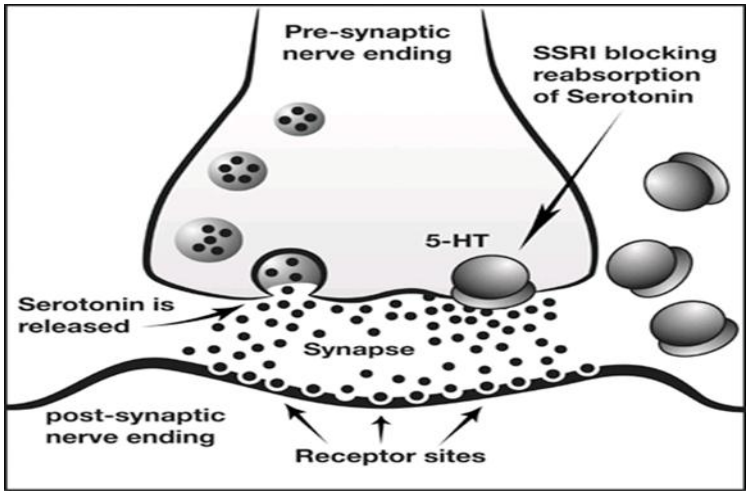

Fig: Depression of SSRI's.

3.1. Uses[7,8]

3.1.1. Traditional uses

- In traditional medicine, cumin was used to treat hoarseness, jaundice, dyspepsia and diarrhoea. Its seeds were used for stomachic, diuretic, carminative, stimulant, astringent and abortifacient properties.
- The oil of cumin was used in perfumery and as a seasoning in curry powders, soups, stews, sausages, cheeses, pickles, meats
- In America, Africa and India the drug is used as an abortive and as an emmenagogue.
- In Indonesia, it was used in cases of bloody diarrhea and headache (paste is applied to the forehead). It was also taken orally for rheumatic ailments.
- In India, cumin was used as an abortifacient, for kidney and bladder stones, chronic diarrhea, leprosy and eye disease.

- In Unani system of medicine, the fruits of *Cuminum cyminum* were used as an astringent, carminative, emmenagogue, for the treatment of corneal opacities, ulcers, boils, styes and to relieve cough and inflammation.

3.1.2. Other uses

The previous pharmacological studies revealed that Cuminum cyminum exerted antimicrobial, insecticidal, anti-inflammatory, analgesic, antioxidant, anticancer, antidiabetic, antiplatelet aggregation, hypotensive, bronchodilatory, immunological, contraceptive, anti-amyloidogenic, anti-osteoporotic, aldose reductase, alpha-glucosidase and tyrosinase inhibitory effects, protective and central nervous effects.

4). Stress Models[30-32]

4.1: Chronic Mild Stress

In comparison to LH and FSH/TST procedures that on relatively short term aversive stress exposure, the Chronic Mild Stress (CMS) paradigm was developed to study neural changes that results from stress of a more chronic nature. CMS paradigm aim of model a chronic depressive like state that develops gradually over time in response to stress and considered more naturalistic in the induction. Rats are exposed to a series of different stress conditions over a period of several weeks. Several stressors i.e. 6-8 are applied 1 or 2 per day for several hours each day. Typically stressors include overnight illumination, periods of food and water restriction, cage tilt, and isolation or crowded housing. The sequential and CMS exposure decreases the likelihood of animals habituating to anyone reoccurring condition.(Aguilera, 1998; Magarin ~os and McEwen, 1995;Tannenbaum et.al., 2002).

4.2: Amphetamine Potentiation

Amphetamine isa sympathomimetic agent,which promotes neuroexocytosis or displacement of transmitter from axonal terminal. This test is used as screening methods detects adaptive changes in dopaminergic and noradrenergic system after repeated treatment with antidepressant drugs. Repeated treatment with antidepressants enhances the amphetamine induced locomotor hyperactivity.

5). Animal models

5.1 Tail Suspension Test[33-38]

PRINCIPLE

When a rat is suspended by its tail, the immobility is displayed because of inescapable

stress. It reflects the behavioural despair. The antidepressant drugs decreases the immobility in a tail suspended rat.

PROCEDURE

•The total duration of immobility induced by tail suspension will be measured according to the method described by Steru et al., (1985) as a facile means of evaluating potential antidepressants.

•Three groups of rats are divide and proper food, water are givenControl, test, standard groups are divided and subjected to the respective drugs

•The rats are suspended upside down through its tail i.e: 58cm above the floor. At the start of test, The rat try to escape but was unable and become immobile after sometime.

•The readings were taken for 6min's by using camera or visually and the time for activity and immobility was recorded and compared with the test and standard groups.

EVALUATION

The duration of immobility of standard and test was compared with control groups and the decrease in duration of immobility was calculated(ED50 value).

GROUPING

Group-I : Control (Normal saline 10ml/kg; p.o)

Group-II : Fluoxetine (20mg/kg; p.o)

Group-III : Test drug (EECC) with low dose (100mg/kg; p.o)

Group-IV : Test dug (EECC) with high dose (200mg/kg; p.o).

STATISTICAL ANALYSIS

Results were analysed by one-way ANOVA and the values $P>0.05$ were considered significant.

5.2. Forced Swim Test[39-40]

PRINCIPLE

When rats are subjected to force swim in a limited space without no way to escape, then a characteristic immobility develops in them after some time of forced swimming.

The antidepressant drugs decrease the duration of immobility. It is most widely used method for screening of acute anti-depressants.

PROCEDURE

•Behavior despair was proposed as a model to test for antidepressant activity by Porsolt et al. (1977, 1978).

•Adult rats are allowed to swim in a cylindrical glass jar (25×12×25 cm3) with no escape and it contain fresh water of 15 cm height and maintained at 25 ºC.

•Rats were considered to be immobile when it remained floating in the water without struggling, making only minimum movements of its limbs and necessary to keep its head above water.

•When the rats are forced to swim in water initially it was hyperactive but approximately 5min's later activity slow down and the phase of immobility starts.

•After 15min's the rats were removed and allowed to dry. The total duration of immobility will be recorded during the next 4 min of a total 6 min test.

•The same activity was done for standard and test groups then the drug was administered 1hr before earlier when the test starts.

EVALUATION

The changes in duration of immobility was measured for the test, control, and standard groups treated with drugs.The antidepressant drugs decreses the duration of immobility.

GROUPING

Group-I : Control (Normal saline 10ml/kg; p.o)

Group-II : Fluoxetine (20mg/kg; p.o)

Group-III : Test drug (EECC) with low dose (100mg/kg; p.o)

Group-IV : Test dug (EECC) with high dose (200mg/kg; p.o).

STATISTICAL ANALYSIS

Results were analysed by one-way ANOVA and the values $P>0.05$ were considered significant.

DISCUSSION

Mental health problems such as anxiety, depression and insomnia are among the most common reasons for individuals to seek treatment with complementary therapies.[41] Several surveys have focused on the use of complementary and alternative medicine by patients with psychiatric disorders. A range of therapeutic approaches are available, the most widely used, in developed countries, is antidepressant drugs.[42] However these are associated with a

number of problems including poor compliance and toxicity in overdose (particularly with the older tricyclic drugs) while the more modern selective serotonin uptake reinhibitor (SSRI) drugs may be associated with increased incidence of self-harm in young people and of suicide.

Patients may turn to complementary therapies due to side effects of medication, time and effort associated with nonpharmacological therapies, lack of response or simply preference for the complementary approach. Use of plants and active components from plant as antidepressant agent is one of them. Many researches have proved that many plant components or crude extract possess significant antidepressant activity. Although a multitude of natural medications are available for the treatment of mood disorders, the evidence for their effectiveness remains limited for most, if not demonstrated at all for many. A few natural psychotropics have been more extensively examined in reasonably well-designed, placebo-controlled, double-blind studies, and in systematic reviews and meta-analyses.[43,44]

In the present study were made to study detailed phytochemical investigation and pharmacological action, particularly antidepressant activity.The phytochemical analysis of the cumin was showed the presence of carbohydrates, alkaloids, tannins, phenolic compounds, volatile oils, flavonoids and glycosides.

The characteristic odour of cumin is attributed to the presence of “cuminaldehyde”, 1, 3-p-menthadien7al, 1-4-p-menthadien-7-al, 14 free amino acids, 18% protein, flavonoid glycosides, including apigenin-7-glucoside, luteolin-7-glucoside and luteolin-7-glcuronosyl glucoside, tannin, resin, gum. The other constituents are moisture, fat, crude fiber, carbohydrate, mineral matter, calcium, phosphorus, sodium, potassium, iron, vitamin A, B1, B2 & C, etc.[23,24]

Cumin seeds stimulant, antispasmodic, diuretic, aphrodisiac, emmenagogue, carminative, stomachic, astringent and useful in diarrhea, colic & dyspepsia, particularly in veterinary medicine. It is considered also very cooling, prescribed for whooping cough, the spitting up of blood, spasmodic cough and enters into most of the prescriptions for gonorrhoea. It is used in as a lactagogue. Cumin seed prescribed for snake-bite and scorpion–sting.[25] Thus the antidepressant activity was assessed using few well established protocols like tail suspension test and forced swimming test. Further to ascertain mechanism of effect some of experiments were studied.

Since its introduction was made almost 20 years ago, the tail suspension test has become one of the most widely used models for assessing antidepressant-like activity in mice or rats. The test is based on the fact that animals subjected to the short-term, inescapable stress of being suspended by their tail, will develop an immobile posture. Various antidepressant medications reverse the immobility and promote the occurrence of escape-related behaviour. Thus, a reduction in the total duration of immobility indicates an antidepressant effect.[45] Additionally, many studies have shown that the test is highly sensitive to the major classes of the clinical antidepressants, including the selective serotonin reuptake inhibitors (SSRIs), the tricyclic antidepressants (TCAs), and the monoamine oxidase inhibitors (MAOIs).[47] In present study the cuminumcyminum extract will significantly decreased total duration of immobility.

Forced swimming is the accepted stress models of depression. Immobility has been shown to reflect a state of 'behavioral despair and variants' or 'failure to adapt to stress'.[48,48] Immobility displayed in this behavioral despair models has been hypothesized to reflect behavioral despair which in turn may reflect depressive disorders in human. There was a significant correlation between clinical potency and the potency of antidepressants in this model. Thus, this model is usually used to screen or evaluate antidepressants.[50] In this assay, mice or rats are forced to swim in a restricted space from which there is no escape, and will, after periods of agitation, cease attempts to escape and become immobile. In present investigation of study that was studied the cuminumcyminum ethanolic extract will significantly decreased total duration of immobility.

CONCLUSION

From the above study, it can be concluded that the natural extract was having many pharmacological and medical activities along with the antidepressant activity which can be compared with the standard drug Imipramine will shows the satisfied ED50 values by performing the FST and TST. However, further research are necessary to find the exact mechanism of anti-depressant effect.

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