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RESEARCH ARTICLE

Pharmacological Evaluation of Antidepressant Activity of Piper Betel Leaves and Clove

Shaik Salmasultana*, P. Sukumari, SK. Shafi, D. Maheswari, P. Ramsai, K. Sasikumar, A. Sravani

Department of Pharmacology, Jagan's College of pharmacy, Gangalakandriga, Nellore

ABSTRACT

The antidepressant activity of eugenol excluded clove extract was investigated using two different models of stress induced depression (forced swim test and Tail suspension method). Animals were divided into different groups each group receiving specific agent ranging from 2% Gum acacia, Standard drug, Eugenol and Eugenol excluded clove extract. Standard drug produced significant results where as eugenol excluded clove extract has got values which are nearly comparable to the standard when compared with the other groups. Higher doses of eugenol produced muscular in coordination activity which was not seen with the other one. Piper betle Linn, is commonly known as Betel leaf or paan, belonging to the family Piperaceae. The leaves are pungent, bitter sweetish acrid in nature. It is commonly found in lowland tropical rainforests. Many species of piper have been used for treating different disease in many traditions examples P. cubeba as a cigarette flavoring. P. darienense is used to intoxicate fish. Depression is a heterogeneous mood disorder that has been classified and treated in a variety of ways. Although a number of synthetic drugs are being used as standard treatment for clinically depressed patients, they have adverse effects that can compromise the therapeutic treatment. Thus, it is worthwhile to look for antidepressants from plants with proven advantage and favourable benefit-to-risk ratio. A number of medicinal plants per se and medicines derived from these plants have shown antidepressant properties by virtue of their medicinal constituents. The causes of depression are decreased brain levels of monoamines like noradrenaline, dopamine and serotonin. Therefore, drugs restoring the reduced levels of these monoamines in the brain either by inhibiting monoamine oxidase or by inhibiting reuptake of these neurotransmitters might be fruitful in the treatment of depression. The present review is focused on the medicinal plants and plant-based formulations having antidepressant activity in animal studies and in human Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings, and sense of well-being. A depressed mood is a normal temporary reaction to life events such as loss of a loved one. It is also a symptom of some physical diseases and a side effect of some drugs and medical treatments. Depressed mood is also a symptom of some mood disorders such as major depressive disorder or dysthymia.

Keywords: Clove, Piper betel leaves, Depression, Neurotransmitters, Eugenol.

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CORRESPONDING AUTHOR

Shaik Salmasultana
Department of Pharmacology,
Jagan 's College of pharmacy,
Gangalakandriga, Nellore, A.P, India.
MS-ID: IJCPs3655



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1. Introduction

Depression: Depression may be defined in terms of a state of feeling sad. It may also be defined as a psychoneurotic disorder characterised by mental and functional activity, sadness, reduction in activity, difficulty in thinking, loss of concentration, perturbations in appetite, sleeping, and feelings of dejection, hopelessness and generation of suicidal tendencies. It is a common and recurrent disorder causing significant morbidity and mortality worldwide. Depression, a kind of mental illness, includes arousal of grief which may affect the overall thinking process, behaviour and feelings. Such persons suffer from an imbalanced sleep and sleeping disorders. Several workers have described the causes of depression which include genetic, heterogeneous parental behaviour to the siblings, neglect and sexual abuse.

- I. Psychotic depression characterised by severe depression.
- II. Postpartum depression characterised by perturbations in the levels of hormones and physical features after Child birth.
- III. Seasonal Affective Disorder (SAD) concerning specially the winter months with less sunlight. In the women, the depression arises also due to extra work load, domestic responsibilities, child care, strained relationship, care of aged parents and poverty. In addition to all these indices, the psychological, biological and hormonal factors also significantly contribute in depression.

The premenstrual dysphoric disorder (PMDD) or premenstrual syndrome (PMS) and osteoporosis in women can play important role in development of depression. Depression in men may be associated with sufferings from serious diseases such as cancer and cardiac diseases, extreme tiredness, irritation, disinterest in once-pleasurable activities, loss of balance, less sleep and getting aggressive. In older men, arteriosclerotic depression (vascular depression) has been observed.

Pathophysiology of depression

There are no useful biomarkers or imaging abnormalities to determine pathophysiology of depression during life time. The post-mortem study of brain does not reveal any consistent structural or neurochemical abnormality. Majority of the currently available medications were discovered empirically. Most current theories are based on “amine hypothesis”. The most important hypothesis of mood disorder is related to the alterations in the levels of biogenic amines. It states that depression is caused by a functional deficiency of catecholamines, particularly norepinephrine (NE), whereas mania is caused by a functional excess of catecholamines at the critical synapses in the brain. The occurrence of depression has been found to be associated with the alterations in the levels of biogenic

amines in the brain such as NE, dopamine (DA) and epinephrine, indolamine, serotonin, 5-hydroxytryptamine (5-HT) and two catecholamines.

Signs and symptoms

Depressed mood, reduced interest or pleasure in activities previously enjoyed, loss of sexual desire, unintentional weight loss (without dieting) or low appetite, insomnia (difficulty sleeping) or hypersomnia (excessive sleeping), psychomotor agitation, for example, restlessness, pacing up and down, delayed psychomotor skills, for example, slowed movement and speech, fatigue or loss of energy, feelings of worthlessness or guilt, impaired ability to think, concentrate, or make decisions, recurrent thoughts of death or suicide, or attempt at suicide.

Causes

The causes of depression are not fully understood and may not be down to a single source. Depression is likely to be due to a complex combination of factors that, genetics, biological changes in neurotransmitter levels, environmental, psychological and social (psychosocial). Some people are at higher risk of depression than others.

Risk factors include:

Life events: These include bereavement, divorce, work issues, relationships with friends and family, financial problems, medical concerns, or acute stress.

Personality: Those with less successful coping strategies, or previous life trauma are more susceptible.

Genetic factors: Having a first-degree relative with depression increases the risk. Childhood trauma.

Some prescription drugs:

These include corticosteroids, some beta-blockers, interferon, and other prescription drugs.

Abuse of recreational drug:

Abuse of alcohol, amphetamines, and other drugs are strongly linked to depression.

A past head injury:

Having had one episode of major depression: This increases the risk of a subsequent one.

Chronic pain syndromes:

These and other chronic conditions, such as diabetes, chronic obstructive pulmonary disease, and cardiovascular disease make depression more likely.

Diagnosis: Depression is a mood disorder characterized by persistently low mood and a feeling of sadness and loss of interest. It is a persistent problem, not a passing one, lasting on average 6 to 8 months. Diagnosis of depression starts with a consultation with a doctor or mental health specialist. It is important to seek the help of a health professional to rule out different causes of depression, ensure an accurate differential diagnosis, and secure safe and effective treatment. Some questionnaires help doctors to assess the severity of depression. The Hamilton depression rating scale, for example, has 21 questions, with resulting scores

describing the severity of the condition. The Hamilton scale is one of the most widely used assessment instruments in the world for clinicians rating depression.

Treatment: Depression is a treatable mental illness. There are three components to the management of depression:

- Support, ranging from discussing practical solutions and contributing stresses, to educating family members.
- Psychotherapy, also known as talking therapies, such as cognitive behavioral therapy (CBT).

Antidepressants:

Antidepressants are those drugs which help in the reduction in symptoms of depressive disorders by altering chemical imbalances of neurotransmitters in the brain. The change in mood and behaviour is due to chemical imbalance. Neurotransmitters are the communication link between neurons in the brain. Neurotransmitters are located in vesicles found in nerve cells. The neurotransmitters such as serotonin, dopamine and noradrenaline or norepinephrine are released by the axonic end of one nerve and received by the other; the phenomenon called as reuptake.

Antidepressants and their classification:

Imipramine was discovered in 1958 as an antidepressant regimen. The antidepressants have been divided into five groups:

- i. Tricyclic antidepressants (TCAs),
- ii. Selective serotonin-reuptake inhibitors (SSRIs),
- iii. Monoamine oxidase inhibitors (MAOIs),
- iv. Serotonin-norepinephrine reuptake inhibitor (SNRI) and
- v. Non-TCA antidepressants.

Exercise and other therapies: Aerobic exercise may help against mild depression since it raises endorphin levels and stimulates the neurotransmitter norepinephrine, which is related to mood. Brain stimulation therapies - including electroconvulsive therapy - are also used in depression. Repetitive transcranial magnetic stimulation sends magnetic pulses to the brain and may be effective in major depressive disorder.

Electroconvulsive therapy: Severe cases of depression that have not responded to drug treatment may benefit from electroconvulsive therapy (ECT); this is particularly effective for psychotic depression.

Types of Depression

Unipolar and bipolar depression: If the predominant feature is a depressed mood, it is called unipolar depression. However, if it is characterized by both manic and depressive episodes separated by periods of normal mood, it is referred to as bipolar disorder (previously called manic depression). Unipolar depression can involve anxiety and other symptoms - but no manic episodes. However, research shows that for around 40 percent of the time, individuals with bipolar disorder are depressed, making the two conditions difficult to distinguish.

Major depressive disorder with psychotic features: Major depressive disorder with seasonal pattern. Previously called seasonal affective disorder (SAD), this condition is related to the reduced daylight of winter - the depression occurs during this season but lifts for the rest of the year and in response to light therapy. Countries with long or severe winters seem to be affected more by this condition.

Plant profile of Piper Betel

Piper betle is glorified as evergreen and perennial plant that God designed and have given the shape of his own heart. The heart shaped of Piper betle leaves are initiate in ancient Sanskrit texts, include Charaka, Sushruta Samhita and Astanga Hridayam. Piper betle L. has been use in Chinese, Indian traditional medicine for centuries. The purpose of it is to reveal the possible effect of this plant in the development of therapeutically active herbal drugs.

Taxonomical classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnolipsida
Order: Piperales
Family: Piperaceae
Genus: Piper
Species: Betle

Chemical constituents of betel leaves:

The Piper betle leaf has been described to have Piperol-A, Piperol-B, methyl piper betlol and they also have been isolated. 10 Component Percentage of Components Chavibetol 53.1 Caryophyllene 3.71 Chavibetol acetate 15.5 Allylpyrocatechol Diacetate 0.71 Chavibetol methyl ether 0.48 Campene 0.48 f-Pinene 0.21 Eugenol 0.32 u-Limonene 0.14 a-Pinene 0.21 1,8-Cineol 0.04 Saprobe 0.11 Allylpyrocatechol Monoacetate 0.23 Components % of components.

Pharmacological study design:

Antioxidant, Antiproliferative, Anti fertility effect, Cytotoxicity, Anticancer, Potential Anti Diabetic Leaves, Antimalarial, Antioxidant.

Traditional use:

The paste of Piper betle leaves assorted with salt and hot water able to be administering for filariasis. For curing obesity, one Piper betle leaf mix with Piper nigrum is prescribed for two months. Juice of Piper betle with honey is accommodating to treat coughs, dyspnoea, and in indigestion, amongst children. Leaves of Piper betle smeared with oil are useful on the breasts of lactating women; it is supposed to promote milk secretion. A local application is recommended for inflammatory swelling such as orchitis, arthritis and mastitis. For childhood and old people, leaves are mixed with mustard oil, warmed and are apply to the chest for treatment to reduce cough and dyspnoea. Recovers bad breath, body odor and prevent tooth decay. Prevents and treats vaginal ejection, and reduce itching of the vagina. Stop bleeding in the nose. It contains vitamins such as thiamine, niacin, riboflavin and carotene. In India, leaves used for curing eczema, lymphangitis, asthma and rheumatism. Paste of leaves is applied on cuts and wounds. Roots with black pepper used to generate sterility in women. Oil used for irritation in throat, larynx, bronchi, gargle and inhalation in diphtheria.

Modern medicinal use:

Betle leaves are advantageous in pulmonary infection in childhood and old age. The leaves, mixed in mustard oil warmed and applied to the chest to relive cough and intricacy in breathing. Limited application of the leaves is efficient in procuring sore throat. The flattened fruit or berry should be mixed with honey and used to reduce

irritating cough. Betle leaves are helpful for the treatment of nervous pain, nervous exhaustion and debility. The extract of few betle leaves, with honey serve up as a good tonic. On applied locally, betle leaves are valuable in the treatment of swelling such as arthritis and orchitis i.e. inflammation of the testes. Betle leaves also shows analgesic and cooling properties. It is also a priceless remedy for boils. A leaf is lightly warmed till it gets soft, and then coated with a layer of castor oil. The oiled leaf is placed over the inflammation. A hot poultice of the leaves or their extract mixed with some bland oil as refined coconut oil which can be applied to the loins with beneficial results in lumbago. The leaves can also be used to heal wounds. The juice of the leaves should be extracted and applied locally to the wounds. The application of leaves coating with oil and said to encourage secretion of milk when applied over the breast during lactation. According to Unani system, these leaves has a sharp taste and good smell which helps to improve appetite. It also used as a tonic for brain, heart and liver. It also helps to promote healthy teeth and skin. It helps in procurement of Disorders in physiological function of body, Skin diseases, and several Eye diseases. Betle leaf also contains diuretic property. Juice of leaves given with milk or honey helps in easing urination. Betle leaf is used in aphrodisiac i.e. an agent that stimulates sexual desire. The essential oils which contains in the leaves are antibacterial, antiprotozoal and antifungal properties. Therefore, the oil kills or inhibits expansion of outrageous bacteria causing typhoid, cholera, tuberculosis etc and helps in proper evaluation and exploitation. The leaves are nutritive and hold considerable quantity of vitamins and minerals and therefore, six leaves with a small bit of slaked lime are said to be equivalent about 300 ml of cow milk mainly for the vitamin and mineral nutrition. The leaves also hold the enzymes like diastase and catalase as well as major amount of all the essential amino acids except lysine, histidine and arginine, which are found only in trace.

Plant profile of Clove

The clove of commerce is its dried unopened flower buds. Whole and ground cloves are used to enhance the flavor of meat and rice dishes and used widely in curry powders and masalas. They are highly valued in medicine as a carminative and stimulant and are said to be a natural anthelmintic.

Common names: Cloves, Caryophyllus, Caryophyllus, clovos.

Botanical names: Eugenia caryophyllus, Syzygium aromaticum.

Family: Myrtaceae

phytochemical constituents of clove: Various studies have been carried out to find various constituents of *S. aromaticum*. Clove buds contain 1520% essential oil, which is dominated by eugenol (70.85%), eugenyl acetate (15%) and -caryophyllene (5.12%). Other essential oil ingredients of clove oil are vanillin, crategolic acid, tannins, gallotannic acid, methyl salicylate, flavonoids eugenin, kaempferol, rhamnetin, eugenitin and triterpenoids like oleanolic acid. The constituents of the oil also include methyl amyl ketone, methyl salicylate, and -humulene, benzaldehyde, -

ylangene and chavicol. The minor constituents like methyl amyl ketone, methyl salicylate etc., are responsible for the characteristic pleasant odour of cloves.

Characterized six sesquiterpenes, namely: -cubebene (1.3%), -copaene (0.4%), - humulene (9.1%), -caryophyllene (64.5%), -cadinene (2.6%) and -cadinene (2.6%) in the hydrocarbon fraction of the freshly distilled Indian clove bud oil.

Therapeutic applications of clove: Its parts including leaves and buds are commercially used in cooking, food processing, and perfumery. Some parts of the plant have been shown to be useful for treating the digestive system disorders. Some components of clove have been advised against bacterial and fungal infections. It has also been documented that some parts of the plant and its ingredients have a good cytotoxic and even anti-cancerogenic properties. The extracts of this plant have been considered to have benefits against oral bacteria especially those which are accompanied with dental caries and periodontal diseases. The clove oil has also been used for acne, warts, scars, and parasites. It has also been shown that the essential oil from clove inhibits the smooth muscle tone. The useful effects of the plant in allergic asthma have also been reported. The analgesic effects of the plant in subjects suffering from toothache and anal fissure have been reported. The anesthetic effects of the essential oil from several parts of this plant have also been shown in fish.

2. Materials and Methods

Preparation of plant extract

Preparation of bettle leaf extract: The shade dried leaves were powdered using a mechanical grinder. The powder was macerated in hydro alcoholic solution (containing ethanol-70% and water 30%) in the ratio of 1:2.5 for 24h and successively extracted with a mechanical percolator. Extract was filtered and evaporated by using water bath.

Preparation of clove extract:

Take 40gms of clove powdered by using a mechanical grinder. Add 400ml ethanol and 400ml distilled water and successively extracted with soxhalation apparater. Extract was filtered and evaporated by using water bath.

Preparation of clove and betle leafs extract:

Take 10g of clove extract mix with 2g of piper bettle extract & use for the experimental procedure (10:2).

Experimental procedure:

Twenty four albino rats (100-200 gms body weight) of male were randomly selected and grouped into 6 groups (n=4). They were acclimatized and housed in animal house with 12hr: 12hr light-dark cycle at 27±2°C temperature and 45-55% relative humidity. Food and water supplied ad libitum. The work was approved by the Institutional Animal Ethical Committee (IAEC). Control animals were treated with distilled water. Drugs like imipramine (10mg/kg), test drug bettle leaf, clove & both clove & bettle leaf extract 10:2 ratio (10 mg, 20mg/kg) were dissolved in distilled water and administered orally once daily for five days. After 24 hours of every dose tests were repeated. Forced swimming test rats were forced to swim individually for 10min, in a glass beaker of 11cm diameter, 15cm height containing fresh water up to a height of 6cm, at a

temperature of $27 \pm 2^\circ\text{C}$. This constituted the “pre-test” session. Twenty four hours later each rat was once again forced to swim in a similar environment for a period of 6 min in a “test-session”. The test-session was conducted before (0 day) and after the drug treatment (on 5 day). The rat was considered immobile when it floats motionlessly or made only those movements necessary to keep its head above the water surface. The total duration of the immobility during the last 4 min of the 6 min test was recorded.

Priliminary phyto chemical screening

Piper betel leaves & clove: The components analyzed were Alkaloids, Flavonoids, Anthroquinone, Saponins, Phenol, Protein, Coumarin, Reducing Sugar, Tannins, Phytosterols, Anthrocyanides, Triterpinoids, Phlobatannins, Acids and Glycosides. Phytochemical Screening of Spices Phytochemical screening was carried out on methanol, ethanol, acetone, chloroform and distilled water extracts of spices for its chemical composition. The following tests were performed to detect various phytochemical constituents present in them.

Experimental procedures

a) Force swim test

Requirements:

- Animal : male Rats (100-200g)

- **Drugs :** imipramine (10 mg/kg,ip)
- **Equipment:** Rectangular glass jar (25 x12x25 cm³) containing fresh water, thermometer, and stopwatch. One may use circular jar.

Procedure:

Weigh and number the animals. Randomize the animals into two groups according to the body weights. Each group consist 4 rats. Allow the individual animal to swim inside the jar containing water up to 15 cm height and maintained at 25°C . Allow the rat to swim for 6 minutes. Note that after initial struggle to escape for 1-2 minutes, the animal becomes immobile or has little movements to keep floating in the water. Measure the total immobility period during the six – minute test. Consider the animal immobile when it ceases to struggle and remain floating motionless in water making only those movements necessary to keep its head above water. In the second group inject imipramine (10 mg/kg ip) Thirty minutes later subject the animal to swim. Note the immobility period and compare it with vehicle treated group. Inference of Imipramine significantly decreases the immobility time in rats. Imipramine showed antidepressant activity in rats.

3. Results and Discussion

Table 1: Group of animals for control and standard

	FST
Distilwater (0.5ml/animal)	Group 1
Imipramine (10mg/kg)	Group 2
Betelleaves(10mg/kg)	Group 3
Clove (10mg/kg)	Group 4
Betelleaves&clove(10mg/kg)	Group 5
Betelleaves&clove (20mg/kg)	Group 6

Table 2: Results for force swim test

Days	Distilled water	Imipramaine	Betel leaves	Clove	Betel leaves&clove (10mg/kg)	Betel leaves&clove (20mg/kg)
DAY-1MOBILITY TIME	177(sec)	275(sec)	240(sec)	180(sec)	173(sec)	264(sec)
IMMOBILITY TIME	40(sec)	50(sec)	110(sec)	58(sec)	34(sec)	25(sec)
DAY-2MOBILITY TIME	160(sec)	277(sec)	260(sec)	238(sec)	298(sec)	338(sec)
IMMOBILITY TIME	10(sec)	30(sec)	48(sec)	58(sec)	40(sec)	58(sec)
DAY-3MOBILITY TIME	153(sec)	265(sec)	295(sec)	262(sec)	280(sec)	323(sec)
IMMOBILITY TIME	12(sec)	40(sec)	23(sec)	40(sec)	45(sec)	17(sec)
DAY-4MOBILITY TIME	176(sec)	310(sec)	397(sec)	383(sec)	390(sec)	470(sec)
IMMOBILITY TIME	58(sec)	59(sec)	55(sec)	59(sec)	56(sec)	40(sec)
DAY-5MOBILITY TIME	150(sec)	410(sec)	470(sec)	481(sec)	544(sec)	505(sec)
IMMOBILITY TIME	40(sec)	48(sec)	60(sec)	65(sec)	75(sec)	15(sec)

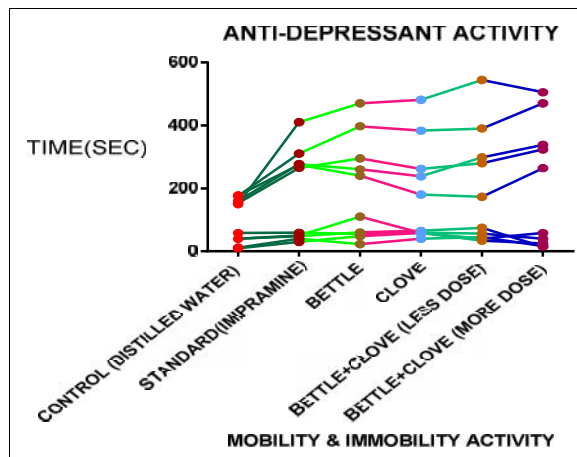


Fig 1: Mobile and immobility activity of betel leaf and clove

Table 3: Antidepressant significant value(p value)

Table Analyzed	Data				
Two-way ANOVA	Ordinary				
Alpha	0.05				
Source of Variation	% of total variation	P value	P value summary	Significant	
Row Factor	84.98	< 0.0001	****	Yes	
Column Factor	5.579	0.0006	***	Yes	
ANOVA table	SS	DF	MS	F (DFn, DFd)	P value
Row Factor	1.181e+006	9	131203	F (9, 45) =45.00	P <0.0001
Column Factor	77524	5	15505	F (5, 45) = 5.318	P = 0.0006
Residual	131205	45	2916		
Number of missing values	0				

Table 4: Preliminary screening tests results

Phytochemicals compound	Betelleafs	Clove	Betelleaf and Clove
Alkaloids	+	-	+, -
Saponins	+	-	+, -
Phenol	-	+	-, +
Protein	-	-	-, -
Coumarin	+	-	+, -
Reducing sugars	-	-	-, -
Tannins	-	-	-, -
Phytosterols	-	+	-, +
Anthroquinone	-	-	-, -
Anthrocyanides	-	-	-, -
Triterpinoids	-	+	-, +
Phlobatannins	-	-	-, -
Acids	-	-	-, -
Glycosides	+	-	+, -
Flavoloids	-	-	-, -
Carbohydrates	-	-	-, -

4. Conclusion

The collection of herbal plants showing the antidepressant activity were tabulated from the various journals and were reported above as we can conclude that herbal plants are very rich source of substance which are responsible of increasing the antidepressant activity. The present study was carried out to evaluate anti-depressant activity of ethanolic extract of piper betel leaves and clove from the mobility and immobility studies and preliminary phytochemical screening we concluded that the piper betel and clove were the very rich source of substances which are responsible for increasing the antidepressant activity. We concluded that the combination of both piper betel and clove were having more antidepressant activity when compared to use as an individual dosage forms.

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