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Determination of antidepressant activity of cinnamaldehyde per se and its interaction with escitalopram using tail suspension test in Swiss Albino mice

Hemant Tanwani[1] and Ritesh Churihar[*2]

[1]*Department of Pharmacology, M.G.M. Medical College, Indore, M.P., India*
[2]*Department of Pharmacology, Govt. Medical College, Ratlam, M.P., India*

Abstract

Background: Cinnamon is one of the best-known spices used as an herbal medicine. Cinnamaldehyde (CNM) is the most important constituents of cinnamon.
Objectives: The present study was aimed to evaluate the antidepressant activity of CNM *per se* & its interaction with standard antidepressant drug, escitalopram in Swiss albino mice using tail suspension method.
Method: Healthy mice of either sex weighing 20-30 grams were divided into groups of 6 animals each. For this CNM (100, 200 & 400 mg/kg), escitalopram 10 mg/kg & combination (CNM 100/200 mg/kg + escitalopram 10 mg/kg) were given orally daily for 21 days. TST was done on 0, 7th, 14th & 21st day.
Results: On acute administration escitalopram as well as CNM at lower doses i.e.100mg/kg showed the antidepressant activity as compared to control. ($p< 0.05$) however at higher doses of 200 & 400 mg/kg CNM did not show any effect. While on sub acute and chronic administration of CNM for 14 and 21 days respectively, CNM (100 mg/kg) has antidepressant activity ($p< 0.05$), while increasing doses of 200 and 400 mg/kg did not change any time of immobilization significantly as compared to control but when CNM 200mg/kg was given in combination with escitalopram 10mg/kg, decrease in the antidepressant effect of escitalopram was observed.
Conclusions: CNM at lower dose alone as well as in combination with escitalopram showed antidepressant activity in both acute and chronic study while at higher dose i.e. 200/400 mg/kg did not. But combination of CNM 200mg/kg with escitalopram showed decrease in the antidepressant effect only on chronic administration.
Keywords: TCADs, SSRI, BDF, Neurotic disorder, Neurotransmitter.

***Correspondence Info:**
Dr. Ritesh Churihar
Department of Pharmacology,
Govt. Medical College, Ratlam,
Madhya Pradesh, India

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1. Introduction

Depression, anxiety and sleep disturbances are the most common type of neurotic disorders which have affected the productivity of nations worldwide in terms of economic and manpower loss. Neurotic disorders include anxiety neurosis, obsessive compulsive disorder, hysteria, social phobias, post-traumatic stress disorder and endogenous depression. Depression is characterized by intense sadness of mood, loss of interest in routine work, severe negative and nihilistic thoughts (life is not worth living), low or high appetite, insomnia and severe suicidal tendency. These symptoms are dependent upon release of neurotransmitters like nor epinephrine, dopamine etc and for management various antidepressant drugs like escitalopram is used.

Cinnamon is one of the oldest and best-known spices in the world and is used as an herbal medicine. [1] Commonly known as dal-chini, darchini or dall chini in Hindi. It belongs to the family *lauraceae* and is found in South India, Srilanka, Indonesia, Vietnam, Bangladesh and Nepal. The active component of commercial cinnamon is the dried inner stem-bark of aromatic evergreen tree 10-15

meters tall. The most important constituents of cinnamon are Cinnamaldehyde (CNM) and eugenol, which are present in the essential oil of the bark thus contributing to the fragrance and to the various biological activities observed with cinnamon.[2] Cinnamon has been investigated for antioxidant property [3], inhibition of tau aggregation [4], anti-inflammatory activity [5], anti-nociceptive activity [6], peptic ulcer protection effects [7-8], effect on cardiovascular system [8-10], hepato-protective effects[11], antihyperlipidemic activity [12] and antidiabetic. [13] The present study was planned to investigate whether CNM has any antidepressant effect *per se* and how does it interact with Escitalopram?

2. Materials and Methods

CNM for present study was obtained from the Science centre, Indore (M.P.) – having 98% purity. The CNM was first dissolved in Tween twenty 20% to make a suspension.

2.1 Animals

Swiss albino mice of either sex (except pregnant females), having 18-30 gm weight were procured from central animal house, M. G. M. Medical College, Indore (M.P.). Animals were housed under standard conditions of 25°C±5°C temp with 50% relative humidity on a 12-h light/dark cycle. The animals were fed with standard diet and water. On the day of experiment animals were kept on overnight fasting with water *ad libitum*. All experiments were performed between 9 am and 5 pm.

2.2 Drugs

- CNM - Science centre, Indore (M.P.) – having 98% purity.
- Tween twenty - Science centre, Indore (M.P.)
- Tablets escitalopram 5 mg

2.3 Principle

The tail suspension test is a novel test for antidepressant activity, based on the observation that a mouse suspended by the tail shows alternate periods of agitation and immobility. The immobility displayed by rodents when subjected to an unavoidable and inescapable stress has been hypothesized to reflect behavioural despair which in turn may reflect depressive disorders in humans.[14]

The cumulative immobility time is a measure of the animal's degree of helplessness ("depression"). Treatment with antidepressant drugs reduces the immobility time. The main advantages of this test are the use of a simple, objective test situation, the concordance of the results with the validated behavioural test from Porsolt and the sensitivity to a wide range of drug doses.[15]

2.4 Drugs treatment groups

Group I Tween-20 20%(10ml/kg, p.o.),
Group II escitalopram (10mg/kg, p.o.),
Group III (100mg/kg, p.o.)
Group IV CNM (200mg/kg, p.o.),
Group V CNM (400mg/kg, p.o.),
Group VI CNM + escitalopram (100mg/kg + 10mg/kg, p.o.),
Group VII CNM + escitalopram (200mg/kg + 10mg/kg, p.o.).[16]

2.5 Procedure

TST was performed according to the method described by Streu *et al* [17] with slight modifications. Mice of all groups were administered the different drugs/ combinations orally daily for 21 days. TST was done on day 0, 7th, 14th, 21st day. On day 0, TST was done before and after one hour of the drug treatment. On the test day the drugs were given 1 hour before the test session. The test was conducted by suspending the mice by their tail at a height of 58 cm above the table top, from a metal rod strung between two stands. An adhesive tape placed about 1 cm from the tip of the tail was used to do this. Each mouse was suspended individually. The movements of the mice were observed and recorded for a period of 6 min. Periods where the mice lay motionless or passive were considered as the immobile phase.

3. Observations

Observations are as per the table no. 1.

Table 1:- Effect of cinnamaldehyde *per se* and its interaction with Escitalopram (ESC) on immobility period in Tail Suspension Test

Treatment	Dose (mg/ kg) p.o.	Immobility period (sec / 6min)				
		Day 0		Day 7	Day 14	Day 21
		Pre drug treatment	Post drug treatment			
Control tween-20 20%	10 ml/kg	231.33±5.07	228.50±8.25	278.67±9.33$^{\#}$	299.33±29.43	311.67±3.49
ESC	10	261.50±3.30	172.67±3.23*	166.17±4.78*	155.33±1.92*	147.00±5.49*
CNM	100	280.83±3.48	160.17±2.13$^{*\#}$	158.00±3.04$^{*\#}$	160.17±3.57$^{*\#}$	162.50±4.80$^{*\#}$
CNM	200	222.50±8.14	221.33±3.81	284±21.87	291.67±2.61	311.33±6.56
CNM	400	280.83±3.37	214.50±3.510	298.33±10.44	330.33±4.43	336.00±5.36
CNM + ESC	100 + 10	232.50±4.14	156.21±3.16$^{*\#}$	155.35±2.61$^{*\#}$	152.26±3.16$^{*\#}$	140.22±2.26$^{*\#}$
CNM +ESC	200 + 10	263.00±2.95	227±3.96	225.50±8.77	255.17±8.68	267.33±10.52
One Way ANOVA	F	17.293	42.37	41.02	23.25	259.11
	P	<0.001	<0.001	<0.001	<0.001	<0.001

One way ANOVA followed by multiple tukey's comparison test. Values are mean ± SEM, n=6, DF = 5, 36, $^{*}P<0.05$, compared to control group. $^{\#}P>0.05$, compared to escitalopram.

4. Result

Escitalopram 10mg/kg, CNM at 100 mg/kg and their combination group showed significant decrease in immobility period as compared to control ($p<0.05$) during whole study period test days i.e. 0 (post drug), 7^{th},14^{th} and 21^{st}.

CNM at 100 mg/kg showed antidepressant activity per se and in combination with escitalopram 10mg/kg but as the dose of CNM was increased to 200 and 400 mg/kg no antidepressant activity per se was seen, also escitalopram 10mg/kg in combination with CNM haven't shown any activity.

5. Discussion

Depression is characterized by emotional disturbances in the form of deeply sad mood, affect, anxiety, loss of interest, decreased concentration, loss of sleep, loss or excess of appetite, nihilistic ideas (life is not worth living-to the extent of suicidal ideation and loss of energy in doing daily activities.

Depression is affected or superimposed by many factors like environmental, jobs related, poverty, over stress due to inadequate coping skills superimposed on genetic factors. Genetic factors often determine deficiency of various neurotransmitters like serotonin, nor epinephrine and dopamine. Depression is often acute or chronic in the time course of the disease. Frequency of occurrence being one of every four persons in its lifetime in the USA.

Depression can be treated by CBT (cognitive behavior therapy), may be benefitted by pranayama and yoga but those persons who experienced depression should be treated with proper management, one of them is early pharmacological intervention. Current drugs of choice for depression are the selective serotonin-reuptake inhibitor (SSRI) group like fluoxetine, escitalopram and fluvoxamine which have lower side effects as compared to previous drugs which were MAOI and TCADs (tricyclic anti depressants) that were associated with more side effects like cardiac arrhythmias, hypertensive crisis in the form of cheese reaction, anti cholinergic side effects etc. Though escitalopram like drugs also cause few effects like decreased libido in females while serotonin syndrome, retrograde ejaculation and dysorganesmia in males.

Cinnamon (*Cinnamomum burmannii*) as one of the commonly found cooking ingredients worldwide including India is believed to provide multiple health benefits. Cinnamon contains various chemical compounds like cinnamaldehyde, flavonoid and terpenoid polyphenols that work as an antidepressant through a mechanism that is in line with the theory of BDNF's (Brain Derived Neurotropic factors) influence on depression, neuro-inflammation and the presence of free radicals in the pathogenesis of depression hypothesis.[18-20] As a traditional herb with long history of usage in cooking, it is also believed that cinnamon posses a very low risk of toxicity in overdose.

5.1 Possible mechanisms of actions for cinnamon having antidepressant activity.

Although exact mechanism by which plant extract cinnamon produces elevation of mood and antidepressant activity are not known, but circumventional evidences indicate about BDNF's anti-inflammatory and antioxidant properties responsible for above through neuroplasticity which possibly release serotonin and nor epinephrine.[18]

Literature has indicated about one of the cinnamon byproducts in the body include sodium benzoate (NaB) metabolite where NaB is possibly able to increase the levels of BDNF neurotrophin expression *in vivo* in rat.[18] In addition to cinnamaldehyde, cinnamon plants also yield proanthocyanidin which includes condensed tannin compounds.[21] Proanthocyanidin is proved to be protective against depression and anxiety, where it has antidepressant activity by increasing BDNF expression in the hippocampus and frontal cortex of chronically stressed mice.[22] It was found that administration of antidepressants can increase BDNFs and the administration of BDNF infusion has an antidepressant effect.[23]

Studies have also indicated about cinnamon reducing the levels of lipopolysaccharides in plasma which can induce tumour necrosing factor (TNF) in blood. TNF-α is known to induce release of various cytokines like IL-1β, IL-6, IL-8 and IL-12 which probably induce inflammation in hippocampus and amygdela in the brain. TNF-α is stated to be able to induce depressive behavior in mice.[24] Further meta-analysis study has proved that there is a decrease in IL-1 β after administration of antidepressant drugs like SSRI. [25-27]

The effects of chronic stress on brain and nervous system can produce a considerable reduction in the levels of BDNF in areas like hippocampus (along with glutamate induced calcium influx related neurocytotoxicity) which can reduce the levels of serotonin which is the main contributory factors in episodes of depression on the scientific basis. Similarly neuronal damage over a long term can cause a deficiency of dopamine or dopamine receptor deregulation by acting probably at the level of mRNA at nucleus level of hippocampus cells. Further studies have indicated about use of antidepressants on chronic use with increased levels of BDNF which can release serotonin and dopamine from neuronal cells. [27-28]

The chronic brain inflammation is associated with reduced density of glial cells which are main supporting connective tissue for active neurons. The stress related glial injury shall in long term will produce brain cortical atrophy

(prefrontal cortex) which we propose as the cause of loss of memory felt by chronically depressed persons. Similarly chronic stress is also associated with release of corticosteroids. Corticosteroids may be trying to reduce inflammation through intra nuclear receptors as their established mechanism. Excessive cytokines may be ameliorating the functions of P38 Mitogen–Activated Protein Kinase (MAPK) which is known to cause down regulation of steroid receptors thus endogenous glucocorticoids may not be able to cope up and reduce stress related inflammation.

5.2 Possible role of cytokines on serotonin and dopamine transporters

There is possibility of enhanced activity of serotonin and dopamine transporters which carry or transport neurotransmitters to pre synaptic neurons due to activation of P38 sub variety of MAPK17. There may also be role of indol amine stimulating 2, 3 dioxygenase (IDO) cytokine which may be inhibiting conversion of tryptophan to serotonin, thus lowering its availability in body. [27]

Cinnamon also possesses linalol and eugenol chemicals which reduce lipid peroxidation which is known to produce oxidation induced free radicals (responsible for inflammation). Peroxidation activity is high as suggested by presence of malondialdehyde in generalized anxiety disorders. [26, 28]

Another pathogenesis of depression is the presence of an oxidant and antioxidant imbalances due to an increase in glucocorticoid secretion which causes a slight impact by an increase in reactive oxygen production (ROS), that can reduce serotonin and dopamine production. [26,28]

We have tried to search literature for typical neurotransmitter reuptake property of cinnamaldehyde similar to well known SSRI & TCADs, but either very little or no activity was observed by researchers. Though one publication has indicated about slight activity of it while comparing MAO-I (Mono amino oxidase inhibition) property of various food additives. [29]

6. Conclusion

Different dose of cinnamaldehyde (100 mg/kg) and its combination with Escitalopram work effectively as an antidepressant in Swiss albino Mice while 200 mg/kg and 400 mg/kg did not shown any effect. Further studies are recommended on various combinations as well as individual agent which may prove to be very good complementary regimens for the treatment of many disorders. Pharmacokinetic studies are also required to further explore the bio enhancing property (if any) and to characterize exact extent and mechanisms of such interactions.

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Conflict of interests

There is no conflict of interest among the authors.

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