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Antidepresant effects of Cinnamon (Cinnamomum burmannii) extract in depressed induced rats using 3-minutes Tail Suspension method

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ABSTRACT

Background

The increasing prevalence of depression gives rise to challenges in not only elucidating its diverse causes, but also in finding an effective treatment. One of the factors linked to depression is the imbalance of serotonin, norepinephrine, and dopamine neurotransmitters. Cinnamon (*Cinnamomum* burmannii) as one of the world's wellknown cooking ingredients is believed to be able to regulate the neurotransmitters imbalance with the help of terpenoids and flavonoid polyphenols as one of its content.

Objective

This study aims to determine the effectiveness of cinnamon extract as an antidepressant in depressed induced animal model.

Methods

An experimental *in vivo* with *pre-post control group design* was conducted in twenty five Wistar strain white rats that were divided into 5 treatment groups that received fluoxetine as positive control, aquades, and different dose of cinnamon extracts (50 mg/kgBW, 100 mg/kgBW, and 200 mg/kgBW). Depression induction method used was 3-minute Tail Suspension Test, done for 14 days. The antidepressant effectiveness test was carried out by calculating the immobility time duration with Forced Swimming Test method and was further analyzed using one-way ANOVA test.

Results

One-way ANOVA test results showed that there were differences in the mean duration of immobility time between treatment groups after being given cinnamon extract (p value = 0,000). Groups that were given 100 mg/kgBW cinnamon extract and 200 mg /kgBW showed a p value>0.05 when compared with positive control group receiving Fluoxetine although displayed a similar reduced immobility time.

Conclusion

Cinnamon (*Cinnamomum* burmannii) extract showed a promising potential as an effective antidepressant tested in animal model.

Keywords: cinnamon, extract, depression, immobility time, rat

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Introduction

Depression is a condition that contributes greatly to the occurrence of suicides every year[1]. The prevalence of depression continues to increase with a risk of two to three times more frequent in women than men. Depression itself is characterized by emotional disorders in the form of depressive affect, anxiety, decreased concentration, loss of interest, and loss of energy in doing daily activities. It is known to be influenced by several factors including genetics, environmental, one's personality, as well as abnormalities in the number and function of neurotransmitters in body.

Depression is often not only a one-time episode but it can occur repeatedly, leading to impairment in one's activities. A person who experienced depression should be treated with proper management, one of them is pharmacological treatment. Current drug of choice for depression is the Selective Serotonin-Reuptake Inhibitor (SSRI) group which has lower side effects compared to previous drug of choice which was MAOI antidepressants and tricyclics[2]. Yet the use of SSRI shows various side effects such as sexual dysfunction in women in the form of decreased libido, and anorgasmia arousal and erectile dysfunction in men [21.]

Cinnamon (*Cinnamomum burmannii)* as one of the commonly found cooking ingredients worldwide including in Indonesia is believed to provide health benefits. Cinnamon (*Cinnamomum burmannii*) contains various chemical compounds like flavonoid and terpenoid polyphenols that work as an antidepressant through a mechanism that is in line with the theory of BDNF's influence on depression, neuroinflammation, and the presence of free radicals in the pathogenesis of depression hypothesis [3,4,5] As a traditional herb with long history of usage in cooking, it is also believed that cinnamon posseses a very small risk of toxicity. Thus it is believed to be an alternative treatment for depression with a minimum side effects.

Methods

This was an experimental *in vivo* study with *pre-post control group design.* As many as twenty five white male wistar rats were divided into 5 groups. The first group was administered with fluoxetine as a positive control, the second group was administered with aquadest as a negative control, third, fourth, and fifth group were administered with various dose of Cinnamon extracts, namely 50 mg/KgBW, 100 mg/KgBW and 200mg/KgBW.

Phytochemical Test

In this study, a phytochemical test was conducted to identify active compounds in the cinnamon extract. The examinations carried out were tests of flavonoids, phenols, alkaloids, quinones, steroids, saponins, and tannins.

Cinnamon Extract

Two hundred and fifty grams of powder Simplicia cinnamon was macerated with 96% ethanol. Extracts was then obtained through evaporation using *vacuum rotary evaporator*, before it then dried and crushed to homogeneous.

Administration of antidepressant drugs

The antidepressant drug as positive control being used in this study was a 20 mg fluoxetine capsules. Since the usual dosage in adult humans is around 20mg, then the dose of Fluoxetine for mice is being converted with following equation: 70/50 x 20mg x 0.018 = 0.504 mg / 200gBW = 2.52 mg / KgBW (0.018 is the dose conversion factor from human to rat).

Antidepressant Test for Cinnamon Extracts

Twenty five rats were divided into 5 groups where it underwent the depression induction for two weeks. All the animals were hanging in a pole as high as ± 50 cm for 3 minutes before they were being weighted and observed for depression behavior. After being treated with cinnamon extracts for two weeks, the test animals then underwent a post-test which is Forced Swimming Test (FST) to assess the effectiveness of each cinnamon extracts[6.7]. The FST was carried out in an open tube (± 50 height cm, 20 cm in diameter) containing water with a height of 30 cm. The last 8 minutes, 2 minutes of the first as acclimatization and 6 minutes as the calculation of *immobility time* of test animals.

Results

Results manufacture simple worth as much as 250 grams of the extract obtained as much as 26 grams with results Rdt 10%. The phytochemical test was carried out to cinnamon extract with the following results:

Table 1. Phytochemical Test

Examination	Results	Identification
Phenol	colour black strong	+
Flavonoids	colour orange	+
Alkaloids	formed colour red	+

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Steroids	Blue 1.5 cm foam not lost given HCL	+
Saponin	2N	+
Quinon	Red	+
Tanin	Black	+

There were behavioural changes observed after the induction. Majority of the rats showed a decreased appetite hence the decreasing body weight as it can be seen on table 1. The rats also showed passive behaviour compared to before induction.

Table 1. Body Weight Before and After Induction

Group	N	Before Weight Loss Induction Average ± SD	Body Weight After Induction Average ± SD
Fluoxetine	5	218.6 ± 7.7	212.8 ± 12.3
Aquades	5	215.6 ± 8.1	211.6 ± 11.1
Cinnamon Extract 50	5	203.8 ± 4.7	181 ± 17.8
Cinnamon Extract 100	5	197.4 ± 3.5	198.8 ± 8.4
Cinnamon Extract 200	5	210.2 ± 13.6	197.4 ± 12.2

Soon after each group was being given cinnamon extract for two weeks, a *post-test was* carried out. *Immobility time* data is presented in the following table 2.

Table 2. Differences between *immobility time pre-test* and *post-test*

Treatment Group	Immobility Time Pre ± SD	Immobility Time Post ± SD	*p-value*
Fluoxetine	142.8 ± 8.07	62.8 ± 8.4	0,000
Aquades	133.4 ± 10.9	145.2 ± 9.7	0.226
Cinnamon Extract 50	140.4 ± 6.02	134.8 ± 7.79	0.181
Cinnamon Extract 100	135.4 ± 6, 2	74.8 ± 7.75	0,000
Cinnamon Extract 200	142.4 ± 14.7	61.2 ± 13.1	0,000

Paired Sample T Test , p <0.05

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Differences in *immobility time pre-test* and *post-test* in each treatment group was analyzed using the *Paired Sample T Test*. As it can be seen in table 2, there were differences in the mean *Immobility time pre-test* and *post test* in three groups: fluoxetine group (*p value* = 0,000), cinnamon extract 100 mg/kgBW (*p value* = 0,000), cinnamon extract 200 mg/kgBW (*p value* = 0,000). The other two groups which are aquades (*p value* = 0.226), and cinnamon extract 50mg/kgBW (*p value* = 0.181), showed no differences in mean *immobility time pre-test* and *post-test.*

Table 3. Differences in Average *Immobility Time Post-Test*

Treatment Group	N	Average ± SD	*P value*
Fluoxetine	5	63.8 ± 8.4	
Aquades	5	147.2 ± 9.7	
Cinnamon Extract 50	5	137.8 ± 7.7	0,000
Cinnamon Extract 100	5	78.8 ± 7.7	
Cinnamon Extract 200	5	66.2 ± 13.1	

one way anova , p <0.05

Based on the one-way ANOVA test, difference meaningful *immobility time* deliver group treatment, then *post hoc* tests were compared to each treatment group. fluoxetine group compared with the Aquades group and the group of cinnamon extract dose 50 mg / kgBW obtained *p-value* 0,000 (p <0.05) the meaning different significant whereas the fluoxetine group is compared with cinnamon extract dose of 100mg / kgBW (*p-value* = 0.225) and 200 mg / kgBW (*p-value* = 1,000) which means there is no significant difference on group, so be concluded that the dose of cinnamon extract having an effective similar to those observed with fluoxetine in reducing *immobility time* on rat there is on cinnamon extract of 100mg / kgBW and 200mg / kgBW.

Discussions

Before the test animals were given an induction of depression, all test animals were weighted. After the two weeks induction, the test animals were weighted again. It can be inferred from table 1 that there were changes in weight before and after the induction. These changes might be due to changes in appetite becaused of the occurence of depression in animal test. Dietary symptoms including changes in appetite are one of the most commonly identified symptoms in depression. Some experience decrease of appetite (35%), while some experience increase of appetite (48%). These two

conditions are caused by different mechanism in quite a same pathway. Major depression with an increased appetite is caused by increased activity of *blood-oxygen-level-dependent* (BOLD) in the brain involving the *reward* system *(anterior insula, orbitofrontal cortex, ventral striatum, the ventral pallidum,* and *putamen),* while major depression with decreased appetite decreases *blood-oxygen-level-dependent* (BOLD) activity in the mid-insula part[8].

The cinnamon extracts contain various substances with cinnamaldehyde as the major component. Cinnamaldehyde metabolism in the body produces sodium benzoate (NaB) metabollite where NaB is thought to be able to increase BDNF neurotrophin expression *in vivo* in rat[3]. In addition to cinnamaldehyde, cinnamon extracts also contain other active substances namely proanthocyanidin which includes condensed tannin compounds[10]. 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[11]. The application of chronic stress can provide a variety of effects on the neuron system, one of which is a decrease in the synthesis of BDNF mRNA in the hippocampus which causes a decrease in serotonin as one of the most important factors in depression. In another study, it was found that administration of antidepressants can increase BDNF and the administration of BDNF infusion has an antidepressant effect[12].

In previous study it was stated that Cinnamon extracts increase dopamine at doses of 50 mg / kgBW, 100 mg / kgBW and 200 mg / kgBW[13]. In depression, dopamine dysfunction can cause dysregulation in the reward, arousal or spirit system, making depressed people became hedonic deficits[14]. Aqueous extract of cinnamon for 6 days can reduce lipopolysaccharide which induces *tumour necrosis factor-α (* TNF-α) in serum. TNF-α is stated to be able to induce depressive behaviour, which in line with the discovery of elevated serum levels of *IL-1β, IL-6, IL-8, IL-12* and *TNF-α* together with a decrease in anti-inflammatory *IL-10* in depressed people[15]. A meta-analysis study proves that there is a decrease in IL-1 *β* for administration antidepressant SSRI[19]. The presence of inflammation is thought to cause microglia activation which is associated with hippocampal connectivity disorders that affects on depression. Other hypothesis mechanism in depression like cytokine hypothesis, is the activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis. Its activation leads to the increment of cortisol, responding to inflammation by inhibiting *Nuclear Factor Kappa* B (NF-kB). However, excessive cytokines due to persistent inflammation can activate P38 *Mitogen-Activated Protein Kinase* (MAPK). This will further cause disruption of glucocorticoid receptor function which has an impact

on failure of inhibition in NF-kB, leading to failure in inhibiting of the production of excessive cytokines[16]. The next hypothesis is that cytokines will activate serotonin transporters, which is an extracellular transporters that work to bring back serotonin (5-HT) to pre synapse due to activation of P38 MAPK[17]. The final hypothesis of depression is indoleamine-stimulating 2,3- *dioxygenase* (IDO) cytokines. It is an enzyme that convert the amino acid tryptophan as a 5-HT precursor to a kynurenine metabolite so there will be an imbalance in serotonin availability. This supports the results of research that proves the difference in 5-HT ratio to Kynurenine metabolites are found to be higher in depressed people[18] .

As previously stated, other than containing cinnamaldehyde, cinnamon is also known to contain others substances, like linalool and eugenol for intstance. These two substances are known to reduce lipid oxidation [19]. This function matters because lipid peroxidase will increase in conditions of psychological stress such as depression. The presence of lipid peroxidase activity causes free radical formation in major depressed patients and *Generalized Anxiety Disorder* (GAD) with the discovery of malondialdehyde (MDA). Another pathogenesis of depression is the presence of an oxidant and antioxidant imbalances due to an increase in glucocorticoid secretion which causes an increase in reactive oxygen production (ROS). The presence of MDA as an indicator of oxidative stress can cause a decrease in serotonin and inhibit serotonin from binding to the receptor[17,18].

Conclusion

Certain dose of cinnamon extracts work effectively as an antidepressant in Wistar strain white rats that were induced with depression through two weeks of 3-minutes Tail Suspension method. Further investigation on its antidepressant potential in humans is needed.

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