

# The Efficacy of Noni Fruit Methanol Extract (*Morinda citrifolia*) to Brain Derived Neurotrophic Factor (BDNF) on Male Swiss Webster Mice Induced By Immobilization Stress

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## 2 The Efficacy of Noni Fruit Methanol Extract (*Morinda citrifolia*) to Brain Derived Neurotrophic Factor (BDNF) on Male Swiss Webster Mice Induced By Immobilization Stress

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**Abstract.** Aging process is associated with declines in certain cognitive abilities such as learning and memory ability and impact on high risk of dementia, physical disability and death. Oxidative stress is believed as basic mechanism of aging process. *Morinda citrifolia* (Noni fruit) has long been used as a traditional plant in worldwide and was proven empirically in traditional medicine as antioxidant. This study was to determine the effect of noni fruit methanol extract on BDNF levels in white mice of Swiss Webster strain induced by immobilization stress. This research is experimental study with post test only control group design. Male Swiss Webster Mice were induced by immobilization stress and randomized into seven groups (5 mice/groups). The first group was negative control group; Group 2,3,4,5 and 6 was given treatment with varied concentrations of *Morinda citrifolia* (50, 100, 200, 400 and 800 mg/kgBW). Vitamin E (70 mg/kgBW), standart antioxidant was used as positive control (Group 7). Brain BDNF level of the white mice were measured by using ELISA method. Experiment result showed that treatment with *Morinda citrifolia* extract (50, 100, 200,400 mg/kgBW) and Vitamin E 70 mg/kg BW showed a significant differences in BDNF level compare with the negative control rats. There is no significant differences between 200 mg/kgBW Metanol Extract of *Morinda citrifolia* group and vitamin E ( $p=0,301;p>0,05$ ). Metanol Extract of *Morinda citrifolia* could prevent the decrement of BDNF level due to stress.

**Keywords :** *Morinda citrifolia*, Noni fruit, BDNF, stress

### 1. Introduction

Aging process is a gradual and irreversible decrease in the physiological capacity of the body system to the extent of failure and death. Aging is a major cause of decreased brain function such as learning and memory processes (1,2). An increase of the elderly population along with the high life expectancy around the world causing cognitive decline caused by aging has become one of the serious problem in health care system. The decrease of cognitive function will have an impact on the high risk of dementia, physical disability and death (3,4). Aging process is believed to be mediated by oxidative stress. Oxidative stress is a redox state caused by an imbalance between the production and detoxification of reactive oxygen species (ROS) that can cause oxidative damage to lipids and proteins and decrease natural glutathione and antioxidant levels in the synapse of nerve cells (1,5,6).

Brain-derived neurotrophic factor (BDNF) is a neurotrophin family that plays a role in the proliferation, differentiation and survival of nerve cells (7). BDNF also protects nerve cells from oxidative stress caused by



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hypoglycemia, ischemia, hypoxia and ethanol toxicity (8). Stress, both acute and chronic, affects the synthesis of BDNF in the brain. Chronic stress decreases BDNF protein expression (9,10) whereas acute stress is quite the opposite (11,12).

Previous studies have shown that *Morinda citrifolia* could increase the levels of antioxidant enzymes (13), as well as inhibit the formation of malondialdehyde (MDA) and Nitric Oxide (NO) (14). The extract of methanol and ethyl acetate of noni fruit can prevent oxidation of Low Density Lipoprotein (LDL) induced by Copper (15) and inhibit oxidation process due to lipid hyperoxidation or superoxide anion (16).

Until now, many studies have been conducted on the antioxidative and antiinflammatory capabilities of noni fruit, the pharmacological effects of noni fruit as antioxidant and antiinflammatory are also thought to be able to protect the nerve damage caused by oxidative stress so that the need to be studied and examined how the effect of giving extract methanol of *Morinda citrifolia* against BDNF levels in white mice of swiss strains of male Webster induced chronic immobilized stress.

## 2. Materials and Methods

### 2.1 Preparation of Extract

*Morinda citrifolia* fruits were collected from Tebedak, Ogan Ilir, South Sumatera Indonesia during the month of October 2016. The fruits were washed, blotted, dried and sliced into 100 mesh. Five hundred grams of dried fruit powder were macerated with 1000 ml of methanol for 24 hours, stirring regularly, filtered. The residual residue is macerated again 3 times so that all the substances contained in the mengkudu fruit is extracted. All the filtrate is then collected and evaporated in rotary evaporator.

### 2.2 Animal and Experimental Design

The research subjects were 35 of Mus Musculi 10 to 12-week-old male Swiss Webster strain with the weight ranging from 25 to 35 grams, conserved in the Animal House of Medicine Faculty of Sriwijaya University. Each cage housed eight mice fed by food and drinks every day ad libitum. The conservation room was well ventilated with the maintained room temperature of 25 to 30 °C, humidity of 50 % to 60% and the cycle ratio of darkness to brightness of 12:12 hours.

Seven days after acclimatization, the subjects were then randomly divided into four groups with five mice for each. Group 1 was negative control group; group 2,3,4,5 and 6 was given treatment with varied concentrations of *Morinda citrifolia* (50, 100, 200, 400 and 800 mg/kgBW. Vitamin E (70 mg/kgBW), standart antioxidant was used as positive control (Group 7). All mice were put in a particular plastic canister, specially designed to ensure the mice would stay in dorsal recumbent position without access to food and drink. Such immobilized stress would be applied for two hours (10 am to 12 pm) for 21 consecutive days.

### 2.3 ELISA Assay

Mice had to be sacrificed 24 hours after the last training session by decapitation to obtain fresh tissues by decapitation procedure without anesthesia as outlined by Institutional Animal Care and Use Committee (IACUC). Brain was separated from the skull and brain stem manually with a scalpel blade and a micro tweezer, then was restored at -80°C. The brain tissue sample was homogenized with blade homogenizer after being added with PBS. Next, the sample was centrifuged with the velocity of 3,000 rpm for 20 minutes in 4°C temperature. BDNF levels of brain tissue were measured by the ELISA method as described in manufacturer's instructions of ELISA kit

### 3. Results and Discussion

#### 3.1 Result

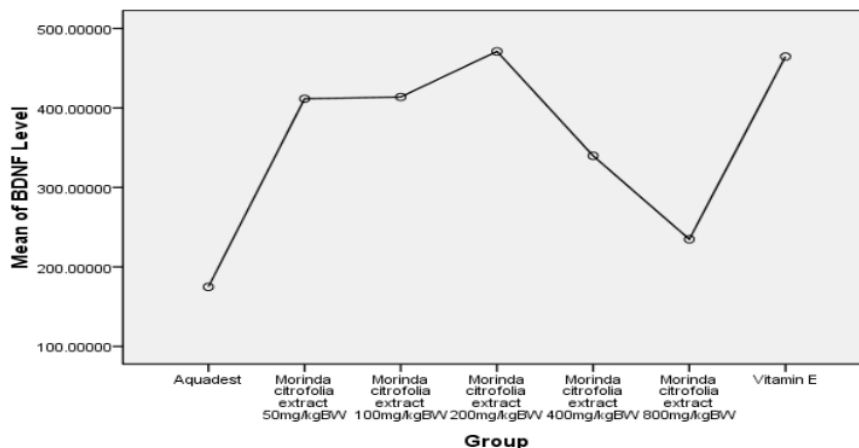
The mean BDNF levels for all groups were between (174.8 ± 6.81) and (470.93 ± 10.9) pg/ml.

**Table 1 The Efficacy of *Morinda citrifolia* Extract on BDNF Level (pg/ml)**

<b>Vitamin E</b>	<b>464,53± 6,53</b>
<b>Aquadest</b>	174,8± 6,81 <sup>b</sup>
<i>Morinda citrifolia</i> extract 50mg/kgBW	411,40± 8,24 <sup>b</sup>
<i>Morinda citrifolia</i> extract 100mg/kgBW	413,67± 6,57 <sup>b</sup>
<i>Morinda citrifolia</i> extract 200mg/kgBW	470,93± 10,9 <sup>a</sup>
<i>Morinda citrifolia</i> extract 400mg/kgBW	339,67± 8,57 <sup>b</sup>
<i>Morinda citrifolia</i> extract 800mg/kgBW	234,73± 15,94 <sup>b</sup>

Independent T Test, a :  $p > 0,05$  vs vitamin A. b :  $p < 0,05$  vs vitamin A; Significance level was determined by one way ANOVA followed by LSD pos-hoc test.

Table 1 showed BDNF Level as negatif control and subjected to *Morinda citrifolia* extract (50,100,200,400,800 mg/kgBW) and Vitamin E. Treatment either extract and Vitamin E significantly increased BDNF Level ( $p < 0,05$ ) compare with negative control. But, there was no differences between Vitamin E group and *Morinda citrifolia* extract 200mg/kgBW groups in BDNF Level after treatment ( $p = 0,301$ )  $p > 0,05$ ).



**Figure 1 Average Graph of BDNF Level (pg/ml)**

### 3.2 Discussion

As the main organ that responds to stress, brain undergoes structural and chemical changes (17). It is a form of brain adaptation (allostasis) in maintaining homeostasis. Although the brain is able to adapt, extreme and repetitive stress exposure can cause brain plasticity abnormalities, while lowering the ability to control stress (allostasis overload). Some forms of brain plasticity include neurogenesis (18), dendrite remodeling (19,20) and synaptic reinforcement (21).

The glucocorticoid hormone is the last effector of the HPA axis that plays an important role in stress management (22). The interactions of glucocorticoids hormones and their receptors affect the expression of some of the genes involved in cell metabolism, the structure and transmission of synapses, such as enzymes, neuropeptides, growth factors, and cell adhesion molecules (23). One candidate who plays an important role in brain plasticity is the brain-derived neurotrophic factor (BDNF) (24). Glucocorticoid hormone has been shown to influence the expression of the BDNF gene (25).

BDNF expression in the brain is strongly influenced by the development of phylogenetic brain, type, intensity and duration of stress, as well as the rhythm of the glucocorticoid hormone in the blood regulation (25). In addition, the role of epigenetic factors, such as CREB as transcription factor, methyl-CpG-binding protein 2 (MeCP2) as transcriptional repressor, Ca<sup>2+</sup> ions and other intracellular signaling cascades also affect BDNF gene expression (26,27).

In this study, the cerebroprotective effect of Noni fruit methanol extract on BDNF was clearly demonstrated using stress immobilization model mice. The results of this study showed that the extract of 200mg / kgBW dose of Noni fruit methanol extract showed the highest increase of BDNF, but the increase of dose of methanol extract to 400 mg/kgBW or 800mg/kgBW did not show better improvement than the 200mg/kgBW dose. It was concluded that the effect of Noni fruit methanol extract of 200 mg / kg BW can significantly increase BDNF levels compared to vitamin E and methanol extract of noni fruit on BDNF concentration in this research is flat dose.

The efficacy of Noni fruit (*Morinda citrifolia*) as a neuroprotector against cell damage caused by oxidative stress has long been proven. It is mediated by the active chemicals contained in noni fruit, including enzymatic antioxidant (Superoxide dismutase, catalase, peroxidase, glutathione reductase, glutathione-s-transferase) and non enzymatic antioxidant (ascorbic acid, alpha tocopherol, vitamin A, flavonoids, phenols and tannins (28). Studies have also reported that Noni fruit extract could also pass the blood brain barrier (29).

Research conducted by Muralidharan *et al.* (2010) mentioned that giving ethyl acetate fraction of noni fruit in mice with beta-amyloid induced cognitive dysfunction model at dose of 400 mg/kg/day could increase serotonin, dopamine and antioxidant enzyme serum levels (30). According to Achauri *et al.* (2012) giving ethanol extract of noni fruit and ethyl acetate fraction in mice enhanced memory and brain blood flow and decrease oxidative stress and acetylcholinesterase activity (31). The same result is also conveyed by Hussin *et al.* (2007) who mentioned that giving ethanol extract of noni fruit could inhibit lipid peroxidation where it is characterized by decrease serum MDA level and increased activity of antioxidant enzyme (32).

#### 4. Conclusion

Noni fruit extract of 200mg/kgBW dose was effective in increasing BDNF levels in white mice of Swiss Webster strain induced by immobilized stress which the effect of noni fruits extract on BDNF levels was flat dose.

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