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Effect of Extract Omega-3 Fatty Acids Consumption from Mackerel as Adjuvant of Antidepressant Fluoxetine (*Rastrelliger kanagurta)* on Decreasing Cortisol Hormone Levels

Aisyah Izzatinisa[1]*, Novita Angkirani[1], Zabrina Zerlinda[1], Jessica Audrey William[1], Azizah Hanun Yasmin[1], Ziske Maritska[2]

[1]Medical Study Program, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
[2]Departement of Biology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
E-mail: 04011382126199@student.unsri.ac.id

ABSTRACT

Depression, one of the common mental disorders; generally identified by feelings of sadness or disappointment when experiencing a change, loss, or failure and becomes pathological when unable to adapt. According to WHO, Indonesians have a suicide ratio of 3,7 per 100.000 population. People with depression have some dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis, which takes a part in the organism's reaction to depression. As a hormonal response to stress signals, thus the cortisol hormone will be released. The cortisol hormone mainly modulates emotions, especially fear and anxiety. Hence, patients with depression tend to have higher cortisol hormone levels. The most commonly used psychopharmacological medication is antidepressants. However, only about 40-60 out of 100 individuals are helped by taking antidepressants. Thereupon, as support for antidepressants, an adjuvant, i.e., omega-3 fatty acids in mackerel (*Rastrelliger kanagurta*) is needed. Therefore, the author uses Google Scholar, WHO, PubMed, and HealthLine as references for this literature review. After reviewing the literature, omega-3 fatty acids in mackerel can act as an adjuvant to antidepressants in lowering cortisol hormone levels. The dosage of omega-3 fatty acids needs to be analyzed to optimize the potential of adjuvant therapy for fluoxetine.

Keywords: omega-3 fatty acid in mackerel (*Rastrelliger kanagurta*), cortisol, depression, antidepressant, adjuvant therapy

1. Introduction

Depression, one of the common mental disorders, generally identified as feelings of sadness or disappointment when experiencing a change, loss, or failure, and becomes pathological when the patient can't adapt to that effect.[1] Nowadays, regardless of age, not only adults but also children and teenagers, depression commonly happens to society.[1] Depression can affect the patient effectively, physiologically, cognitively, and behaviorally.[1,2] Thus, depression can change the usual pattern and response of the human body. This condition can become chronic and repetitive to the point of interfering with an individual's ability to carry out their daily life.[3] At its most severe level, depression can lead to suicide.[1] The World Health Organization (WHO) states that depression ranks fourth worldwide as a disease, predicted to become a primary health problem.[4] Depression is more prone to occur at a young age. According to WHO (2019), around 800.000 people die from suicide each year.[4] Indonesians have a suicide ratio of 3,7 per 100.000 population.[1] The stigma of depression makes people think it is just a feeling that could come and go. Depression can seriously affect an individual's behavior, emotions, and way of thinking.[3,4]

The main characteristic of depression is the dysfunction of the Hypothalamic-pituitary-adrenal (HPA) axis, which has a dominant part in the organism's reaction to stress, anxiety, and depression.[5] Hypothalamic-pituitary-adrenal (HPA) axis

dysfunction triggers the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, which then triggers the release of glucocorticoids from the adrenal cortex.[6,7] In human body, cortisol hormone is the fundamental glucocorticoid that modulates metabolism, cognitive processes, and emotions, notably fear and anxiety.[6,7] The most commonly used psychopharmacological treatment for this condition is antidepressants.[8] Two classifications of antidepressants, i.e., older antidepressants (Tricyclic antidepressants/ TCAs) and newer antidepressants (Monoamine Oxidase Inhibitors/MOAIs, Selective Norepinephrine Reuptake Inhibitors/ SNRIs), and Selective Serotonin Reuptake Inhibitors /SSRIs.[9,10]

Depression will activate the sympathetic nervous system (SNS) and will be responsible for the fight or flight response. Thus, it will become an agent of hormonal and physiological responses.[10] The amygdala will process emotional stimuli and send stress signals to the hypothalamus.[10] Then, the hypothalamus will activate the SNS, which will cause the adrenal glands to release an outpouring number of catecholamines, named as epinephrine.[10] This condition will cause an increased heart beat and respiratory rate so that the body carries on to perceive the stimulus as a threat.[10,11] The hypothalamus will activate the HPA axis so that cortisol is discharged from the adrenal cortex. Increasing level of cortisol allows the body to remain alert.[10,11] Many types of research show that SSRI consumption increases BDNF levels, reduces HPA axis activity, heightens long-term potentiation, and reduces depression-like behavior.[12] But, the efficacy varies: 30-40% of patients do not give a significant response, and 60-70% of patients do not have an improvement in their condition.[12] Therefore, adjuvant therapy is needed to support fluoxetine as an antidepressant.

To help overcome depressive disorders, researchers utilized the extracts of omega-3 fatty acids found in one of the widely consumed fish populations in Palembang City, namely mackerel. One of the nutritious ingredients of mackerel (*Rastrelliger kanagurta*) is omega-3. The three principal constituents of omega-3 fatty acids are eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA).[13,14] The main ingredients found in fish are DHA and EPA.[14] When the body is in a depressive phase, omega-3 fatty acids help decrease cortisol hormone levels.[14] Adequate consumption of omega-3 fatty acids can inhibit ACTH, therefore reducing cortisol levels.[14] Omega-3 is an essential polyunsaturated fatty acid (PUFA).[15] Omega-3 can't substitute antidepressants, but it can help people with depression as an adjuvant in increasing DHA and EPA levels, to help the effects of antidepressants.[16,17] Based on research, taking antidepressants helps around 40-60 out of 100 individuals to improve the symptoms of depression they are experiencing.[16,17]

Therefore, this literature review contains some research that can prove the effectiveness of omega-3 fatty acids in mackerel in lowering cortisol hormone levels as an antidepressant adjuvant.

2. Method

The method used is a narrative literature review. Journals were selected within the last five years. The search for literature is based on search engine, i.e.: Google Scholar, WHO, PubMed, and Nature with the keywords: Depression, Antidepressants, Omega-3 Fatty Acids, HPA Axis, and Cortisol Hormones. The criteria using English and Indonesian journals, literature review, and meta-analysis with themes and keywords related to the topic of this literature review.

3. Results and Discussions

3.1. Pathophysiology of depression

Decreased construction of proteins that are associated in neurogenesis and synaptic plasticity can be the cause of depression.[18] The target gene for brain-derived neurotrophic factor (BDNF) is one potential site of defects in signal transduction from monoamine receptors.[18] Changes in monoamine neurotransmitters and decreased numbers of BDNF can lead to apoptosis and/or atrophy of susceptible neurons inside the hippocampus and other brain areas.[18] Some neural losses are reversible, i.e., restoration of monoamine-related signal transduction using antidepressants can increase BDNF and other trophic factors and potentially restore lost synapses.[18] Neurons originating from the hippocampus and amygdala can suppress the Hypothalamic-pituitary-adrenal (HPA) axis so that when stress occurs, it causes the hippocampal and amygdala neurons to atrophy. Due to loss of inhibition to the hippocampus, it will cause overactivity of the HPA axis.[18,19]

Increased HPA activity is one of the stress responses and the relationship between depression and chronic stress biology.[19] Depression with hypercortisolemia suggests central disturbances such as decreased 5-HT inhibitory tone; drive upgrades from NE, ACh, or CRH; or decreased hippocampal feedback inhibition.[19]

3.2. Correlation between depression and cortisol hormone

Patients with depression (especially major depressive disorder/MDD) have abnormal signaling of the glucocorticoid receptor, which is associated with chronic corticotropin-releasing hormone (CRH) hypersecretion of the (Hypothalamic-pituitary-adrenal (HPA) axis.[5,6] This hypersecretion shifted to an even higher set point of HPA activity.[6] Therefore, the main characteristic of the depressive patient is dysfunction of the HPA axis.[6] CRH triggers the pituitary gland to discharge adrenocorticotropic hormone (ACTH), which will induce the absorption of glucocorticosteroids, such as cortisol.[7]

Cortisol is a steroid hormone produced by the adrenal glands, functioning in increasing metabolic substrate, maintaining vascular integrity, and protecting from an exaggerated response to the immune system (Nyoman, 2017).[20] Cortisol is the end product of the HPA axis, stimulated by stress, inflammatory, emotional, or physical pain.[20] Under physiological conditions, stress hormones are released in small amounts.[20] But, when faced with a stressful situation, levels of these hormones increase dramatically.[20]

Both physical and psychological stress can increase ACTH secretion, which increases cortisol hormone levels.[20] The first time CRF is released from the hypothalamus into the bloodstream, which eventually reaches the pituitary gland (located just below the hypothalamus).[20] The release of adrenocorticotropic hormone (ACTH) is stimulated by CRf in the pituitary gland.[21] This stimulates the adrenal glands to let out various hormones. One of them is the hormone cortisol.[21]

The hormone cortisol circulates in the body and plays a role in coping mechanisms.[21] The stronger the stressor received by the hypothalamus, the secretion of CRF will increase.[21] Thus, the pituitary gland will receive more stimulation, and the secretion of the hormone cortisol will also increase.[21] If the patient's emotional condition is calm and balanced, the coping mechanism becomes positive. This will cause the signal in the brain to inhibit the release of CRF and the stress-hormone cycle repeats itself.[21] In a state of anxiety, anxiety, and depression, the

secretion of the cortisol hormone will increase.[21]

3.3. Antidepressant classification and SSRIS' mechanism of action

Treatment of depression generally uses antidepressants.[8] Antidepressant is divided based on their mechanism of action, i.e., Serotonin Norepinephrine Reuptake Inhibitors (SNRI), Selective Serotonin Reuptake Inhibitors (SSRI), Monoamine Oxidase Inhibitors (MOAI), Tricyclics (TCA).[8]

SSRIs are often used as the first line because of the safer side effects. The side effects of SSRI classes are headache, insomnia, fatigue, anxiety, sexual dysfunction, and weight gain.[8] This class of drugs has a high affinity for monoamine receptors but a low affinity for α-adrenoceptors, histamine, muscarinic, or acetylcholine, which are also found in tricyclic antidepressants.[22] Some examples of drugs that belong to the SSRI class are citalopram, fluvoxamine, paroxetine, fluoxetine, and sertraline.[22]

Selective Serotonin Reuptake Inhibitors (SSRIs) will inhibit the uptake of 5-HT into presynaptic neurons.[22] By the presynaptic axon terminal, SSRIs will inhibit the serotonin transporter (SERT). This inhibition makes the increasing number of serotonin (5-hydroxytryptamine) remain in the synaptic cleft. Therefore, they are able to trigger postsynaptic receptors for an extended duration.[22]

3.4. Omega-3 fatty acid in mackerel (*Rastrelliger kanagurta*)

Fish is a food source that contains lots of protein, fat, vitamins, and minerals, as well as is the largest producer of omega-3 fatty acids (PUFA), notably docosahexaenoic (DHA) and eicosapentaenoic (EPA).[23] DHA and EPA are beneficial to the health of the human body, but they can't be produced in the human body.[23] Various types of fish, such as salmon and tuna are famous for their abundant omega-3 content. However, mackerel (*Rastrelliger kanagurta*), which has more omega-3 content, also has an affordable price.[23]

The chemical composition of fish varies among individuals within one species and even between body parts within an individual.[14] Salamah et al.'s research (2004) states that mackerel contains omega-3 fatty acids, including DHA, EPA, and linolenic acid.[14,24] The amount of omega-3 fatty acids varies from each body part, i.e., linolenic acid in the head ranges from (0.026-0.160) g/100g, stomach between (0.043-0.190) g/100g; meat between (0.031-0.199) g/100g, EPA on the head (0.031-0.199) g/100g; stomach between (0.120-0.212) g/100g; meat between (0.035-0.132) g/100g. DHA in the head (0.034-0.084) g/100g; stomach between (0.076-0.157) g/100g; meat between (0.041-0.176) g/100g.[25]

Omega-3 fatty acids (PUFAs) contain many double bonds and are derivatives of the essential fatty acid precursors linoleic and linolenic.[26] Omega-3 fatty acids are used primarily for the synthesis of complex fatty molecules. The complex fatty molecules are used to construct cell membranes of neurons and glia and cellular signaling molecules.[27] Omega-3 content in the form of DHA can help the process of brain development, including synaptogenesis, neurogenesis, brain plasticity, neuroprotection, inflammatory signaling, and preventing apoptosis.[23,28] Omega-3 fatty acid, such as DHA and EPA have the potential preventive and therapeutic effects on mental disorders, such as depression and anxiety.[23,28]

3.5. Mechanism of omega-3 fatty acid as adjuvant of antidepressant fluoxetine on decreasing cortisol hormone levels

Fluoxetine is one of the SSRI drugs, commonly prescribed for depression. Many types of research show that SSRI consumption increases BDNF levels, reduces HPA axis

activity, heightens long-term potentiation, and reduces depression-like behavior.[8] But, the efficacy varies: 30-40% of patients do not give a significant response, and 60-70% of patients do not have an improvement in their condition.[12] Therefore, adjuvant therapy is needed to support fluoxetine as an antidepressant.

Researchers in France (Delarue et al. 2003) did a study regarding the correlation between depression and omega-3 fatty acids. They concluded that adequate intake of omega-3 fatty acids could inhibit adrenal activation.[29] Thus, will inhibit CRH from activating the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which will decrease cortisol hormone levels.[8,29]

The antidepressant effects of omega-3 fatty acids are correlated to their capability to dampen the inflammatory response, in which psychological stress is involved with the release of proinflammatory cytokines (TNF, IL-1, IL-6).[30] A low level of proinflammatory cytokines are able to stimulate the HPA axis independent of CRH, thus reducing cortisol hormone levels.[27,30] Hamazaki and Itomura (2000) showed reduced acute stress hormone, norepinephrine (which will lead to increased cortisol levels when significantly elevated) concentration in students who consume DHA and EPA.[29] Buydens-Branchey (2000) found that EPA and DHA reduced anger scores (high cortisol levels equate to anger).[24,29] Those studies confirm the effect of omega-3 fatty acids in decreasing the cortisol hormone.

4. Conclusion

Depression can happen to anyone, regardless of age, not only in adults but also children and teenagers, including Indonesian society. EPA and DHA are found on polyunsaturated fatty acids (PUFA) in mackerel (*Rastrelliger kanagurta*). EPA and DHA have the capability to prevent and give therapeutic effects on psychiatric disorders, such as anxiety and depression. Adequate consumption of omega-3 fatty acids can inhibit ACTH, therefore lowering cortisol levels. In addition, the antidepressant properties of omega-3 PUFAs are related to their ability in reducing proinflammatory responses. Thus, will stimulate the HPA axis independent of CRH, thereby reducing cortisol levels. There should be more research on adjuvant antidepressant therapies such as mackerel. Hence, the substantial depression in Indonesia can be handled properly.

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