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Active Compounds of Red Ginger as Antioxidant Activity in the Supplementation and Treatment of Depression

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ABSTRACT: This study examined compound active of red ginger related for supplementation and treatment of depression. Depression prevalence in Indonesia from the national population survey 6.9% had severe depression symptoms, 21.8% moderate to severe. Red ginger provided gold potential and demonstrated prominent natural phenomena and coexistence, abundant benefits. Standard herbal medicine and phytopharmaceuticals as one effort in dealing with depression disorder. Problem Statement. The use of medicines for depression disorder in the long term becomes a serious problem affecting various sectors and needs to be thought of side effects and complications. Objective. Antioxidants in red ginger (Zingiber Officinale Rosc. Var Rubrum has a secondary metabolite considered for treatment or supplementation in depression disorders. This study was experimental analytical study for analyzing secondary metabolism using phytochemical screening tests and examining active compounds with the combination of liquid chromatography with tandem mass spectrometry (LCMS/MS).Red ginger extracts contain secondary metabolic flavonoids of 48.79 mgQE/g, phenol 92.73 mgGAE/G and antioxidants of 39.96 ppm. Establishment of the active compound that has an effect as an antioxidant α-Eleostearic acid (C18 H30 O2) chemspider result 10, mzcloud 96, L Histidine (C6 H9 N3 O2) chemspiders result 6, mzcloud 94,8. Tetrahydrocurcumin (C21 H24 O6) chemspider result 41, mzcloud 92,5. Active compounds of red ginger antioxidants are diarylheptanoid, phenylbutenoid, flavonoid, diterpenoide, sesquiterpenoid, gingerol and shogaol. Red ginger extract content of active flavonoid compounds and has an effect as an antioxidant is potentially used as a supplement in the treatment of depression disorders.

Keywords: antioxidants, active compounds, depression, red ginger, tetrahydrocurcumin

I. INTRODUCTION

Mental health has advanced significantly in recent times. In fact, it is crucial to see mental health as a real and increasingly common problem [1]. Depression as a mental illness is very common worldwide with an estimated prevalence in about 5% of adults suffer from depression [2]. Estimated in 2019, around one billion people including 14% of adolescents in the world were living with mental disorders. Suicide accounts for more than 1 in 100 deaths and 58% of suicides occur before the age of 50. Mental disorders are a leading cause of disability, causing 1 in 6 people to live with a disability. People with severe mental health conditions had life expectancy lowered 10 to 20 years earlier than the general population, mostly due to preventable physical illnesses. Childhood sexual abuse and being a victim of bullying are leading causes of depression.

Social and economic inequality, public health emergencies, war, and climate crisis are some of the global and structural threats to mental health [3]. Depression and anxiety increased by more than 25% in the first year of the pandemic alone.

Population has depression estimated 3.8%, including 5% of adults (4% in men and 6% in women), and 5.7% of adults over 60 years of age. About 280 million people in the world have depression [4]. Depression is about 50% more common in women than men. Worldwide, more than 10% of pregnant women and women who have recently given birth have depression [5]. Each year, more than 700,000 people commit suicide. Suicide is the fourth leading cause of death among those aged 15 to 29. Even though there are known effective treatments for mental disorders, more than 75% of people in low- and middle-income countries do not receive treatment. Barriers to effective treatment include lack of investment in mental health care, lack of trained healthcare providers, and social stigma associated with mental disorders.

II. LITERATURE REVIEW

Role of bioactive compounds extracted from medicinal plants in maintaining sustainable human health has been widely documented in traditional medicine for the cure of human diseases. The last decade has seen many medicinal uses incorporating medicinal plants with minimal side effects. There is great interest and demand to identify active compounds with potential as potent phytopharmaceuticals from relatively safe herbs to produce safe products with low side effects to treat depressive disorders [6].

First step taken for the analysis of active metabolites contained in red ginger (Zingiber Officinale Roscoe Variant Rubrum) by conducting a simple examination in the form of plant identification then continued with the examination and isolation of bioactive compounds from medicinal plants with phytochemical screening of ethanol, n-hexane fraction, and ethyl acetate fraction of red ginger including examination of alkaloid compounds, saponins, flavonoids, tannins, glycosides and steroids/triterpenoids. After obtaining the active metabolites, LCMS/MS (Liquid chromatography-mass spectrometry) examination was continued to identify the active compounds contained in red ginger [7]. Zingiber Officinale Roscoe Variant Rubrum known as red ginger is a family of *Zingiberaceae* and has long been used as a food ingredient, spice, supplement, and food flavoring and used as traditional medicine for more than 3000 years in countries such as Arabia, Burma, China, Congo, Germany, Greece, India, Indonesia, Japan, Sri Lanka, Tibet and America because it has characteristics that provide many benefits such as giving spicy taste, aroma and has nutritional content and pharmacological activity [8].

According to the World Health Organization depressive disorders are common mental disorders that involve depressed mood or loss of pleasure or interest in activities for an extended period of time. Depression differs from ordinary mood swings and feelings about everyday life in that it affects all aspects of life, including relationships with family, friends and community, school and workplace environments. The WHO Work Plan 2013-2030 highlights the steps needed to provide appropriate interventions for people with mental disorders including depression and self-harm/suicide are some of the priority conditions covered by the Mental Health Gap Action Programme (mhGAP) [6]. Depression can affect anyone, regardless of socioeconomic status; however, people with mental health conditions continue to face stigma, discrimination, and violations of their human rights. Individuals who have suffered from abuse, severe loss, or stressful events are more likely to suffer from depression [9]. A depressive episode occurs when a person is depressed (feeling sad, irritable, and empty). They may experience a loss of enjoyment or interest in activities. Depressive episodes are distinct from normal mood swings. For at least two weeks, these episodes lasted the majority of the day, almost every day. Other symptoms may include: poor concentration, excessive guilt or low self-esteem, hopelessness about the future, thoughts of death or suicide, sleep disturbances, changes in appetite or weight, feeling very tired or lacking energy. Physical health is closely related to and influences depression. Many of the factors that contribute to depression (such as lack of physical activity or excessive alcohol consumption) are also risk factors for diseases such as cardiovascular disease, cancer, diabetes, and respiratory disease. As a result of their difficulties in managing their conditions, people suffering from these diseases may develop depression [9].

Effective treatments for depression include psychological treatments and medications, one of which is a selective serotonin reuptake inhibitor (SSRI), such as fluoxetine. Healthcare providers should consider the side effects associated with long-term use of antidepressant medication, the ability to deliver the intervention (in terms of expertise, and/or availability of treatment), and individual preferences. Antidepressants should

not be used treat depression in children and are not a first-line treatment in adolescents, so should be used with extreme caution [10]. Herbal plant, red ginger is widely recommended for digestive problems, fatigue and loss of energy, nausea, especially during pregnancy. According to some studies ginger also has an anti-inflammatory effect used in rheumatic diseases, from invitro and in vivo studies show ginger is effective in preventing and treating prostate, ovarian, stomach, colon rectum cancer, as well as preventing metastases from breast cancer. The plant also contains powerful antioxidant, antibacterial, anti-fungal and antiviral effects. In general, ginger is considered a medicinal plant that is considered safe, although it is necessary to consider the side effects of gastric irritation and intestinal cramps when used excessively in some people [11].

The role of active compounds from ethanol extracts of red ginger has been widely documented to maintain health. Red ginger has efficacious substances that can be used for treatment to cure diseases in humans, this decade the use of drugs with minimal side effects sourced from medicinal plants. A new finding that has novelty gives hope to medicinal plants that are proven to have minimal side effects, strong drug molecules from medicinal plants [12]. Depressive disorders are reported to be a common psychiatric disorder during this period. Oxidative stress is a mechanism that causes depressive disorders. Oxidative stress occurs due to an imbalance between oxidants and antioxidants where oxidants are higher, due to a decrease in the antioxidant capacity system. Antioxidants are a defense system that limits damage associated with free radicals, oxidative stress as a phenomenon caused by the disruption of the normal balance in the production of free radicals, which is associated with several diseases, such as diabetes and depression [13]. In depression, oxidative stress is defined as an excess of reactive oxygen species (ROS) and a lack of antioxidant response, which causes inflammation, neurodegeneration, tissue damage, and cell death.1 ROS are essential for regulating and maintaining the homeostatic balance of cellular processes [12, 13].

Studies of oxidative stress-related depressive disorders have implicated a number of cellular and molecular mechanisms, including poor stress responses, the presence of extensive inflammatory processes in the innervation system, imbalances in neurotransmitter-mediated signaling (with a focus on serotonin), as well as issues with neurogenesis and synaptic plasticity, which are largely mediated by brain-derived neurotrophic factor (BDNF). All of these factors are amplified in the presence of high levels of oxidative stress, even leading to an increase in stress levels [14, 15].

Cells have specific antioxidant defense mechanisms to protect against the adverse effects of high levels of ROS especially enzyme systems such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). In addition, antioxidants, both endogenous and exogenous also play a role in maintaining the health of the organism and most importantly maintaining homeostasis, where ROS production must be balanced with antioxidant consumption [2]. The HPA axis plays a role in the response to depressive disorders. This axis responds to triggers that come from psychological and physical problems by releasing, corticotrophin-releasing hormone (CRH) from the hypothalamus and then this hormone activates the pituitary gland to release adrenocorticotropin hormone (ACTH), activates the adrenal glands to produce glucocorticoids and plays a role in responding to stress such as catecholamine [16].

Pathophysiology of depressive disorders is due to high ROS production in the mitochondria which is closely related to the inflammatory process that triggers oxidative stress. Several oxidative stress markers have been found to increase in alcohol use which induces aggressive behavior and suicidal behavior [17]. Immune system affects the neural network system that is involved in the occurrence of depressive disorders. Elevated levels of oxidative stress result in dysregulation of the inflammatory response. The resulting modification of cell signaling by oxidative stress can increase the production of proinflammatory factors. Triggering proinflammatory responses, especially neuroinflammation in the central nervous system, is modulated by oxidative stress [18]. Studies supporting the link between oxidative stress and neurogenesis and synapse plasticity damage in depression, especially in relation to BDNF. Recently another study focused those low levels of neurogenesis under stress can induce depression in mice which was rescued by upregulation of the mitochondrial antioxidant sirtuin 3, giving hope that it can provide resilience and recovery against stress and depressive behavior [19].

Brain-derived neurotrophic factor (BDNF)-protein kinase B (Akt)/related signal kinase 2 (ERK2) signaling pathway was improved after administration of *Tagetes minuta* flower essential oil, in this study, oxidative stress was also reduced as indicated by reduced depression-like behavior in mice. Administration of the antioxidant carvedilol to depressed mice can increase brain glutathione and BDNF concentrations, as well as reduce MDA levels and provide antidepressant-like effects [20]. Similar observations were made by

administering luteolin-7-O- glucuronide to mice. This compound is reported to have antioxidant properties and ameliorate depression-like behavior, activating BDNF signaling that can modulate neurogenesis and neuroplasticity [21]. *Celastrol* and thymoquinone also reduced depressive and anxiety-like behavior in mice by restoring acetylcholine, dopamine and serotonin concentrations, which were previously decreased by aluminum chloride exposure. In addition, these compounds increased BDNF expression and downregulated *oxidoinflammatory* markers (such as MDA and IL-6) in the brain of mice [22].

III. MATERIALS AND METHODS

1. RESEARCH DESIGN OF THE STUDY

Biochemical analysis of plant products the first step is red ginger was obtained at the traditional wholesale market Lau Chi, *Simpang Selayang* Village, Medan North Sumatra. Identification of plants carried out at the Cibinong Bogor Botanical Institute, Phytochemical examination of simple active metabolites in the phytochemical laboratory of the faculty of pharmacy, Universitas Sumatera Utara Phytochemical screening of ethanol extract, n-hexane fraction, and ethyl acetate fraction of ethanol extract of red ginger includes examination of alkaloid compounds, saponins, flavonoids, tannins, glycosides and steroids/triterpenoids.

2. DATA COLLECTION AND ANALYSIS

Determination of antioxidant composition of active compounds containing antioxidants was carried out at the University of *Kebangsaan Malaysia* sent through the pharmacology laboratory of the faculty of pharmacy of the Universitas Sumatera Utara which has had cooperation in the development and examination of active compounds from medicinal plants. and isolation of active compounds further in the form of freeze dryer to remain stable before LCMS / MS examination. Examination of active compounds from red ginger extract was carried out through a 3 x 24 freeze dryer process to obtain red ginger extract in crystalline form at the Nanomaterial for Renewable Energy Research Centre Medan, North Sumatra. Furthermore, the ethanol extract of red ginger that has been in the freeze dryer is then examined Liquid Chromatography Tandem Mass Spectrometry (LCMS / MS) at *Universiti Kebangsaan Malaysia* Medical Molecular Biology Institute. LCMS/MS analysis using the AB SCIEX Triple Time of flight (TOF) 5600 system is an instrument that has a hybrid triple quadruple TOF that combines high sensitivity, fast scanning speed, and accurate mass and high-resolution performance. The system is comprehensive and enables qualitative exploration, rapid profiling and high-resolution quantitation workflows on a single platform. Used for data analysis, identification and quantitation of protein and peptide quantities, validating profiling and biomarker discovery.

IV. FINDINGS AND DISCUSSION

The process of ginger kneading with a wet weight of 4 kg is followed by the drying process in a drying cabinet at a temperature of 500C for 5 days and then weighing the dry weight of the simplisia is found to be 1123 grams, then smoothing the simplisia is found to weigh 1114 grams of simplisia powder. The characteristics of red ginger simplisia are listed in the table below:

Table 1. Characteristics of Red Ginger Simplisia

No.	Parameters	Result
1	Total ash content	5,32%
2	Acid insoluble ash content	1,39%
3	Water content	5,49%
4	Water soluble cider content	9,34%
5	Ethanol soluble cider content	9,67%

Maceration of *simplisia* powder soaked 1000 grams of 10 liters of ethanol soaked 5 days and carried out 2 repetitions (1000 grams of powder), then filtered to get a thick extract then warmed with a temperature of 400C - 500C then rotary for 3 days. Weight 86 grams, then carried out Phytochemical Screening. The results

of the phytochemical screening test of red ginger extract (Zingiber officinale Rosc. Var Rubrum) are as follows listed in the table below:

Table 2. Phytochemical Screening Test Results of Ethanol Extract Red Ginger

No.	Secondary Metabolite		Reaction Result
1	Alkaloid	Mayer Bouchardat Dragendorf	+
2	Flavonoid	Powder Mg + HCL p +amil alcohol	+
3	Glikoside	Molish+H2SO4	+
4	Saponin	hot distilled water/shake	+
5	Tanin	FeCl3	-
6	Steroid/terpenoid	Lieberman-Bourchat	+

The total flavonoid content of red ginger ethanol extract was carried out by measuring the absorbance by UV-Vis spectrophotometer at a wavelength of 430nm, found to be 48.79 mgQE/g extract. The total phenol content test was 92.73 mgGAE/g extract and the antioxidant content determination test of red ginger ethanol extract using the 2,2- diphenyl-1 picrylhydrazyl (DPPH) free radical scavenging method found an IC50 of 39.96 ppm. A meta-analysis of 48 studies involving 2,788 subjects showed that higher flavonoid intake may improve depressive symptoms. The role of antioxidant and anti-inflammatory supplementation in phytopharmaceuticals to manage depression risk has been explored in depth, suggesting that anti-inflammatory and antioxidant supplementation may prevent and/or aid in the treatment of depressive disorders [23].

Tabel 3. Determination of Secondary Metabolite Level of Ethanol Extract of Red Ginger

No.	Secondary Metabolite	Level
1	Flavonoid	48,79 mgQE/g extract
2	Fenol	92,73 mgGAE/g extract
3	Antioxidants (IC50)	39,96 Ppm

The results of the examination of active compounds contained in the ethanol extract of red ginger found the content of amino acid L-Histidine, fatty acid *α-Eleostearic* acid, and *tetrahydrocurcumin* which is a derivative of flavonoid polyphenols.

Tabel 4. Determination of Active Metabolites Antioxidants Contains

No.	Active Compound	Formulation	Chemical Spider Results	mzCloud Best Match	Sample
1	L-Histidine	C6 H9 N3 O2	6	94.8	Detected
2	α-Eleostearic acid	C18 H30 O2	10	96	Detected
3	Tetrahydrocurcumin	C21 H24 O6	41	92,5	Detected

Previous studies have shown that oxidative stress and oxidant or antioxidant imbalance are involved in the pathophysiology of psychiatric disorders. Trigonelline (TRG) is a pyridine alkaloid that has various pharmacological effects including *hypoglycaemic*, neuroprotective, and memory enhancing properties. To investigate the antidepressant and anxiolytic effects of TRG focusing on oxidative stress, TRG significantly decreased malondialdehyde (MDA), nitric oxide (NO) as well as increased antioxidant capacity. The findings from this study suggest that the beneficial effects of TRG may, at least in part, be mediated through reduced oxidative stress and increased antioxidant capacity. Oxidative stress can result in an imbalance between the production and accumulation of ROS in cells and tissues and thus modify the ability of biological systems to detoxify these reactive products. ROS have several physiological roles one of which is cell signaling, and are usually generated as a by-product of oxygen metabolism; however, environmental stressors such as UV, ionizing radiation, pollutants, and heavy metals and xenobiotics i.e., antiblastic drugs contribute

significantly to the production of ROS which can cause an imbalance leading to cell and tissue damage or oxidative stress [24].

Antioxidants that are able to protect other molecules from the damaging effects of such ROS can be used as excipients in formulations or as biologically active compounds that prevent oxidative stress. Bioactive compounds such as polyphenols, flavonoids, and vitamins that exhibit antioxidant properties are suitable for fortification of food products to enhance their function [25]. The role of plant-derived antioxidants in the treatment and prevention of depression, as well as other biomolecules with high antioxidant and anti-inflammatory potential, such as molecules secreted *paracrinely* by mesenchymal stem cells, as well as preclinical and clinical evidence demonstrating the potential effects of various antioxidant and anti-inflammatory biomolecules as antidepressants. Antioxidants can remove free radicals and suppress oxidative stress pathways, which protect against neuronal damage in the brain; thus, theoretically resulting in the remission of depressive or anxiety symptoms [26].

Oxidative stress is increased in depressed patients as measured by an increase in different oxidation markers. Examples are serum and urine levels of *isoprostane* F2 excretion, a derivative of free radical-mediated lipid peroxidation and plasmatic levels of lipid peroxidation end products: MDA. The former reflects peripheral oxidation. Interestingly, brain DNA damage caused by oxidative stress was increased in depressed patients compared with healthy controls, suggesting that oxidative stress-induced damage to oligodendrocytes and the resulting white matter changes may be involved in the pathogenesis of depressive disorders. There is a growing body of evidence demonstrating the potential of plants and their derivatives in the treatment of neuropsychiatric disorders, including depression and depressive symptoms such as anxiety or depressed mood. This opens the door to alternative treatments that can help patients who do not respond to conventional treatments or who experience complications, risks, or unpleasant side effects from them. Thus, plant antioxidant-based treatments may offer a safer alternative to depression treatment or a more effective alternative to atypical depression treatment [27, 28].

Natural compounds with antioxidant activity show promise as a strategy for avoiding or delaying the onset of depressive symptoms, or as a safer alternative to currently available medications. However, more evidence is required to support their antidepressant effects, as well as stricter regulations in the production and characterization of these natural compound. Likewise, further studies are needed to test whether the antioxidant effects of these natural compounds and antidepressant drugs are sufficient to support Higher total antioxidant intake was significantly associated with lower odds of depression along with improvements in depression and anxiety conditions, further confirming the therapeutic potential of antioxidant supplements as adjunctive therapy to conventional antidepressants [29, 30]. L-histidine intake may improve cognitive function (e.g., reducing appetite, anxiety, and stress responses and improving sleep quality) potentially through the metabolism of histidine to histamine; however, this relationship remains ambiguous in humans. At high histidine intake (>24 g/d), studies report histidine side effects such as decreased serum zinc and cognitive impairment. Subjects taking histidine supplements showed reduced reaction times on cognitive performance tests, reduced fatigue, and improved scores for clear thinking and attention evaluated with the *CogHealth* test battery, Profiles of Mood States Scale, and visual analogue scale [30]. *Tetrahydrocurcumin* is a derivate of *cucumin* that plays a role in the cleansing process and prevents the formation of free radicals. This product is colour-free, unlike the yellow colour of other turmeric extracts [27].

Since centuries curcumin is often associated with traditional *medicinesystems* to treat various diseases, because it has functions as an antidepressant, immunomodulator, antioxidant, neuroprotective, antiapoptotic, and antiproliferative which is possible due to its anti- inflammatory, antioxidant, anticancer, antiepileptic effects but the available information regarding the clinical efficacy of curcumin in neurodegenerative cases is still minimal [31]. A comprehensive summary of animal trials examining the antidepressant and anxiolytic effects of curcumin in animal trials consisted of acute stress exposure such as forced swim test, tail suspension test, sleep deprivation, immobilization-induced restraint stress, and cold restraint stress. Chronic stress exposure consists of the chronic unpredictable stress (CUMS) model, restraint stress for periods ranging from 20 to 56 days, and acute or chronic administration of anxiety or depression-inducing exogenous agents such as corticosterone, *pentylenetetrazole* (a γ-aminobutyric antagonist), reserpine (a monoamine antagonist), 4-aminopyridine (a potassium channel blocker), lead, mercuric chloride, and lipopolysaccharide (a major component of the outer membrane of Gram-negative bacteria). Surgical

procedures such as ovariectomy, bilateral olfactory bulbectomy, and sciatic nerve ligation have also been used to examine curcumin's effects on stress, depression, and anxiety using the above tests and procedures. In most of these trials, curcumin was administered orally or via intraperitoneal injection from 21 days to 30 minutes before the stressor. When curcumin was administered before the stressor, antidepressant and anxiolytic effects in animals were commonly observed, as measured by changes in behavior, appetite, socialization, and weight loss [31]. A growing number of studies support the efficacy of curcumin as a treatment for depression. These antidepressant effects have been demonstrated in animal and human trials and have been confirmed by several meta-analyses. Depression is associated with a variety of biological disturbances that may cause or contribute to a range of behavioral, affective, cognitive, and physical symptoms. Curcumin has multifactorial physiological effects on the body, which may explain its antidepressant and anxiolytic effects [31].

V. CONCLUSION

Depression is associated with low antioxidant intake. Higher intake of certain micronutrients may contribute to reducing the incidence and severity of depression. The use of ethanol extract of red ginger as supplementation and treatment of depressive disorders containing active compounds, amino acids, fatty acids high in antioxidants has an important role. Natural compounds with antioxidant activity hold promise as a strategy for avoiding or delaying the onset of depressive symptoms, or as a safer alternative to currently available drugs. However, more evidence is required to support their antidepressant effects, as well as stricter regulations in the production and characterization of these natural compounds. Overall, existing evidence suggests that supplementation and treatment using ethanol extracts of red ginger are proven to address treatment-resistant depression. Nonetheless, more preclinical and clinical research is required to establish whether antioxidant supplementation is essential for efficacy in depression treatment of antidepressants already in use.

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