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Original Article

Ghrelin and Serotonin Expression on Restricted Feed with *Curcuma xanthorrhixa* Roxb. and Iron Supplementation

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ABSTRACT

Background: Nutritional shortages and acute malnutrition are caused by insufficient protein and calorie consumption. With severe short- and long-term morbidity and death, malnutrition is a serious public health concern. In cachectic situations, the peptide ghrelin level raises making people more hungry. Life protein deficiency changes crucial neurotransmitters, including serotonin, and the brain redox status that underlies neurobehavioral expression.
Aim: This study aimed to determine whether the combination of *Curcuma xanthorrhixa* Roxb. and iron supplementation regulates serotonin and ghrelin expression.
Methods: This study employed a true experimental posttest-only control group design. The study subjects were 25 male Wistar rats divided into five groups. *Curcuma xanthorrhiza* Roxb. Rhizome extract at 80 mg/kg BW/day and elemental iron at 0.054 mg/kg BW/day were administered orally for 14 days after malnutrition induction. The differences between the groups before and after the completion of study interventions were calculated.
Results: *Curcuma xanthorrhiza* Roxb. rhizome extract groups with elemental iron and combinations did not differ significantly in ghrelin levels. (p=0.88, Kruskal-Wallis H test). Serotonin levels did not differ between the groups (p=0.84, Kruskal-Wallis H test).
Conclusion: Elemental iron, *Curcuma xanthorrhiza* Roxb., and the combination treatment did not alter the expression of serotonin or ghrelin. More studies are required on the effects of *Curcuma xanthorrhiza* Roxb., elemental iron, and a combination of these factors to reverse the effects of malnutrition. Further research is required to utilize higher macronutrient diets and supplements after malnutrition induction.

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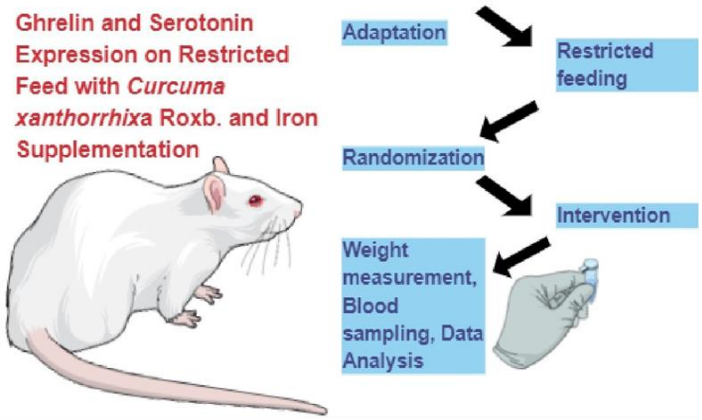
GRAPHICAL ABSTRACT



Introduction

Malnutrition remains the leading cause of mortality, morbidity, and unrealized potential, which increases the likelihood of long-term cognitive development deficits in the future [1]. Malnutrition can be caused by an inadequate or unbalanced diet, or a medical condition that affects digestion or nutrient absorption from food. Nutritional deficiency, caused by insufficient protein or energy consumption, is known as acute malnutrition. The need for sufficient food supply brought on by social, economic, and environmental factors is a common problem in developing countries. The most frequent reasons for secondary acute malnutrition are underlying illnesses that cause abnormal nutrient loss, increased energy expenditure, or decreased food intake [2].

Undernourishment remains a severe problem, especially in developing countries, including Indonesia [3]. Malnutrition has historically been researched and addressed in two distinct areas: undernutrition, food instability, poor nutrition or overweight, obesity, and dietary excess [4]. The liver continuously produces a serum protein called albumin, which accounts for approximately 5% of total protein content in the body. One sign of long-term nutritional problems is albumin, which has a half-life of 14-20 days. Albumin primarily serves as a carrier protein and contributes to the maintenance of osmotic pressure. Specific substances, including ions, bilirubin, hormones, enzymes, and medications, are incorporated into the bloodstream along with albumin. As a result, lower albumin levels are associated with malnutrition [5]. The protein molecules globin and heme compounds are combined with iron (Fe^{2+}) to produce haemoglobin. Therefore, both iron and protein should be present. PD/D1 cells in the stomach are not only the primary producers of ghrelin, but they are also present in the pituitary, pituitary-adrenal axis, brain, and small intestine [6]. In addition to iron, the following elements affect Hb formation: proteins, vitamin B6, and folic acid. Growth hormone deficiency in children and adults: Ghrelin and GH-IGF-1 axis relationships (GHD). Hytochemicals of plants, such as phenols and flavonoids, seem to act in various ways to protect health [7]. In malnourished conditions, the activities of mitochondrial enzymes in the muscle fibres, which are significantly affected by the mitochondrial state, determine the metabolic capacity of skeletal muscles [8]. Numerous studies have shown the curcumin effectiveness in regulating neurotransmitters, inflammatory pathways, excitotoxicity, neuroplasticity, hypothalamic-pituitary-adrenal disturbances, insulin resistance, oxidative and nitrosative stress, and the endocannabinoid system, all of which play a role in neurocognitive pathophysiology [9].

The combination of iron and curcumin resulted in dietary restriction, curcumin, and iron supplementation. Significantly more oxidative stress is present in children with Severe Acute Malnutrition (SAM), which may have contributed to mitochondrial dysfunction [10].

Reactive oxygen species (ROS) and total antioxidant capacity (TAC) increase and decrease, respectively, in malnutrition. Curcumin inhibits reactive oxygen species (ROS) in rat red blood cells and decreases osmotic and haemolytic capacities. Xanthohumol, starch, ash, tannins, turmerol, essential oils, borneol, and protein are additional ingredients in temulawak and curcumin [11]. Anemia due to iron deficiency and concomitant ingestion of faster-acting serotonin antagonists have all been linked to delayed serotonin responses. Owing to the requirement of iron for converting tryptophan to serotonin, a decline in iron may be a factor in serotonin-delayed reactions [12].

A previous study showed that green iron nanoparticles were prepared using a plant polyphenol, which could be extracted from Curcuma and meticulously removed from cationic dyes over 12 min with a solid-liquid ratio of 1:20. Therefore, this highlights the benefit of combining curcuma polyphenols with iron supplementation [13, 14].

We sought to determine the effect of administering a combination of supplements from Indonesian herbal plant extracts, specifically temulawak rhizome extract (*Curcuma xanthorrhiza* Roxb.) and iron in a restricted-feed mouse model.

Materials and Methods

Experimentation

This study was conducted at the Animal Laboratory and Central Laboratory, Faculty of Medicine, Universitas Diponegoro. The research had a true experimental post-test-only control group design, and the study subjects were animals. Wistar rats fed a low-calorie diet were treated with iron supplementation and rhizome extract *Curcuma xanthorrhiza* Roxb.

Animal subjects

Male Wistar rats (*Rattus norvegicus*), 8-11 weeks old, weighing an average of 150-200 g, in good physical condition, appeared active, and had no anatomical anomalies and served as the experimental animals in this study. They were housed in a cage with a 12-hour lighting cycle, free access to food and water, and a temperature range of 28-32 °C, and served as experimental animals. Wistar rats were randomly separated into five groups following malnutrition therapy. The negative control group was healthy and had unlimited access to food, standard care, and beverages. The positive control group was the malnutrition group with a 4 g/100 grams BW/day diet restriction. The Curcuma group received dietary restrictions, and curcumin was administered orally at 80 mg/kg of curcumin each day; the iron supplementation group served as the treatment group receiving an iron supplement and a restricted diet. The administered dose had a conversion factor of 0.018, which was 0.054 mg/kg BW/day in experimental animals. They were administered iron supplements by stomach sonde at a frequency of one through the probe for 14 days. Induction of malnutrition: The mice were fed low-calorie amounts of food (4 g/100 g BW/day for 14 days) on the eighth day to induce malnutrition, and weight checks were performed to ensure that the rats were malnourished. The normal diet had a water content of 14%, total protein content of 19.0%, crude fat content of 3.0%, natural fibre content of 8.0%, total phosphorus content of 9%, total aflatoxin content of 50 g/kg, and amino acid contents of 0.45%, 0.27, 0.27, and 0.17, respectively. A low-calorie diet was administered with 2.8%, total protein content of 1.6%, crude fat content of 0.2%, natural fibre content of 1.3%, total phosphorus content of 1.5%, total aflatoxin content of 4.2 g/kg, amino acid lysine 0.7 %, methionine 0.27 %, methionine and cysteine 0.45 %, and tryptophan 0.01%. Mice were given low-calorie feed at a dose of 4 g/100 g BB/day for 14 days, after which they were acclimatized to their body weight. To track the nutritional status of rats, the mice were weighed once every two weeks to determine body weight.

Extract preparation

Curcuma xanthorrhixa roxib at the Centre for Herbal Medication and verified it at the Central CNI Laboratory, Semarang, Indonesia (voucher no. 41/2022). Furthermore, flavonoid levels in

the extract were measured using a previously described method [15]. *Curcuma xanthorrhiza* Roxb. rhizomes extracted, ethanol solvent, 0.5% CMC (Critical Micelle Concentration), FeSO4, distilled water, 0.1 N HCl, and samples of venous blood and serum. Peeling was followed by thorough washing of fresh ginger. The slices were then drained, cut into 2-cm-thick slices, and quickly dried in an oven at high temperature. Maceration of Curcuma rhizome simplicia after soaking in 96% ethanol. The mixture was stirred after soaking for 24 h. The extract was then filtered to obtain the filtrate. Leftovers were macerated four times. The substances present in *Curcuma xanthorrhiza* Roxb., such as curcumin, are discarded after the roots have been baked and allowed to evaporate after being extracted with ethanol. The concentrated extract was kept in an incubator at 45 ^{o}C for three days after administration at approximately 80 mg/kg BW/day to evaporate the residual ethanol.

Laboratory analysis

Blood was drawn on the first day of the first week, the fourteenth day of the second week, and the fourteenth day of the fourth week. Blood was drawn from the retroorbital region of rats using a 1.5 mL venous plexus as the blood collection site. Albumin. Venous blood serum was the sample; levels were determined using the Bromocresol Green (BCG) method-the ghrelin assay. We used the Elabscience E-EL-R084 ELISA kit and provided the following operating instructions. Each well was filled with 50 mL of active biotinylated detection antibody solution. The cells were incubated for 45 min at 37 °C. The plate was then aspirated and rinsed three times. The HRP conjugate working solution was added to 100 mL-thirty minutes at 37 °C. The plate was aspirated five times. Fifteen minutes of incubation was followed by the addition of 90 L of the substrate reagent at 37 °C. The plate was immediately read at 450 nm wavelength. Determination of results. Serotonin ST/5-HT (serotonin/5-hydroxytryptamine) assay. Serotonin ST/5-HT (serotonin/5-hydroxytryptamine) assay. A serotonin ELISA kit (Elabscience Cat. No. E-EL-0033) was used, and then 100 mL of the standard or sample was added to the wells. After 90 min of incubation at 37 °C, the liquid was removed, and 100 L of biotinylated detection antibody solution was immediately poured into each well. The mixture was then incubated at 37 °C for 60 min. The plate was washed thrice while aspirating. Thereafter, 100 mL of the HRP conjugate working solution was added for thirty minutes of incubation at 37 °C. The plate was then washed five times by aspiration. Substrate reagent (90 mL) was added at 37 °C for 15 min of incubation with 50 mL of stop solution, and the plate was read at 450 nm, and then the outcomes were calculated.

Analytical Statistics

All statistical calculations were performed using IBM SPSS (Statistical Product and Service Solutions) Statistics Version 27.

Results and Discussion

Body weight measurement

Rats were acclimatized for 7-day acclimatization period and received a conventional diet before treatment. Rat weight measurements were carried out after adaptation until the end of the study once every two weeks, as displayed in Figure 1.

Albumin

There were no significant differences between the negative control, positive control, and Curcuma xanthorrhixa Roxb. group, iron supplementation group as well as combination group. There was no statistically significant difference between the pretest albumin, post-test albumin, and albumin in the unpaired difference test (Table 1).

Serum ghrelin and serotonin on food restriction after supplementation

The ghrelin expression results are presented in Table 2. The Kruskal-Wallis test findings for ghrelin were not significant in all groups ($p>0.05$). Serotonin expression is presented in Table 2 and The Kruskal Wallis test showed $p=0.84$.

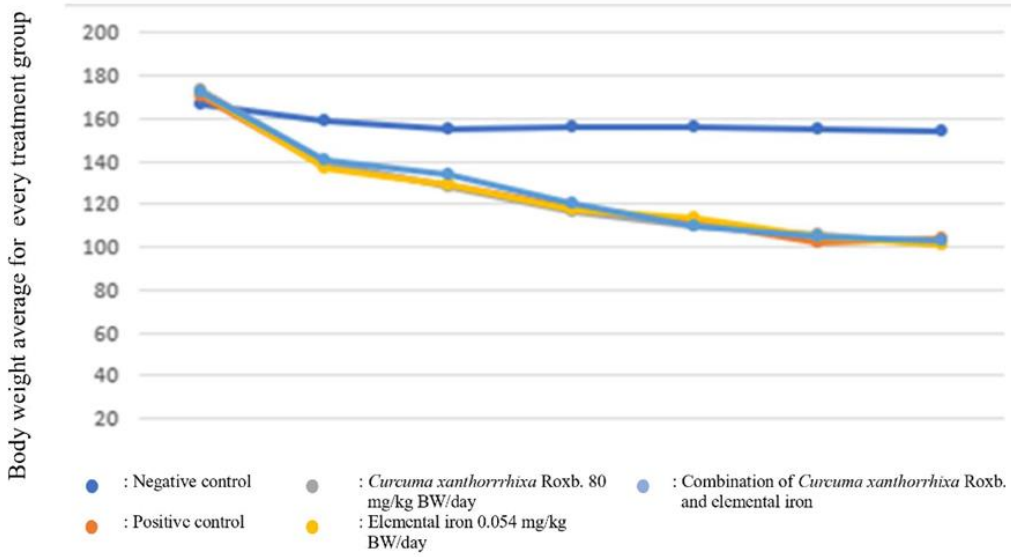


Figure 1: Body weight of each treated group

Table 1: Alterations in album difference between pre-test, post-test, and difference

Group	Albumin (g/dL)			
	Pretest	Post-test	P	Difference
Negative control group	2.54 ± 0.31	1.93 ± 0.57	0.187[c]	0.53 ± 0.92
Positive control group	2.52 ± 0.55	1.97 ± 0.30	0.130[c]	0.46 ± 0.69
Curcuma xanthorrhixa Roxb. extract	2.59 ± 0.30	2.52 ± 0.56	0.820[c]	0.13 ± 1.72
Elemental iron group	2.83 ± 0.12	2.35 ± 0.88	0.262[c]	0.45 ± 0.83
The combination of *Curcuma xanthorrhixa* Roxb. extract and elemental iron group	2.62 ± 0.23	1.93 ± 0.61	0.080[d]	0.67 ± 0.64
P	0.635[§]	0.428[§]		0.633[b]
Levene	0.233[a]	0.238[a]		0.715[a]

[a]*Homogeneous (p > 0.05), and One-way ANOVA,* [b]*Kruskal-Wallis,* [c]*Paired t,* [d]*Wilcoxon.*

To our knowledge, this is the first study to identify the expression of serotonin and ghrelin during feeding restriction. *Curcuma xanthorrhixa* Roxb.

The containment of flavonoid was 43.42%, and curcuminoid was 1.99% for 100 grams of measured the results of observations of behavioural characteristics when given a restricted diet for 28 days showed signs of malnutrition such as dull skin; continuous weight loss compared to the beginning of the study, palpable ribs, and decreased activity. After adaptation, signs of malnutrition began to appear on day of the 7th study. Based on this, the provision of a restricted diet can show signs of malnutrition, which can be used as a reference in developing malnourished rat models. Ghrelin has long been known as the "hunger hormone" because of its propensity to rise during fasting and fall following. Serotonin improves mood and controls ghrelin activity. Ghrelin increases Corticotropin-releasing hormone (CRH) levels, leading to an increase in corticosteroid secretion. CRH negatively impacts ghrelin expression [16]. Ghrelin is hypothesized to be a component of a neuronal network involved in feeding regulation, influencing the appetitive response to food cues and enhancing brain activity in regions in charge of visual processing, attention, and memory connected to food imagery. It is known to improve appetite, increase food consumption, and increase fat accumulation [17]. When the stomach is empty (during fasting), ghrelin secretion is promoted and inhibited when the stomach is enlarged. Ghrelin levels in the body are regulated mainly by food consumption (after a meal) [18]. Unacylated ghrelin, the primary circulating form, and acyl-ghrelin, the active form

produced by otanoylation of the serine at position 3, a process mediated by ghrelin O-acyl transferase, are both present in the circulation (GOAT) [19]. Unacetylated ghrelin (UAG) was previously believed to be the breakdown product of ghrelin, with minimal biological activity. However, recent research has shown that it works as a specific hormone and may even act as a functional restraint of ghrelin [20]. Ghrelin is one of the most effective orexigenic signals, and targeting the ghrelin system in individuals with a negative energy balance may be an appealing therapeutic strategy. Malnutrition in cachexia is another illness for which ghrelin may be necessary [21].

Temulawak (*Curcuma xanthorhiza* Roxb.) is a ginger-family medicinal plant widely cultivated in Indonesia and is used as a primary ingredient in traditional medicine. Temulawak (*Curcuma xanthorhiza* Roxb.) is a ginger-family medicinal plant commonly grown in Indonesia and used as a primary ingredient in traditional medicine. Our previous study has shown that *Curcuma xanthorrhixa* Roxb. (temulawak), combined with *Nigella sativa*, can lower triglyceride and total cholesterol levels [22]. Indonesia has native tropical forests [23]. The primary component of *Curcuma xanthorhiza* Roxb. is the rhizome of temulawak. The primary constituents of temulawak rhizome are proteins, carbohydrates, and essential oils, such as camphor, glucosides, turmerol, and curcumin. Curcumin has anti-inflammatory, anti-hepatotoxic, and anti-bile effects [24]. Both thymoquinone and curcumin play essential roles in several cellular processes in temulawak. Nigelon is a polymer form of thymoquinone that suppresses the activity of cyclooxygenase and lipoxygenase enzymes in arachidonic metabolism and is used as an analgesic, antiallergic, anti-inflammatory, and anticancer agent.

Temulawak has pharmacological properties, including hepatoprotection, cholesterol reduction, anti-inflammatory, laxative, diuretic, and joint analgesic effects [25]. Flavonoids, curcuminoids, xanthorrhizol, and essential oils are the active components of *Curcuma xanthorrhiza* Roxb [25, 26].

Proteins made from peptides and amino acids can increase iron solubility and improve iron absorption. In addition, the body's ability to absorb iron can be affected by its state. When there are few deposits of iron, the body absorbs more iron. Less iron is used to produce new haemoglobin and replace damaged haemoglobin when iron absorption declines, resulting in a decrease in ferritin levels [27]. Nutritional inefficiency is a significant non-genetic contributor to neurogenesis abnormalities, which can be seen in the suppression of specific gamma-aminobutyric acid (GABA) interneuron circuits. Many investigations, particularly those involving neurotransmitter systems, have discovered biochemical alterations in neurological systems of malnourished experimental animals [28]. Tryptophan is an essential amino acid and precursor of serotonin, and food is the only known source. Therefore, it is possible that extreme diet restriction and starvation lower brain serotonin levels because the precursor is less readily available to the rate-limiting enzyme of 5-HT production, which typically occurs unsaturated with its substrate [29].

The provision of sufficient nutrients and energy required to develop and operate every cell in human body is known as nutrition [30].

Table 2: Levels of serum ghrelin and serotonin during food restriction after supplementation

Group	Ghrelin (ng/ml) Mean (SD)	*P*[a]	Serotonin (pg/ml) Mean (SD)	*P*[a]
Negative control group	0.98 ± 0.43 (0.97)	0.88	281.6+95.2 (212.89)	0.84
Positive control group	1.44 ± 0.63 (1.40)		345.40+88.14908(197.10)	
Curcuma xanthorrhixa Roxb. extract	1.22 ± 0.42 (0.93)		309.20+94.39(211.07)	
Elemental iron group	0.96 ± 0.21 (0.47)		273.66+43.33(96.89)	
The combination of *Curcuma xanthorrhixa* Roxb. extract and elemental iron group	1.25+ 0.54 (1.21)		266.60+71.91(258.63)	

[a]*Kruskal Wallis.*

Poor nutrition, on the other hand, has the opposite effect and contributes to brain diseases. Although the gastric mucosa mainly releases, its ghrelin is also found in the pituitary gland, central nervous system, and other tissues [31]. Ghrelin alters microglial function and affects the development of neurodegenerative diseases. It alters the neuroinflammation effects on microglial activity in neurodegenerative disorders and the neurometabolic changes that go along with them [32]. The peptide ghrelin, which increases hunger, increases in cachectic conditions. It affects nutrient intake and growth and reflects the nutrient status of the periphery. Serum ghrelin levels were higher in protein energy-deficient individuals than in healthy children, especially those with marasmus [33]. Underweight patients had higher ghrelin levels, which may be related to anorexia. It can also be used as a nutritional predictor [33]. Goal-directed behaviour and environment flexibility depend on cognitive abilities, known as prefrontal cortex executive functions [34]. The serotonergic (5-HT) system in the brain has undergone considerable changes in a rat model of prenatal protein malnutrition. Executive functions controlled by the prefrontal cortex (PFC) are implicated in depression, schizophrenia, cognitive decline, and attentional issues.

Dysregulation of neurotransmitter systems of the PFC has been linked to these diseases [35]. The brain chemical 5-hydroxytryptamine (5-HT, often known as serotonin) maintains energy balance in various ways. Serotonin can be found in hematopoietic stem cells, the enteric nervous system, the gastrointestinal tract, and platelets, among other places outside the central nervous system (CNS) [36]. Acyl-ghrelin, an orexigenic digestive hormone, is abruptly upregulated during fasting. Ghrelin is a growth hormone secretagogue receptor (Ghsr) ligand that increases the dentate gyrus levels of neurogenic transcription factor Egr-1, promoting mature hippocampal neurogenesis [37].

Conclusion

In the present study, the expression of serotonin and ghrelin was not changed by elemental iron, *Curcuma xanthorrhiza* Roxb., or the combination treatment. Our study is the first to identify a correlation between the induction of restricted feed and expression of serotonin and ghrelin. However, malnutrition was successfully induced in rats. However, no significant differences were observed between the treated groups. Further research is required to determine the effects of iron and *Curcuma xanthorrhixa* Roxb. supplementation in the presence of food restrictions. Additional analyses using enhanced macronutrient diets and supplementation following the malnutrition induction period should be performed. The present study suggests the scope for future research with a more detailed examination of the containment of active compounds in *Curcuma xanthorrhixa* Roxb., usage of different doses, and a more extended period of observation.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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Authors' Contributions

DSR and ANS conducted the formal analysis, research execution, data curation, writing (including first draft writing), editing, and review of ANS and KT, financing acquisition, and DSR techniques for research, KT, and validation of ANS RH, ANS, and PKD. PKD, RH, inquiry, ANS, and DSR conducted formal assessments. The

most recent draft was reviewed and approved by all the authors.

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