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The Effect of Chlorogenic Acid Content in Coffee Can Reduce *Malondialdehyde* (MDA) and Increase *Testosterone Hormone* Levels in DM Conditions

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ABSTRACT

Hyperglycemia is an uncontrolled condition of DM in the body, which causes a decrease in cell functions due to an increase in free radicals (ROS). This study explored the effects of Chlorogenic Acid found in coffee on mitigating MDA levels and augmenting testosterone in the context of Diabetes Mellitus (DM). Chlorogenic Acid, recognized for its substantial antioxidative properties, may ameliorate cellular impairments resulting from high glucose concentrations, consequently elevating Testosterone levels. The methodology employed was a *Randomized Control Posttest Group* Design involving 20 male *Rattus norvegicus* rats, aged 8-12 weeks, divided equally into four distinct groups. DM was simulated by administering 40mg/KgBB of streptozotocin and verifying the onset of Hyperglycemia through blood glucose evaluations three days post-administration. Following the confirmation of Hyperglycemia, a 14-day intervention with Robusta Coffee was initiated, with subsequent blood sampling on the fifteenth day to measure MDA and Testosterone concentrations. Results indicated that the groups KP, KP1, and KP2 exhibited notable variations in their responses when contrasted with KP, achieving statistical relevance Of ANOVA ($p<0.05$). However, no marked difference was observed in Testosterone levels between KP1 and KP2 ($p>0.05$). The investigation corroborated that *Chlorogenic Acid* in coffee plays a crucial role in reducing MDA and increasing testosterone hormone levels in DM conditions.

Keywords: *Robusta Coffee, Chlorogenic Acid, Testosterone, Hyperglycemia, Diabetes Mellitus*

INTRODUCTION

In cases where Diabetes Mellitus (DM) is poorly controlled in a person, Hyperglycemia develops. Diabetes Mellitus (DM) represents a chronic metabolic condition in which the individual's body either fails to generate enough insulin or cannot efficiently utilize the insulin that is produced, resulting in increased glucose concentrations in the blood (Sofyanita & Iswara, 2021). The 2018 Riskesdas report also showed a 1.5% increase from the 2013 Riskesdas in those diagnosed by a doctor in the population aged ≥ 15 years (Milita et al., 2021). Study of (HE et al., 2021) Research indicates that Diabetes Mellitus (DM) frequently leads to complications within the male reproductive system. These complications are characterized by reduced sperm quality, including diminished motility, lower sperm concentration, abnormal sperm morphology, reduced sperm volume, decreased production of seminal plasma components, and sperm DNA damage.

Infertility is a disease that occurs in the reproductive system, resulting in failure to achieve pregnancy after sexual intercourse without contraception. Data shows that 10-12% of married couples experience infertility, which is classified based on gender factors, namely women 41%, men 24%, both parties 24%, and the remaining 11% have no known cause (Perintis et al., 2022).

The relationship between Hyperglycemia and infertility is based on research (HE et al., 2021).In individuals with Diabetes Mellitus (DM), male reproductive dysfunction is primarily attributable to Hyperglycemia. This condition adversely affects diabetic vascular neuropathy and causes injuries through oxidative stress, alters zinc processing, and contributes to insulin resistance syndrome. Within diabetic contexts, both a lack of insulin and its resistance contribute to impairments in critical reproductive sites, including the hypothalamus, pituitary gland, gonads, and adjacent perigonadal areas. Such impairments typically precipitate a decrease in the secretion of several sex hormones such as gonadotropin-releasing hormone, Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), and Testosterone. Notably, LH plays a pivotal role in maintaining Leydig cells that are essential for Testosterone production. A diminished release of LH leads to a lower population of Leydig cells, ultimately resulting in decreased Testosterone synthesis. This cascade of hormonal disruption underscores the intricate link between DM-induced Hyperglycemia and male reproductive challenges (Widodo, 2020).

Hyperglycemic therapy, especially for infertility complications, is still expensive, such as Hormone Replacement Therapy (HRT), and excessive use of sildenafil causes toxic effects, so alternatives are needed that are rich in antioxidants, one of which is found in coffee. Numerous bioactive compounds are present in coffee, which provide considerable health benefits. These include caffeine, flavonoids, tannins, saponins, Chlorogenic Acid, trigonelline, carbohydrates, fats, amino acids, organic acids, volatile compounds, and minerals. Chlorogenic Acid is particularly prominent, making up 8% of the total acids found in unroasted Robusta Coffee beans and 4.5% in those that are roasted. (Farhaty & Muchtaridi, 2016). The mechanism of chemical compounds in the form of steroids, alkaloids, and flavonoids as aphrodisiac ingredients occur through vasodilation, nitric oxide formation, increased testosterone levels, and gonadotropins to increase sexual activity in men (Suharno & Zen, 2023). Chlorogenic Acid has been found to reduce levels of glucose in the blood by blocking fatty acid production, mirroring the biochemical effects seen with metformin, as demonstrated through both in vivo and in vitro studies. Notably, these compounds possess antimutagenic, anticarcinogenic, and antioxidative qualities, providing robust defense mechanisms against reactive oxygen species (ROS) (Farhaty & Muchtaridi, 2016). The xanthine oxidase pathway contributes to the production of reactive oxygen species (ROS) through enzymatic processes, resulting in oxidative stress. This stress, in turn, diminishes the functionality of the Superoxide dismutase (SOD) enzyme (Kaczmarczyk-Sedlak et al., 2019). The study by Metro and colleagues (2017) demonstrated that administering caffeine in a daily amount of 5 mg per kilogram of body weight, distributed over two separate doses, effectively reduced oxidative stress levels. This research suggests a potential therapeutic use of caffeine in managing conditions associated with oxidative stress (D. Metro et al., 2017). In a study conducted by Vivi and Safari (2019), it was observed that administering Robusta Coffee at dosages of 0.108 grams per 200 grams of body weight and 0.162 grams per 200 grams of body weight results in an enhancement of the morphology of normal spermatozoa. (Fitriana and Jatmiko, 2019). The antioxidant content of coffee can reduce free radical levels in the body and prevent oxidative stress. In addition, coffee can also simultaneously reduce blood glucose levels.

Based on this background, the researcher wants to prove whether giving a single coffee bean brew rich in chlorogenic acid can reduce MDA levels and increase testosterone in Diabetes Mellitus (DM) conditions.

RESEARCH METHODOLOGY

Design

In May 2024, this study was conducted using a legitimate experimental approach, specifically through a framework known as *Randomized Post-Test-Only Control Group.* The data obtained were processed using the ANOVA test. The Semarang Health Polytechnic from the Health Research Ethics Committee of the Ministry of Health provided the necessary authorization for this study, as evidenced by the approval reference

Tools and Materials

Rat cages, feeders, 1,2 and 3 cc syringes, pipettes, gastric sachets, measuring cups, analytical scales, scalpels, cutting boards, styrofoam, surgical scissors, needles, tweezers, metformin, standard feed, streptozotocin, Robusta coffee solution, 1% *Sodium Carboxymethylcellulose* (NaCMC) and Testosterone hormone ELISA Kit.

Animal Model

This research involved 20 healthy male white rats (Rattus norvegicus), which were distributed into four distinct groups. The sample size for this study was established in accordance with WHO guidelines, stipulating that experimental research utilizing rat models must include a minimum of five animals per group.

Preparation of Coffee Solution

Preparation of Coffee Solution Pure Robusta coffee powder (*Coffea canephora*) and distilled water were weighed using an analytical balance in a ratio of 1 gram of coffee: 10 ml of distilled water. Coffee is filtered with a V pipette, and distilled water is dripped from the container. Filter. The coffee solution is made every few days to keep it fresh to avoid a decrease in coffee content. In this study, a single-bean robusta coffee or peaberry coffee solution was used. This type of coffee has a higher chlorogenic acid content than double-bean robusta coffee (Wahono, 2016).

Research Procedure

This study began with acclimation of rats for 7 days and continued with streptozotocin induction of 40 mg/kgBB. Measurement of glucose levels after Streptozotocin induction was carried out on the 3rd day after induction to ensure that the experimental animals were in a state of Hyperglycemia and rats were declared Hyperglycemia if fasting blood glucose levels> 125 mg/dl. The study included a negative control group (KN), where

rats with Hyperglycemia were given 1% NaCMC, and a positive control group (KP), where hyperglycemic rats were treated with metformin dissolved in 1% NaCMC, treatment group 1 (P1), hyperglycemia rats were given 1ml/250mgBB coffee solution (12.5% CGA) and treatment group two (P2) hyperglycemia rats were given 2ml/250mgBB coffee solution (25% CGA) for 14 days using a sonde. (Wahono, 2016). On the 15th day after treatment, rat blood was taken to analyze MDA and Testosterone levels using an ELISA reader.

RESULTS AND DISCUSSION

In the experimental group designated as KP2, subjects received solutions over a fortnight. Subsequently, measurements of MDA and Testosterone levels were conducted, and the results are comprehensively presented in Table 1.

Table 1.
Mean ± SD of MDA (µmol/L) and testosterone hormone levels (ng/ml)

Variables	KN	KP	KP1	KP2
MDA Levels	35.45±2.7	29.04±1.89	20.66±0.89	24.51±2.04
Shapirowilk	0.694	0.601	0.883	0.670
Levene test			0.166	
***P value (ANOVA)* = 0.000**				
Testosteron Levels	5.42±0.71	12.90±0.84	13.86±0.39	8.75±441
Shapirowilk	**0.861**	0.387	0.618	0.274
Levene test			**0.268**	
***P value (ANOVA)* = 0.000**				

Table 1 presents data indicating the KP1 group registered the minimal Malondialdehyde (MDA) concentrations, with KP2, KP, and KM groups following in ascending order. Conversely, the highest quantities of Testosterone hormone were recorded in the KP1 group, followed sequentially by KP2, KP, and KN groups. The evaluation of data normality was conducted using the Shapiro-Wilk test, and the assessment of homogeneity was carried out using Levene's test. Both tests established that the dataset was normal and homogeneous, with a significance level above 0.05. Following these evaluations, an Analysis of Variance (ANOVA) was applied, which identified statistically significant variations across the groups ($p<0.05$). The steps were aimed at clarifying the specific distinctions among the groups. The Post Hoc Least Significant Difference (LSD) test was utilized, and the results are illustrated in the figure that follows.

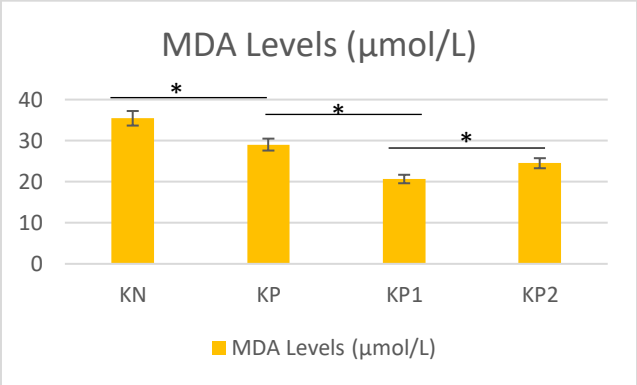

Figure 1. MDA Levels in KP, P, KP1 and KP2. *Post Hoc Test $p<0.05$

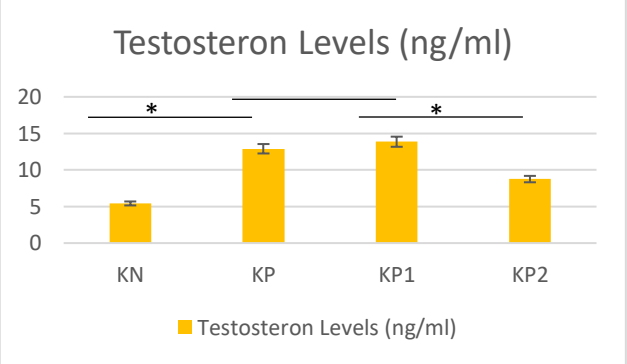

Figure 2. Testosterone hormone levels in KP, P, KP1 and KP2. *Post Hoc Test $p<0.05$

The outcomes of the LSD Post Hoc assessment revealed that the groups designated as KP, KP1, and KP2 exhibited substantial increases in the mean concentrations of MDA and Testosterone when contrasted with the KN group, where the statistical significance was denoted by p-values under 0.05. Additionally, a noteworthy disparity was observed in the average quantities of MDA and Testosterone between the KP1 and KP2 groups, evidenced by p-values falling below 0.05 (as depicted in graphs 1 and 2). The results of this examination indicate that the administration of Chlorogenic Acid, derived from Robusta Coffee, at a concentration of 1ml/250mgBB is associated with more advantageous effects when compared to a higher dosage of 2 ml/250mgBB. Where increasing the dose does not always result in a comparable increase in effect. At low doses, the active compounds in coffee may have optimal effects, while at higher doses, the beneficial effects may be reduced or even become negative. This may be due to homeostatic or negative feedback mechanisms that regulate biological responses to exposure to the active compounds (Ricci et al., 2017).

In addition, toxicity at higher doses may also be the reason why better effects are not seen. Compounds in coffee, such as caffeine, polyphenols, or other compounds, may have toxic effects at higher concentrations, thereby neutralizing or even eliminating the beneficial effects previously seen at low doses (Awwad et al., 2021). The mechanisms of this toxicity may involve oxidative stress,

metabolic disturbances, or other side effects that may interfere with physiological function.

Among the most prevalent metabolic conditions is diabetes mellitus, which is distinguished by an increase in blood glucose levels, impacting various organs throughout the body (Adedara et al., 2019; Shoorei et al., 2019). Significantly, diabetes mellitus has been recognized as a critical factor adversely affecting the male reproductive system. Numerous medical investigations have documented reductions in androgen levels, sperm concentration, motility, and viability, alongside an increase in abnormal sperm morphology (Wankeu-Nya et al., 2019). Numerous investigations have indicated that elevated blood sugar levels are crucial in causing reproductive issues through oxidative stress. Consequently, oxidative stress triggered by Hyperglycemia is deemed a major element impacting testicular performance due to the overproduction of reactive oxygen species (ROS). This condition hampers the body's capacity to neutralize free radicals using both enzymatic and non-enzymatic antioxidants (Akinyemi et al., 2015; Oguntibeju et al., 2020).

Consequently, the reduction of postprandial glucose levels is considered essential to alleviate oxidative stress and prevent secondary complications associated with diabetes mellitus (Smolders et al., 2017). Given that oxidative stress is a significant contributor to reproductive dysfunctions in the testes and epididymis, the employment of antioxidants can mitigate the detrimental impacts of this condition (Shrilatha & Muralidhara, 2007). To explore the impact of diabetes on reproductive health, researchers induced diabetes in male rats using alloxan. This compound, a sugar analog, is known for its ability to cause diabetes mellitus by producing reactive molecules like superoxide radicals and hydrogen peroxide. Additionally, alloxan hinders the activity of glucokinase, a glucose sensor that is mainly found in the liver and pancreatic beta cells (Fujieda et al., 2018)

In the domain of male infertility linked to diabetes, research has demonstrated that testosterone is crucial for the process of spermatogenesis (Choubey et al., 2020; Rato et al., 2015). Moreover, testosterone, a principal output of androgen synthesis, serves as an indicator for testicular injury. Alongside assessing sperm quantity, reproductive hormone levels, including testosterone, were measured across all experimental cohorts (Sofyanita et al., 2019).In the present investigation, a notable reduction in testosterone concentrations was observed in diabetic control rats when contrasted with normal control rats. These findings align with earlier studies, which demonstrated that the induction of diabetes in male rats through alloxan administration resulted in diminished testosterone levels (Akinola et al., 2015; Ghlissi et al., 2013; Sebai et al., 2015). There is evidence indicating that diminished activity of Leydig and Sertoli cells correlates with reduced insulin secretion (Minaz et al., 2019).

This research revealed that the diabetic group exhibited reduced testosterone levels in contrast to the group that consumed a solution abundant in chlorogenic acid derived from Robusta Coffee. The likely cause for this discrepancy is the presence of bioactive compounds in the coffee, which have the potential to activate endocrine functions within the hypothalamic-pituitary axis, subsequently promoting testosterone production in Leydig cells (Maneesh et al., 2006). Chlorogenic acid, a compound found in coffee, has been shown to increase testosterone production through the mechanism of inhibiting the enzyme 17β-hydroxysteroid dehydrogenase. This enzyme plays an important role in testosterone metabolism, so by inhibiting its activity, testosterone levels in the body can increase significantly. Research on mice shows that giving chlorogenic acid can significantly increase testosterone levels in the blood. In addition, chlorogenic acid has also been shown to improve sperm quality. The mechanism is by reducing oxidative stress on sperm cells, which can damage DNA and sperm morphology. Human studies show that consuming chlorogenic acid can significantly increase sperm motility, morphology, and concentration. On the other hand, caffeine, found in coffee, tea, and soda, can also affect testosterone production. Caffeine inhibits the activity of the enzyme phosphodiesterase, which plays a role in testosterone metabolism. Research on mice shows that giving caffeine can increase testosterone levels in the blood. However, caffeine can also affect sperm quality. The mechanism is increased production of free radicals, which can damage DNA and sperm morphology. However, human studies have shown mixed results, with some studies showing decreased sperm quality while others found no negative effects (Plumeriastuti et al., 2021). Multiple elements have been documented as contributors to the progression of diabetes mellitus, with oxidative stress being a significant factor. The harm caused by free radicals due to Hyperglycemia is now recognized as a catalyst for diabetes-related complications. Within diabetes, oxidative stress is propagated through various mechanisms. For instance, within the polyol pathway, the generation of advanced glycation end products (AGEs) and protein kinase C diminishes the efficacy of antioxidant enzymes in the body, resulting in damage to vital organs (Sofyanita et al., 2023; Sofyanita & Yunianti, 2023). Emerging research indicates that oxidative stress can induce DNA damage in testicular tissue and epithelial cells, potentially leading to reduced sperm quality. Furthermore, it can cause irregular secretion of gonadotropins, disrupt normal spermatogenesis, impair semen quality, and trigger abnormal apoptosis in the testes (Alves et al., 2015). Moreover, sperm DNA damage has been correlated with inferior embryo quality, lower rates of embryo implantation, elevated miscarriage frequencies, and subsequent health issues in future generations (Ammar *et al.*, 2019)

Antioxidant compounds are expected to fight free radicals caused by hyperglycemia conditions, one of which is coffee. Coffee has a high content of cellular antioxidant compounds, such as chlorogenic acid, caffeine, and flavonoids. Caffeine can regulate the effects of free radicals (Fitriana and Jatmiko, 2019; Achmad Wahyudi and

Septi Wulandari, 2022). Chlorogenic Acid, identified as a polyphenolic compound, offers protection to DNA, lipid peroxides, and proteins from oxidative damage through the donation of hydrogen atoms from its hydroxyl groups (Wahono, 2016). Free radicals' electron deficiency can be addressed, thus averting their detrimental impacts. This intervention may safeguard the testicles from damage, potentially preserving the integrity of sperm quality in males (Farid et al., 2022; Saad, 2009; Sofyanita & Iswara, 2021). Chlorogenic Acid represents the predominant polyphenolic substance present in coffee beans. These polyphenolic substances function as antioxidants, thereby safeguarding DNA, lipids, and proteins through the neutralization of free radicals. The mechanism of Chlorogenic Acid involves the stabilization of free radicals by contributing a hydrogen atom from its hydroxyl group (Sofyanita et al., 2024). Therefore, the lack of electrons in free radicals can be overcome so that the negative effects of free radicals can be prevented. In addition to chlorogenic acid, caffeine also has a role as an antioxidant and also increases spermatozoa motility. Caffeine can inhibit the enzyme phosphodiesterase so that it will increase the production of cAMP in cells will stimulate spermatozoa motility. Caffeine also has the ability to directly stimulate spermatozoa motility. The limitation of this study is the need to use pure chlorogenic acid that is not mixed with other components so that the results are more detailed on whether the effect is caused by chlorogenic acid or other components.

CONCLUSION

The research findings indicate that administering Chlorogenic Acid Content in Coffee in a concentration of 1 ml/grBB is more effective in reducing MDA concentrations and increasing Testosterone hormone levels compared to a dosage of 2 ml/grBB under conditions of Diabetes Mellitus.

SUGGESTION

Further research needs to be done using pure Chlorogenic Acid to determine the effect of reducing MDA and increasing testosterone hormones, whether from pure chlorogenic acid components or from other ingredients contained in coffee.

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