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RESEARCH ARTICLE

THE EFFECT OF CURCUMA ZEDOARIA EXTRACT ON LIVER DAMAGE BIOMARKERS IN A DIABETIC RAT MODEL

(PENGARUH EKSTRAK KUNIR PUTIH (Curcuma zedoaria) TERHADAP BIOMARKER KERUSAKAN HATI PADA TIKUS MODEL DIABETES MELLITUS)

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ABSTRACT

Uncontrolled hyperglycemia in diabetes mellitus (DM) can cause liver tissue damage. This can be characterized by increased levels of several biomarkers, including transaminase and transferase enzymes and alpha-fetoprotein (AFP) level, as well as decreased bilirubin and albumin levels. White turmeric (Curcuma zedoaria) contains high levels of antioxidants and anti-inflammatory compounds. The objective of this study was to determine the effect of white turmeric extract on liver damage biomarkers in DM rats. This true experimental study used a post-test-only control group design. The test subjects were 28 male Wistar rats divided through two randomizations. In the first randomization, rats were allocated into two groups (control/K1 and the DM rat group) with a ratio of 1:3. DM was induced by an intraperitoneal injection of niacinamide (NA) 45 mg/kg BW followed by streptozotocin (STZ) 110 mg/kg BW 15 minutes later. The second randomization divided the DM rats into three groups: K2 (DM only), K3, and K4 (each receiving white turmeric extract at 9 and 18 mg/g BW, respectively) for 28 days. The next day, liver biomarkers were measured. A one-way ANOVA test for SGOT, GGT, AFP, and albumin levels showed $p<0.05$. Likewise, the Kruskal-Wallis test for SGPT and bilirubin levels also showed significant differences. The levels of SGOT, SGPT, GGT, AFP, bilirubin, and albumin differed significantly among the four groups. AFP and bilirubin levels in K4 were lower than in K3 and K2, while albumin levels were higher than in those groups.

Administration of white turmeric extract reduced transaminase and transferase enzymes, bilirubin, and AFP, and increased albumin levels in DM Wistar rats.

Keywords: diabetes mellitus, liver damage biomarkers, white turmeric

ABSTRAK

Kondisi hiperglikemia pada diabetes mellitus (DM) yang tidak terkendali menyebabkan kerusakan jaringan hati yang ditandai dengan kenaikan biomarker hati: serum glutamic oxaloacetic transaminase (SGOT dan serum glutamic acid pyruvate transaminase (SGPT)), enzim transferase (gamma glutamyl transferase (GGT)), alfa fetoprotein (AFP), bilirubin dan albumin. Kunir putih (Curcuma zedoaria) kaya antioksidan dan antiinflamasi. Tujuan penelitian adalah mengetahui pengaruh ekstrak kunir putih terhadap biomarker kerusakan hati pada tikus DM. Penelitian true experimental menggunakan post-test only control group design. Subjek uji 28 tikus jantan wistar dirandomisasi pertama menjadi 7 ekor di kelompok kontrol/K1, dan 21 ekor diinduksi DM dengan injeksi intraperitoneal niacinamide (NA) 45 mg/kgBB dan streptozotocin (STZ) 110 mg/kgBB. Tikus yang berhasil diinduksi menjadi DM, dibagi menjadi tiga kelompok: Kelompok 2/K2: tikus DM; Kelompok 3/K3 dan Kelompok 4/K4: tikus DM yang diberi ekstrak kunir putih 9 dan 18 mg/200gBB selama 28 hari. Pengukuran kadar enzim transaminase dan transferase, AFP, bilirubin serta albumin dilakukan di akhir penelitian. Hasil uji beda rerata kadar SGOT, GGT, AFP dan albumin dengan oneway ANOVA didapatkan nilai p<0,05. Uji Kruskal Wallis pada kadar SGPT dan bilirubin juga didapatkan nilai p<0,05. Kadar SGOT, SGPT, GGT, AFP, bilirubin dan albumin di keempat kelompok berbeda signifikan. Kadar enzim transaminase dan transferase, serta kadar AFP dan kadar bilirubin di K4 secara signifikan lebih rendah dari K3 dan K2, sedangkan kadar albumin di K4 secara signifikan lebih tinggi dari K3 dan K2. Pemberian ekstrak kunir putih berpengaruh menurunkan kadar enzim transaminase, kadar bilirubin dan kadar AFP serta meningkatkan kadar albumin pada tikus wistar DM.

Kata kunci: biomarker kerusakan hati, diabetes mellitus, kunir putih

INTRODUCTION

Diabetes mellitus is a chronic disease caused by metabolic disorders. It is characterized primarily by hyperglycemia.[1] Hyperglycemia that remains untreated for a long period can cause progressive organ tissue damage, particularly in the liver.[2] Liver cell damage occurs as a result of a continuous inflammatory process that induces oxidative stress and triggers the formation of reactive oxygen species (ROS).[3] Hyperglycemia is primarily caused by insulin resistance, which affects the metabolism of fat, protein, and carbohydrates. This condition can lead to non-alcoholic fatty liver disease (NAFLD) that progresses to non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC).[4]

According to the International Diabetes Federation (IDF), the estimated number of people with diabetes mellitus (DM) worldwide in 2020 and 2045 for the 20–79 age group was at least one hundred thirteen million and one hundred fifty-two million, respectively. As the population ages, the prevalence of DM is projected to

increase to one hundred ninety-nine million by 2030 and to seven hundred million by 2045. DM and its complications are the third leading cause of death in Indonesia.[1] Prevention of DM complications, particularly liver damage, needs to be promoted through the use of natural ingredients such as white turmeric (*Curcuma zedoaria*).

Previous research indicates that the curcumin and flavonoid content in white turmeric can block the activity of nuclear factor kappa beta (NF-κB), a transcription factor that stimulates inflammatory cytokines.[3] Inhibition of NF-κB enhances hepatic myofibroblast apoptosis by suppressing the expression of C-Jun N-Terminal Kinases (c-JNK), leading to fibrosis regression. Curcumin also has a hepatoprotective effect by inhibiting the transient receptor potential melastatin 2 (TRPM2) channel through the restoration of calcium ion (Ca^{2+}) homeostasis, thereby reducing oxidative stress and lowering the risk of non-alcoholic steatohepatitis.[5] Curcumin from white turmeric also exhibits antihyperglycemic properties at a dose of 500 mg/kg BW.[6] Current evidence regarding the potential of white turmeric to ameliorate diabetes mellitus (DM)-related liver cell damage remains limited. This study was therefore conducted to determine the effect of white turmeric on liver damage biomarkers in a DM rat model.

MATERIALS AND METHODS

Research Design

This study employed a true experimental design with a post-test-only control group to determine the effect of white turmeric extract on biomarkers of liver damage in DM rats.

Location and Time of Study

This research was conducted at the Center for Food and Nutrition Studies (PSPG) Laboratory, Gadjah Mada University (UGM), Yogyakarta, from July to August 2024.

Test Subjects

The test subjects consisted of 28 male Wistar rats aged three months and weighing 150–200 g. Rats that had previously been used in other experiments, had anatomical abnormalities, showed wounds or defects, or had a random blood glucose (RBG) level of <200 mg/dL after the DM model was created were excluded. All procedures related to the study followed research ethics for experimental animals and received approval from the Medical/Health Research Bioethics Committee, Faculty of Medicine, Unissula (No. 215/VI/2024/ Bioethics Committee).

Experimental Procedure

Twenty-eight Wistar rats underwent Phase I randomization at a 1:3 ratio. This process produced 7 rats in the normal group (Group I) and 21 rats in the DM group. The

DM group received an intraperitoneal injection of STZ-NA, with nicotinamide (NA) administered at a dose of 110 mg/kg BW to prevent the development of Type 1 DM. This was followed by streptozotocin (STZ) induction at a dose of 45 mg/kg BW fifteen minutes later.[7]

The DM model was considered successful when the random blood glucose (RBG) level measured three days after STZ-NA injection was > 200 mg/dL. The DM rats then entered Phase II randomization and were allocated into 3 groups, each consisting of 7 rats. The distribution was as follows: (1). The negative control group was induced with STZ-NA without receiving white turmeric. (2). K III: Treatment Group I was induced with STZ-NA and administered white turmeric at 9 mg/200 g BW. (3). K IV: Treatment Group II was induced with STZ-NA and administered white turmeric at 18 mg/200 g BW. The K III and K IV groups received treatment for 28 days. Blood samples were collected from the orbital plexus at the end of the study.

Preparation of White Turmeric Extract

White turmeric extract was prepared using the maceration method. Three hundred grams of white turmeric powder were dissolved in 1,500 mL of 97% ethanol in a two-liter Erlenmeyer flask. The resulting macerate was filtered, the residue was re-soaked in 2.5 liters of 97% ethanol for two days, and then filtered again. The filtrates were combined and concentrated using a rotary evaporator until a nearly thick extract was obtained. This extract was further evaporated over a water bath to produce a thick extract.[8] The extract was administered orally using a gavage needle at doses of 9 mg/200 g BW and 18 mg/200 g BW once daily for 28 days.

Measurement of Liver Damage Biomarkers

Measurement of liver damage biomarkers was performed on blood samples collected from the orbital sinus. The levels of SGOT, SGPT, GGT, AFP, bilirubin, and albumin were measured from blood serum using an automatic spectrophotometer after mixing with their respective reagents.

Statistical Analysis

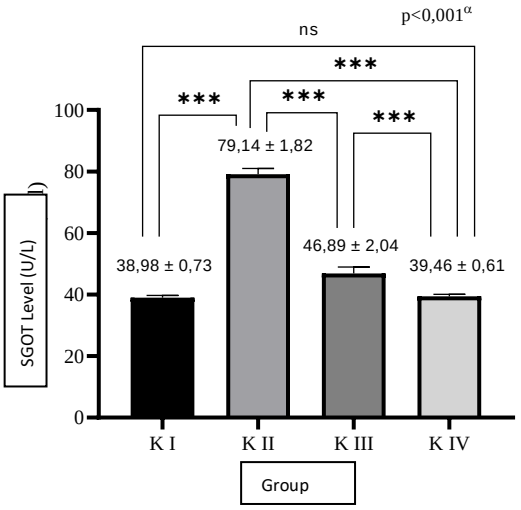
The research data are presented descriptively as mean and standard deviation values. The normality of data distribution was assessed using the Shapiro-Wilk test, and homogeneity of variance was evaluated using Levene's test. One-way ANOVA followed by an appropriate post-hoc test was applied to compare data with a normal distribution. For data that were not normally distributed, the Kruskal-Wallis test followed by the Mann-Whitney test was used.. A p-value of > 0.05 was considered

statistically significant. All data analyses were performed using SPSS version 26.0.

RESEARCH AND DISCUSSION

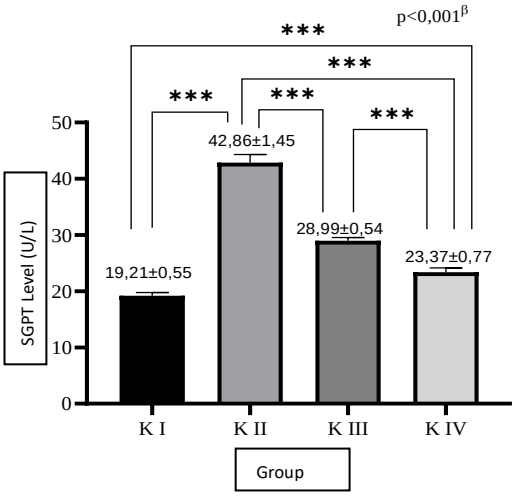
The random blood glucose (RBG) level in the diabetic rats was higher than in the normal rats, with mean values of 258.1±5.1 mg/dl and 69.3±1.3 mg/dl. The independent t-test produced a p-value <0.001, which indicates that the STZ-NA induction successfully created the diabetic model. This finding is consistent with previous research.[7] STZ initiates the formation of nitric oxide (NO) and reactive oxygen species, which can cause pancreatic damage. This condition inhibits the functional production of insulin, leading to elevated blood glucose levels.[9]

The results of the liver damage biomarker measurements across the experimental groups showed that group K II had the highest SGOT level, while group K I had the lowest. The comparison of mean SGOT levels using one-way ANOVA produced a p-value < 0.001, which indicates a significant difference among the four groups. The LSD post-hoc analysis showed significant differences between all group pairs, except between group K IV and group K I (p=0.535) (Figure 1).



α: one-way ANOVA test; ***: p <0.001 from LSD post hoc test, ns: not significant

Figure 1 SGOT levels among the groups.

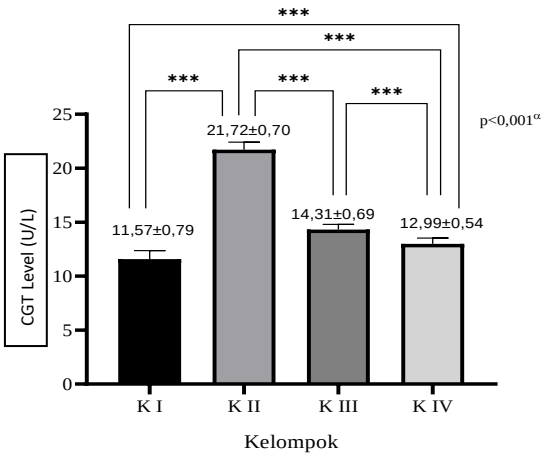


β: Kruskal-Wallis test. ***: p<0.001 Mann-Whitney test

Figure 2 SGPT levels among the groups.

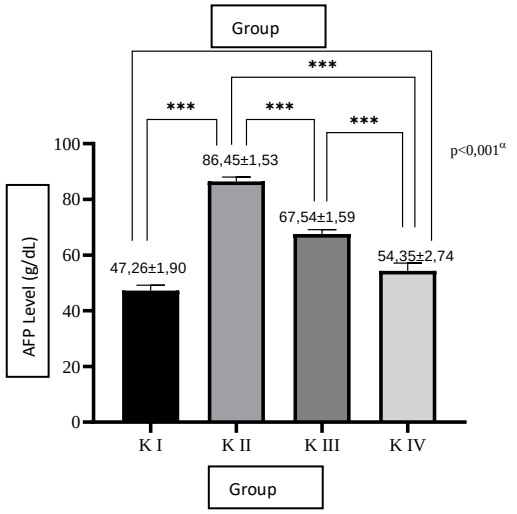
The comparison of mean SGPT levels among the four groups using the Kruskal-Wallis test yielded p<0.001. Subsequent analysis using the Mann-Whitney test showed significant differences in all group pairs (Figure 2). The one-way ANOVA analysis of mean GGT levels showed a significant difference with a p-

value <0.001. Follow-up testing using the LSD post-hoc procedure confirmed that all group comparisons were significantly different (Figure 3).



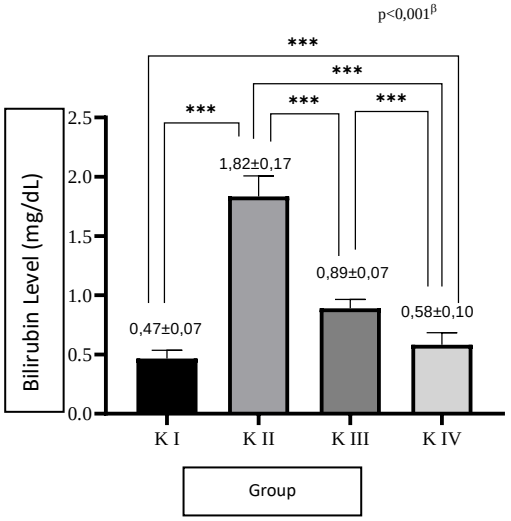
α: one-way ANOVA test. ***: p<0.001 from the LSD post test

Figure 3 GGT levels among the groups.



α: one-way ANOVA test. ***: p<0.001 from the LSD post hoc test

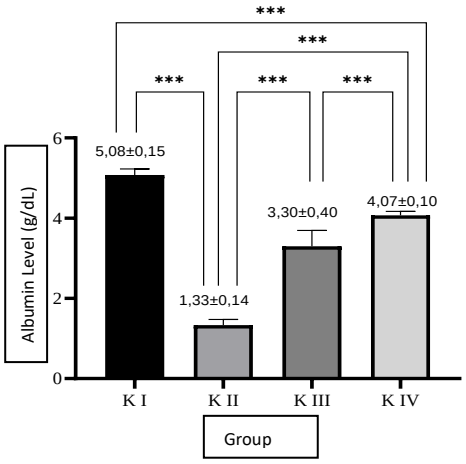
Figure 4 AFP levels among the groups.



β: Kruskal-Wallis test. ***: p<0,001 from Mann-Whitney test

Figure 5 Bilirubin levels among groups.

The mean AFP and bilirubin levels also differed significantly among the four groups (p<0.01). Follow-up analysis using the LSD or Mann-Whitney tests showed significant differences for all group comparisons, with p<0.001 (Figures 4 and 5).



α: one-way ANOVA.***: p<0.001 from the LSD post hoc test

Figure 6 Albumin levels among the groups.

The albumin levels among the four groups also showed significant differences ($p<0.001$). The comparison values between two groups using the LSD post-hoc test also resulted in $p<0.001$ for all group pairs (Figure 6).

STZ-NA induction increased the levels of SGOT, SGPT, GGT, AFP, and bilirubin. This elevation is closely associated with oxidative stress caused by the accumulation of free radicals related to hyperglycemia.[10] The increase in GGT levels following STZ-NA induction occurs through several mechanisms, including adipose tissue destruction, heightened oxidative stress and inflammation, and endothelial cell dysfunction. STZ also causes a marked reduction in reduced glutathione (GSH), which disrupts the plasma membrane and leads to cell necrosis. This condition promotes the release of GGT into the bloodstream.[11]

The effect of STZ-NA on bilirubin levels has also been reported by Muthmainah et al. in a type 2 DM rat model.[12] Hepatic damage due to STZ-NA induction can occur through several pathways, one of which is the increased expression of NF-kβ, which subsequently enhances the expression of NADPH enzyme and superoxide. This increase, along with the increase in nitric oxide (NO), stimulates ROS activity and cellular metabolism.[13]

The rise in AFP levels after STZ-NA induction is similarly linked to hyperglycemia and hepatic inflammation. STZ-NA induces insulin resistance, causing compensatory lipolysis to maintain blood glucose levels. The continuous accumulation of lipolysis products in the liver results in hepatic steatosis,[14] a condition that can trigger an increase in ROS and oxidative stress as well as the secretion of pro-inflammatory cytokines.[15] If this process is prolonged, it can trigger hepatic inflammation leading to Hepatocellular Carcinoma (HCC), one of the markers of which is an increase in AFP levels.[16]

The effect of STZ-NA induction on albumin levels occurs due to disrupted insulin activity. This disruption leads to increased gluconeogenesis, in which proteins or amino acids are converted into glucose for ATP production. Because albumin synthesis depends on amino acids, the increased need for these substrates in ATP generation reduces their availability for albumin formation. As a result, albumin synthesis becomes impaired.[17]

The administration of white turmeric extract at doses of 9 mg/200g BW and 18 mg/200g BW for 28 days was effective in improving the levels of SGTOT, SGPT, GGT, APF, bilirubin, and albumin in DM rats. This effect on multiple liver damage biomarkers is attributed to the

antioxidant and antidiabetic properties of the extract.[18,19]

Curcumin, the compound responsible for the extract's antidiabetic effect, is present at approximately 88.6 mg/100 grams dry weight.[18] The antioxidant compounds in the white turmeric extract are indicated by flavonoids and phenols, which are present at approximately 41.35 mg/g and 81.31 mg/g of extract, respectively.[20]

Curcumin, as an antioxidant, plays a role in inducing the expression of the glutamate-cysteine ligase enzyme gene. This enzyme is essential for the de novo synthesis of glutathione, which helps reduce oxidative stress.[21] he improvement in oxidative stress lowers the risk of liver tissue damage caused by reactions within cellular components and the development of lesions. This improvement can be reflected in the normalization of SGOT levels.[22]

The effect of white turmeric extract on various liver damage biomarkers in DM rats also occurs through the inhibition of the inflammatory pathway. Curcumin and flavonoids act as inhibitors of NF-κB transcriptional regulation, which suppresses the production of inflammatory mediators. NF-kB is a key mediator of hepatocyte stress that initiates liver fibrosis. Therefore, inhibiting NF-κB activation can help prevent liver damage and reduce the circulation of SGOT in the bloodstream.[23]

Regarding the reduction in SGPT levels, the flavonoids and curcumin contained in white turmeric extract act by inhibiting the intrinsic PKC pathway that leads to the production of NF kβ.[5] The decrease in GGT levels induced by white turmeric extract is also attributed to the presence of curcumin and flavonoids. These compounds help suppress the inflammatory process and function as antioxidants.[24]

The decrease in bilirubin levels in STZ-NA DM model rats following administration of white turmeric extract was similarly reported by Zamanian et al.[25] They showed that curcumin prevents complications in STZ-NA-induced diabetic rats by modulating the NF-κB pathway to reduce oxidative stress and inflammation. These two conditions are strongly linked and create a vicious cycle that contributes to the development of cirrhosis and HCC.[26]

The reduction of AFP levels by white turmeric extract also occurs through NF-κB pathway inhibition by curcumin, together with the suppression of the phospholipase A2 pathway by flavonoids. Both actions limit activation of inflammatory pathways and help protect the liver from damage.[27]

The increase in albumin levels is achieved through a hypoglycemic mechanism.[19] This effect is related to the

antidiabetic properties of curcumin,[29] which improve glucose metabolism abnormalities and insulin resistance and enhance insulin sensitivity in a type II DM mouse model.[30] Another mechanism involves the regeneration of pancreatic β cells, which helps regulate albumin production through direct hepatic signaling.[17]

Curcumin and flavonoids also exhibit anti-inflammatory activity by decreasing the production of IL-1β, IL-6, and TNF-α. They inhibit cyclooxygenase-2 (COX-2) and key inflammatory pathways, including NF-κB, mitogen-activated protein kinase (MAPK), activator protein 1 (AP-1), and other inflammatory mediators.[31]

The limitation of this study lies in the dosage selection for the white turmeric extract, which did not yield optimal outcomes comparable to the normal control group. Another limitation is the absence of a phytochemical analysis of the extract.

CONCLUSION

White turmeric extract influences several biomarkers of liver damage in Wistar rats with a DM model. This influence is reflected in decreased levels of transaminase and transferase enzymes, bilirubin, and AFP. It is also evident in increased albumin levels. Future studies may further explore the effect of white turmeric extract on liver cell injury. They may also consider using higher dosages and conducting a phytochemical analysis of the extract.

CONFLICT OF INTEREST

No conflict of interest exists in the writing of this scientific article

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