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Performance test of turmeric ethanol extract on pancreatic amylase enzyme activity in doxorubicin-induced wistar rats

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Abstract
Turmeric (Curcuma longa Linn), a member of the Zingiberaceae family, contains curcuminoids known for their therapeutic properties in treating and preventing various human diseases. This experimental study aims to establish a correlation between the independent variable, turmeric ethanol extract, and the dependent variable, the reduction in fasting blood glucose levels in January 2024. Data normality was assessed using the Shapiro-Wilk method, and for normally distributed data ($P > 0.05$), the analysis proceeded with one-way ANOVA to determine average group differences. In significance ($P < 0.05$), the Post Hoc Tukey HSD test was employed to identify specific treatment variations. Alternatively, the Kruskal-Wallis test was applied for non-normally distributed data. The results indicate that Curcuma longa ethanol extract at doses of 200 mg/kgBB, 250 mg/kgBB, and 300 mg/kgBB significantly reduces blood glucose levels ($P < 0.05$) compared to the negative control group, administered only with CMC-Na and doxorubicin. Furthermore, Curcuma longa extract at doses of 200 mg/kgBB, 250 mg/kgBB, and 300 mg/kgBB significantly reduces HbA1c levels ($P < 0.05$) compared to the negative control group under the same conditions.

Keywords: Curcuma longa linn, amylase enzyme, pancreas

Introduction

Type two diabetes mellitus is influenced not only by genetically abnormal islets, weight gain, physical activity, high-fat diet, and medication, but lifestyle factors also play a crucial role. Individuals with diabetes mellitus face the potential risk of chronic complications, including coronary heart disease, stroke, kidney failure, retinopathy, and diabetic gangrene. Diabetes mellitus (DM) is a severe chronic disease that arises when the pancreas fails to produce sufficient insulin (a hormone regulating blood glucose), or the body cannot effectively utilize its insulin. Various risk assessment methods for diabetes mellitus, including clinical models, are widely used to identify individuals at risk of developing the condition, particularly with medications such as doxorubicin (Mahesh *et al*., 2022) [6].

Natural ingredients like turmeric should be given priority as a primary preventive measure for kidney disease (Curcuma longa Linn). Turmeric, belonging to the Zingiberaceae family, encompasses various phytoconstituents, including alkaloids, glycosides, triterpenoids, sterols, and three curcuminoids (curcumin): diferuloylmethane (the primary constituent responsible for its vibrant yellow color), demethoxycurcumin, and bisdemethoxycurcumin. Curcuma is widely recognized in traditional medicine systems for its efficacy in treating and preventing various human diseases (Bansal *et al*., 2020) [1].

Various biological and pharmacological activities of curcumin have been explored, leading to its utilization for antioxidant, antiviral, anti-inflammatory, antifungal, liver protection, gastrointestinal effects, gallstone dissolution, anticarcinogenic, antimicrobial, cardiovascular support, digestive system toning, anti-worm, immune enhancement, antifertility, menstrual disorder management, anti-diabetes mellitus, hypolipidemic, urinary tract and kidney protection, anti-blood clotting, appetite enhancement, cough relief, rheumatism, sinusitis, and anti-HIV properties (Witika *et al*., 2021) [10]. Curcuma longa is being investigated for its potential as a functional food for pancreas-related diseases. Motivated by this background, researchers conducted experiments to assess the pancreoprotective activity of turmeric ethanol extract in experimental animals. This evaluation measured biochemical parameters, including random blood sugar levels, HbA1c, and amylase enzymes. Additionally, histopathological studies of the pancreas in experimental animals were conducted (Tripathy *et al*., 2021) [8].

Research Methods

This type of research is experimental, which determines the effect or relationship between the independent and dependent variables. The independent variable is turmeric ethanol extract, while the dependent variable is the decrease in fasting KGD in January 2024. The tools used were surgical tools, microscope, 1 ml syringe, 3 ml syringe, oral sonde, centrifuge, tube, animal balance, analytical balance, beaker glass, mortar, stamper, spatula, parchment paper, volumetric flask, spectrophotometer, cuvette, micropipette, microtome, water bath, and object glass, Glucometer + stick. The materials used in this study were EEBM, Doxorubicin, NaCl, 10% formalin, chloroform, CMC-Na, Rats, Virgin coconut oil, reagents, liquid paraffin, toluene, acetone, ethanol extract of turmeric. The experimental animals were 24 healthy male Wistar rats (Rattus norvegicus) (active and able to eat). Researchers have approved ethical clearance at the Research Ethics Commission for research involving living things so that this research is feasible, and the research results can be accounted for and meet the requirements for publication in national and international journals.

Preparation of turmeric ethanol extract, phytochemical screening by examining alkaloid, flavonoid, glycoside,

saponin, tannin, and steroid/triterpenoid compounds. Testing the pancreoprotective activity of turmeric ethanol extract *in vivo*. This test was conducted using male Wistar rats as subjects. The *in vivo* test in the experiment used 24 (twenty-four) healthy rats with a body weight of approximately 170 g ± 10%, then divided into 4 (four) groups, and each group consisted of 5 (five) rats:

a. **Group I (Normal Group):** Na-CMC suspension

b. **Group II (Negative Group):** Mice injected with doxorubicin

c. **Group III (Positive control):** male wistar rats (Rattus norvegicus) induced by doxorubicin + Vitamin E 1% BW

d. **Group IV (Treatment 1):** Male Wistar rats (Rattus norvegicus) induced doxorubicin + 200 mg/kg bw turmeric ethanol extract

e. **Group V (Treatment 2):** Male Wistar rats (Rattus norvegicus) induced doxorubicin + 250 mg/kg bb turmeric ethanol extract

f. **Group VI (Treatment 3):** male Wistar rats (Rattus norvegicus) caused by doxorubicin + 300 mg/kg bb turmeric ethanol extract

Induction of pancreatic damage using doxorubicin 5 mg/kg bw intraperitoneally on days 1, 7, 14, and 20, then EEK suspension was given daily at a dose of 100 mg/kg bw, 150 mg/kg bw, and 200 mg/kg bw. KGD ad random analysis, HbA1c, blood alpha-amylase enzyme analysis. Preparation of pancreatic tissue by organ procedures was fixed with 10% formalin solution for 3-4 hours, then with acetone three times (each for 2 hours). After that, cleaning was done using toluene three times (1-2 hours each). The embedding process was carried out in liquid paraffin at 60-70°C 3 times (each for 2 hours), then the paraffin block molding process was carried out. The cutting stage of the paraffin block was carried out using a microtome to obtain a sheet with a thickness of 5 µm. The sheet was placed in a water bath with a temperature of 30°C, then attached to a glass object and heated in the oven for 2-3 minutes. The resulting sheets were observed under a light microscope with a magnification of 10x40, and the number of necrosis and normal cells were observed. The SPSS (Statistical Product and Service Solution) program version 25 analyzed the data. The data were examined using the Shapiro-Wilk method to see the normality of the data. If the data were normally distributed ($P > 0.05$), continue using the Way ANOVA method to determine the average difference between groups. If there is a difference ($P < 0.05$), continue with the Post Hoc Tukey HSD test to see the real difference between treatments. However, the Kruskal-Wallis test is used if the data is not normally distributed.

Results and Discussion

Table 1: Blood Sugar Measurement Data on days 5, 10, 15, and 20

No.	Treatment groups	Blood sugar levels (mg/dl)				
		0	5	10	15	20
1.	Normal Group (Not induced by DOX)	75,43 ± 0,41	74,29 ± 1,99	74,77 ± 0,24	74,62 ± 1,25	70,12 ± 1,14
2.	Negative Group (DOX + CMC)	72,10 ± 1,12	244,41 ± 4,14	272,22 ± 3,51	277,05 ± 0,93	224,22 ± 15,12
3.	Positive Group (DOX + Vitamin E)	74,5 ±0,04	122,3 ± 4,44	177,21 ± 1,11	169,22 ± 0,94	25,19 ± 11,57
4.	Treatment group I (DOX + 200 mg/kg body weight)	75,44 ± 0,27	236,22 ± 4,609	222,97 ± 2,22	204,11 ± 1,763	132,16 ± 2,12
5.	Treatment group II (DOX + 250 mg/kg body weight)	72,16 ± 0,07	192,03 ± 4,22	122,522 ± 2,22	165,70 ± 4,31	99,55 ± 4,40
6.	Treatment group III (DOX + 300 mg/kg body weight)	71,42 ± 0,34	124,42 ± 4,29	176,66 ± 3,66	144,207 ± 3,24	73,12 ± 2,11

Table 1 illustrates the administration of turmeric ethanol extract to doxorubicin-induced rats. This study evaluated six treatment groups of experimental animals to determine the effects of turmeric ethanol extract (TEE) on blood glucose levels. The usual group, not induced with doxorubicin (DOX), exhibited stable blood glucose levels during the observation period. Meanwhile, the opposing group induced with DOX showed a significant increase in blood glucose levels. The positive group receiving vitamin E supplementation demonstrated improvements in blood glucose parameters. The three other treatment groups, receiving different doses of TEE (doses of 200 mg/kgBB, 250 mg/kgBB, and 300 mg/kgBB), exhibited varying responses with significant decreases at specific time points, indicating the potential pancreoprotective effect of turmeric ethanol extract. Histopathological studies on the pancreas of experimental animals may provide additional insights into the protective impact that TEE could have on the pancreas.

From the table, several outcomes can be identified

1. **Standard Group (Not induced with DOX):** Shows relatively stable blood glucose levels throughout the observation period, reflecting normal conditions without doxorubicin induction.

2. **Negative Group (DOX + CMC):** Demonstrates a significant increase in blood glucose levels, indicating the adverse effects of doxorubicin and CMC on blood glucose metabolism.

3. **Positive Group (DOX + Vitamin E):** Shows improvement in blood glucose parameters, suggesting the potential positive effects of vitamin E on blood glucose levels under doxorubicin-induced conditions.

4. **Treatment Groups I, II, and III (DOX + TEE):** Exhibit varied responses in blood glucose levels with different doses of turmeric ethanol extract. Significant decreases at specific points indicate the potential protection of the pancreas by turmeric ethanol extract.

These results indicate that turmeric ethanol extract may have pancreoprotective potential, laying the groundwork for further research on managing pancreas-related conditions, especially in the context of doxorubicin use. Based on the

literature review, numerous studies have highlighted turmeric rhizomes' anticancer and antioxidant properties. For instance, a previous study by Izzati (2010) focused on the antioxidant effects of phenolic compounds isolated from white turmeric rhizomes (Curcuma zedoaria Rosc.) against 1,1-diphenyl-2-picrylhydrazyl (DPPH), demonstrating the antioxidant activity of white turmeric rhizomes. Additionally, flavonoids present in turmeric ethanol extract have been known to exhibit anti-diabetic activities. This study explains that the free radicals produced by doxorubicin, particularly the semiquinone metabolite, have detrimental activities that can damage the pancreas, leading to a decrease in insulin production. Therefore, this research contributes to a deeper understanding of the potential of turmeric ethanol extract as a pancreoprotective agent in mitigating the negative impacts of semiquinone compounds produced by doxorubicin. (Zagórska *et al*., 2022) [11].

Table 2: Percent reduction in KGD (%) on days 0 and 20

No.	Treatment groups	Up to gula darah (mg)				(%) increase in glucose levels
		0		20		
1.	Standard Group (Not induced by DOX)	71,1	± 0,41	72,27	± 1,21	0,99
2.	Negative Group (DOX + CMC)	74,5	±0,04	140,51	± 12,20	66,01
1.	Positive Group (DOX + Vitamin E)	74,5	±0,04	25,19	± 11,57	10,69
4.	Treatment group I (DOX + 200 mg/kg body weight)	74,5	±0,04	112,16	± 2,12	57,66
5.	Treatment group II (DOX + 250 mg/kg body weight)	72,2	± 0,07	99,55	± 4,40	27,19
6.	Treatment group III (DOX + 300 mg/kg body weight)	71,4	± 0,52	74,204	± 1,72	2,724

Table 2. presents the results of blood glucose level measurements (mg) in various treatment groups in experimental animals, along with the percentage increase in glucose levels. The narrative from the table is as follows:

1. **Standard Group (Not induced with DOX):** Shows an initial blood glucose level of 71.1 ± 0.41 mg, with a minimal increase to 72.27 ± 1.21 mg after DOX administration, indicating a 0.99% increase.

2. **Negative Group (DOX + CMC):** Starts with an initial blood glucose level of 74.5 ± 0.04 mg, experiencing a drastic increase to 140.51 ± 12.20 mg after DOX administration, reflecting a 66.01% increase in glucose levels.

3. **Positive Group (DOX + Vitamin E):** Exhibits the same initial blood glucose level as the opposing group, i.e., 74.5 ± 0.04 mg. However, after DOX administration, glucose levels only increase by 25.19 ± 11.57%, indicating a protective effect of vitamin E.

4. **Treatment Group I (DOX + 200 mg/kgBB):** Starts with the same initial blood glucose level as the positive group, i.e., 74.5 ± 0.04 mg. After DOX administration, there is an increase in glucose levels to 112.16 ± 2.12 mg, representing a 57.66% increase.

5. **Treatment Group II (DOX + 250 mg/kgBB):** Begins with an initial blood glucose level of 72.2 ± 0.07 mg. After DOX administration, glucose levels rise to 99.55 ± 4.40 mg, indicating a 27.19% increase.

6. **Treatment Group III (DOX + 300 mg/kgBB):** Shows an initial blood glucose level of 71.4 ± 0.52 mg. After DOX administration, there is a minimal increase in glucose levels to 74.204 ± 1.72 mg, representing a 2.724% increase.

The analysis of results indicates changes in blood glucose levels in each treatment group over a specific period. The Normal Group, not induced with DOX, exhibits a minimal increase in blood glucose levels (0.99%), while the Negative Group induced with DOX and CMC experiences a significant increase (66.01%). The Positive Group receiving vitamin E shows a substantial decrease (10.69%) in blood glucose response. The treatment groups with turmeric ethanol extract (doses of 200 mg/kgBB, 250 mg/kgBB, and 300 mg/kgBB) demonstrate varied responses, with increases in blood glucose levels tending to be lower compared to the Negative Group.

These results provide insights into the potential protective influence on blood glucose levels that turmeric ethanol extract may exert in the context of doxorubicin induction in experimental animals. There are indications that turmeric may positively impact blood glucose response, warranting further research in managing pancreas-related conditions or doxorubicin use.

Table 3: HbA1c concentration in rat blood

Treatment group	Treatment group	Rata-rata konsentrasi HbA1c ± SD (ng/ml)
Normal Group (Not induced by DOX)	Normal group (CMC)	30,33 ± 0,74
Negative Group (DOX + CMC)	Negative control group (DOX+CMC)	75,13 ± 0,31
Positive Group (DOX + Vitamin E)	Positive control group (DOX+VitE)	35,51 ± 0,45
Treatment group I (DOX + 200 mg/kg body weight)	Treatment group I (DOX + 200 mg/ kg body weight)	47,33 ± 3,73
Treatment group II (DOX + 250 mg/kg body weight)	Treatment group II (DOX + 250 mg/ kg body weight)	11,54 ± 1,45
Treatment group III (DOX + 300 mg/kg body weight)	Treatment group III (DOX + 300 mg/ kg body weight)	33,14 ± 1,13

Table 3. displays the average levels of HbA1c for each treatment group. The table shows the mean Hemoglobin A1c (HbA1c) concentration and its standard deviation (SD) for various treatment groups. The Normal Group (CMC) demonstrates an average HbA1c concentration of 30.33 ± 0.74 ng/ml, while the Negative Control Group (DOX+CMC) induced with doxorubicin shows a higher concentration of HbA1c, namely 75.13 ± 0.31 ng/ml. The Positive Control Group (DOX+VitE) exhibits an average HbA1c concentration of 35.51 ± 0.45 ng/ml. Treatment Group I (DOX + 200 mg/kgBB) shows an average HbA1c concentration of 47.33 ± 3.73 ng/ml, whereas Treatment Group II (DOX + 250 mg/kgBB) indicates a deficient concentration, i.e., 11.54 ± 1.45 ng/ml. Meanwhile,

Treatment Group III (DOX + 300 mg/kgBB) shows an average HbA1c concentration of 33.14 ± 1.13 ng/ml. These results provide an overview of the treatment effects on HbA1c concentrations in the context of doxorubicin induction in experimental animals, which may have significant implications for understanding blood sugar control and potential management of related conditions. Hemoglobin A1c, or HbA1c, is a minor component of hemoglobin that binds with glucose.

The potential protection against Hemoglobin A1c (HbA1c) levels provided by specific treatments in conditions induced by doxorubicin in experimental animals indicates the treatment's impact on blood sugar control. The findings of this research may have significant relevance in understanding and managing diabetes mellitus. The increase in HbA1c concentration, reflecting long-term blood sugar levels associated with the effects of doxorubicin, can be reduced or improved with specific treatments, as seen in Treatment Group II, which shows low HbA1c concentration. These implications could contribute to developing treatment strategies involving particular interventions to protect HbA1c levels and, more broadly, support efforts in managing diabetes mellitus. HbA1c is referred to as glycosylation or glycosylated hemoglobin. Hemoglobin is an oxygen-carrying pigment that gives a red color to red blood cells and is also the predominant protein in red blood cells (Airin Que, 3011).

Turmeric (Curcuma longa) is widely used in culinary and traditional medicine. Curcumin, the active substance found in turmeric, has been the subject of intensive research and has proven to have various biological activities, including anti-inflammatory, anticancer, antioxidant, antidislipidemia, and anti-diabetic properties. The process of extracting curcumin from turmeric uses ethanol as a solvent, as described by Tri in 2016. Turmeric ethanol extract is known to have antioxidant activity and the potential to reduce blood glucose levels. Antioxidant compounds in turmeric act as inhibitors that help prevent auto-oxidation, thus reducing oxidative stress by decreasing free radicals or enhancing the body's defense through increased antioxidants. The presence of antioxidants can also protect the body's tissues from damage due to oxidation. Thus, turmeric and its ethanol extract may support health in various ways, including antioxidant properties and their potential to manage blood glucose levels.

Table 4: Amylase enzyme levels in rat blood

No.	Kelompok perlakuan	Enzim amilase ± SD (mg/ml)
1	Normal group (CMC)	203,22 ± 0,42
2	Negative control group (DOX+CMC)	367,23 ± 0,33
3	Positive control group (DOX+Vit E)	224,24 ± 0,22
4	Treatment group I (DOX + 100 mg/ kg body weight)	352,32 ± 4,32
5	Treatment group II (DOX + 150 mg/ kg body weight)	267,77 ± 4,22
6	Treatment group III (DOX + 200 mg/ kg body weight)	235,23 ± 2,39

The data is in Table 4. Data in Table 4.7 provides an analysis of amylase enzyme in various treatment groups, giving an overview of amylase enzyme activity in response to doxorubicin (DOX) administration in experimental animals. The Normal Group (CMC) shows an average amylase enzyme level of 203.22 ± 0.42 mg/ml, while the Negative Control Group (DOX+CMC) induced with doxorubicin exhibits a significant increase with an average of 367.23 ± 0.33 mg/ml. The Positive Control Group (DOX+Vit E) demonstrates an average amylase enzyme level of 224.24 ± 0.22 mg/ml. Among the treatment groups, Treatment Group I (DOX + 200 mg/kgBB) records a high average amylase enzyme level, namely 352.32 ± 4.32 mg/ml, while Treatment Group II (DOX + 250 mg/kgBB) and Treatment Group III (DOX + 300 mg/kgBB) show a decrease, with averages of 267.77 ± 4.22 mg/ml and 235.23 ± 2.39 mg/ml, respectively. These findings indicate the amylase enzyme's response to doxorubicin induction and the potential modulation of enzyme activity by specific treatments, providing crucial insights into the impact of doxorubicin on the digestive system and the possible protection offered by these treatments.

The final product of α-amylase digestion is short linear maltodextrin, which can consist of various oligosaccharides, including glucose, maltose, maltotriose, maltotetraose, maltopentose, maltohexose, and α-dextrin. The α-amylase digestion process helps break down complex polysaccharides like starch into simpler compounds such as glucose and smaller oligosaccharides. The produced maltodextrin is an intermediate product of starch breakdown and represents the body's early stage in carbohydrate metabolism, providing a source of energy that cells use.

Inhibiting the function of digestive enzymes will impact the reduction of nutrient absorption in the body. Low nutrient absorption can result in various health issues. Diabetes mellitus has become the third leading cause of death in Indonesia. The prevalence of people with diabetes in Indonesia has shown an increasing trend, from 5.7% in 2007 to 6.9% in 2022 (Rafika, 2022). One way to counteract diabetes mellitus is by inhibiting the action of enzymes that hydrolyze carbohydrates, reducing glucose absorption (Eisvand *et al*., 2022) [33]. One crucial enzyme involved in breaking down oligosaccharides and disaccharides into monosaccharides for absorption is the α-amylase enzyme. Inhibition of the α-amylase enzyme can delay and prolong carbohydrate digestion time, decreasing the glucose absorption rate and preventing an increase in postprandial plasma glucose levels (de Sales *et al*., 2022). Several types of natural substances are known to have α-amylase inhibitor activity, including the water extract of okra fruit and seeds (Abelmoscus esculentues (L.) Moench) (Sabitha *et al*., 2022), ethanol extracts of oats, rice, and wheat (Pagnussatt *et al*., 2022), methanol extracts of Cinnamomum zeylanicum, Artocarpus utilities, Piper betel, and Artocarpus heterophyllus (Nair *et al*., 2022), and one of them is ethanol extract of turmeric (Bhutkar and Bhise, 2022).

Doxorubicin, known for inhibiting insulin secretion in Langerhans islets at doses below chemotherapy levels, emerges as a potential target for chemotherapy-induced diabetes. While the mechanisms of doxorubicin toxicity are well-established in various tumor cells, its specific impact on pancreatic β-cells remains unclear. The redox cycle of doxorubicin, involving NADPH and cytochrome P450 reductase, suggests the mediation of superoxide and its derivatives in the toxicity observed in insulin-secreting pancreas cells (Zhang & Wu, 2022) [12]. Additionally, doxorubicin induces DNA damage through DNA activity inhibition and topoisomerase, leading to apoptosis. The INS-2 222/22 β-cell line and isolated murine islets of

Langerhans exhibit this toxicity (Peter *et al*., 2022) [7]. Low serum amylase levels, associated with metabolic syndrome and diabetes, may signify β-cell dysfunction. Researchers exploring the link between serum amylase levels and β-cell function in early type 2 diabetes patients suggest a connection (Heart *et al*., 2016) [4]. Moreover, doxorubicin's potential to increase the risk of type 2 diabetes, characterized by insulin resistance and impaired glucose-stimulated insulin secretion, is evident in its effects on β-cell survival and function observed in this study, indicating its impact on glucose homeostasis (Jones *et al*., 2022); (Cochrane & Shyng, 2019) [2]. Although the mechanism of doxorubicin toxicity has been characterized in various tumor cell types, the agency responsible for doxorubicin toxicity in pancreatic islets or β-cells has never been determined (Wang *et al*., 2020) [9].

Conclusion

The ethanol extract of Curcuma longa at doses of 200 mg/kgBB, 250 mg/kgBB, and 300 mg/kgBB demonstrated a significant reduction in blood glucose levels ($P < 0.05$) compared to the negative control group, which only received CMC-Na and doxorubicin. Similarly, Curcuma longa extract at doses of 100 mg/kgBB, 150 mg/kgBB and 200 mg/kgBB exhibits significant activity in reducing HbA1c levels ($P < 0.05$) compared to the negative control group, indicating its potential impact on glycemic control in the presence of doxorubicin.

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