Potential of Ethanol Extract of Red Curly Chili (*Capsicum annuum* L.) as an Antioxidant and Antidiabetic Agent in Mice

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ABSTRACT

Medicinal plants containing polyphenols (flavonoid dan tannin), quercetin and capsaicin have strong antioxidant properties. These compounds can help inhibit oxidative stress that plays a role in various diseases, including diabetes mellitus. *Capsicum annuum* L is rich in phytochemicals and active compounds such as flavonoids (Quercetin, Luteolin, Kaempferol), tannins, saponins, terpenoids, carotenoids, and vitamin C. This study aimed to evaluate the potential of red curly chili (*Capsicum annuum* L.) ethanol extract as an antioxidant and antidiabetic agent in mice. The mice will be randomly divided into the following groups (6 mice per group): Diabetic control group (induced diabetes with streptozotocin, no treatment), and *Capsicum annuum* L group (Diabetic group treated with *Capsicum annuum* L ethanol extract at dose 100 mg/kg BW, 200 mg/kg BW, 400 mg/kg BW for 21 days). On the 21st day, the mice were anesthetized, and blood samples were collected via intracardiac puncture for the analysis of blood glucose and malondialdehyde (MDA) levels. Oral administration of *Capsicum annuum* L. At 400 mg/kg resulted in a significant reduction in blood glucose and MDA levels ($p<0.05$) compared to the diabetic group. The results approached those of the normal group, although the difference was not statistically significant. The study confirmed that *Capsicum annuum* L. extract effectively alleviates oxidative stress associated with type II diabetes in STZ-induced mice, as evidenced by its ability to lower blood glucose levels and reduce MDA levels.

Keywords: *Capsicum annuum* L, Blood glucose, Malondialdehid, Streptozotocin

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INTRODUCTION

Diabetes is a metabolic disorder characterized by elevated blood sugar (glucose) levels, which occur when the body is unable to produce or utilize insulin properly. There are two main types of diabetes: type 1 diabetes, where the body is unable to produce insulin, and type 2 diabetes, where the body cannot use insulin effectively. Chronic hyperglycemia can elevate the production of reactive oxygen species (ROS) in the body. ROS are highly reactive oxygen molecules that can cause significant damage to cellular components, including lipids, proteins, and DNA. Elevated blood sugar levels further amplify ROS production through various metabolic pathways, such as inefficient glycolysis and the activity of enzymes involved in glucose metabolism. Chronic hyperglycemia can elevate the production of reactive oxygen species (ROS) in the body. ROS are highly reactive oxygen molecules that can cause significant damage to cellular components, including lipids, proteins, and DNA. Elevated blood sugar levels further amplify ROS production through various metabolic pathways, such as inefficient glycolysis and the activity of

enzymes involved in glucose metabolism (Ahmed and Rehman, 2023).

Some medicinal plants, such as ginger, garlic, and green tea, possess potent antioxidant properties due to the presence of compounds like polyphenols, capsaicin, quercetin, and carotenoids. These compounds function by neutralizing free radicals, protecting body cells from oxidative damage, reducing inflammation, and preventing chronic diseases such as heart disease, diabetes, and cancer (López and Mejía, 2020; Saha and Kundu, 2021). Therefore, consuming herbs rich in these beneficial compounds can offer significant protection against oxidative stress and contribute to overall health improvement. It has been reported that *Capsicum annuum* also has strong antioxidant properties (Alvarez and Rodríguez, 2021).

Capsicum annuum L., commonly known as chili pepper, is a well-researched plant renowned for its diverse pharmacological effects. These effects are primarily attributed to its active compounds, including capsaicin, capsanthin, beta carotene, vitamin C, and polyphenols (such as flavonoids and tannins) (Fahad and Tariq, 2023). These bioactive substances contribute to its antioxidant, anti-inflammatory, anticancer, analgesic, and antimicrobial properties, making it a valuable plant for various therapeutic applications (Gholami and Mohammadi, 2022). Although there is growing evidence supporting the pharmacological properties of *Capsicum annuum* L. based on experimental animal models, the antidiabetic potential of curly chili has yet to be scientifically investigated. Therefore, this study aims to evaluate the hypoglycemic and antioxidant effects of curly chili extract in streptozotocin (STZ)-induced diabetic mice (Venkatesh and Anbu, 2023).

METHODS

Experimental animals

Male mice (Mus musculus) of the Balb/c type, aged 8-10 weeks, weighing approximately 25–30 g, were obtained from a laboratory animal research center. The mice used were kept in standard room conditions (temperature 22–25°C, humidity 50–60%, lighting 12 hours light/12 hours dark) with free access to food and water.

Diabetes induction

Diabetes in mice was induced by administering streptozotocin (STZ) dissolved in citrate buffer solution (pH 4.5). Streptozotocin was injected intraperitoneally (IP) with a dose of 40 mg/kg BW per day for 5 consecutive days (Ventura-Sobrevilla et al.; Erwin et al., 2012). Diabetes was confirmed by measuring blood sugar levels in mice that exceeded 200 mg/dL, which was done 2-3 days after induction.

Mice were divided into four treatment groups, namely: Group I (Diabetes Control): Mice induced by streptozotocin (STZ) for diabetes, without curly red chili extract treatment. Group II (Low Dose): Mice induced by STZ, given curly red chili extract at a dose of 100 mg/kg BW. Group III (Medium Dose): Mice induced by STZ, given curly red chili extract at a dose of 200 mg/kg BW. Group IV (High Dose): Mice induced by STZ, given curly red chili extract at a dose of 400 mg/kg B

The curly red chili extract obtained from the ethanol extraction process was given orally to mice in the appropriate treatment groups (groups II, III, and IV) for 3 consecutive weeks. The doses used were 100 mg/kg BW for low doses, 200 mg/kg BW for medium doses, and 400 mg/kg BW for high doses. The extract was given using an oral tube once a day at the same time every day.

Blood sugar level measurement

Blood sugar levels were measured using a glucometer before STZ administration, after STZ injection, and after treatment. Blood samples taken from mice are Random Blood Sugar. Blood samples were taken from the tip of the tail for analysis of blood sugar levels in mg/dL.

Measurement of malondialdehyde (MDA) levels

After 3 weeks of treatment, mice were sacrificed by anesthesia. Tissue samples (liver) were taken for analysis of malondialdehyde (MDA) levels as a marker of oxidative stress. MDA levels were evaluated using a spectrophotometric method based on reactions with thiobarbituric acid (TBARS), with absorbance measurements at a wavelength of 532 nm. MDA measurement results are expressed in nmol/g tissue.

RESULT AND DISCUSSION

Blood sugar levels

At the beginning of the study, blood sugar levels in all mice were measured and it was found that mice in the normal control group showed normal blood sugar levels 90 -110 mg/dL. In contrast, mice in the DM group had significantly increased blood sugar levels ($p < 0.01$) to 220–270 mg/dL, indicating hyperglycemia due to diabetes.

After 3 weeks of treatment, the results of blood sugar level measurements showed a significant decrease in the group of mice given curly red chili extract. The group with a dose of 100 mg/kg BW of curly red chili extract showed a decrease in blood sugar levels of 129.17a ± 35.15 mg/dL which was not significant compared to the DM group ($p < 0.05$). The curly red chili extract group with a dose of 200 mg/kg BW showed a decrease in blood sugar levels of 113.83a ± 19.81 mg/dL and a dose of 400 mg/kg BW showed a significant decrease in blood sugar levels of 109.17a ± 10.94 mg/dL compared to the DM group ($p < 0.05$) which was around 40% ($p < 0.05$) (Table 1).

The diabetes control group (DM) that was not given the extract still showed high blood sugar levels, indicating that curly red chili extract is effective in lowering blood sugar levels in diabetic mice.

Table 1. Average RBS levels under various treatments

Group	Initial RBS (mg/dL) (Mean ± SD)	RBS After STZ (mg/dL) (Mean ± SD)	RBS After 3 weeks (mg/dL) (Mean ± SD)
K+	96,17 ± 8,25	270,00 ± 46,27	$280,83^{a}$ ± 10,66
P1	104,00±13,44	218,33 ± 11,81	$129,17^{b}$ ± 35,15
P2	105,33 ± 3,67	248,50 ±31,97	$113,83^{b}$ ± 19,81
P3	103,83 ± 2,31	241,17 ± 33,62	$109,17^{b}$ ± 10,94

Note: Different superscripts (^{ab}) in the same column indicate a significant difference ($p<0.05$).

Malondialdehyde (MDA) levels

Malondialdehyde (MDA), as an indicator of oxidative damage due to oxidative stress, was measured at the end of the study. The results of measuring MDA levels showed a significant difference ($p<0.05$) between the DM control group which had very high MDA levels (217.67d ± 22.71 nmol/ml) compared to the treatment group, reflecting significant oxidative stress in mice with diabetes mellitus.

In the group given curly red chili extract, there was a decrease in MDA levels. The 100 mg/kg BW dose group experienced a decrease in MDA levels of around 197.25c ± 6.14 nmol/ml, the 200 mg/kg BW dose group showed a decrease of around 178.17b ± 10.40 nmol/ml, while the 400 mg/kg BW dose group also experienced a significant decrease of around 148.58a ± 9.11 nmol/ml ($p<0.05$) when compared to the DM group and the control group (Table 2).

Table 2. Average MDA levels under various treatments

Group	MDA Levels (nmol/ml) (Mean ± SD)
K+	$217,67^{d} \pm 22,71$
P1	$197,25^{c} \pm 6,14$
P2	$178,17^{b} \pm 10,40$
P3	$148,58^{a} \pm 9,11$

Note: Different superscripts (^{abcd}) in the same column indicate a significant difference ($p<0.05$).

This indicates that curly red chili extract can reduce oxidative stress in diabetic mice by significantly reducing MDA levels and a dose of 400 mg/kg BW is the optimal dose in reducing MDA levels in the blood.

This study aimed to evaluate the potential of ethanol extract of curly red chili (Capsicum annuum L.) as an antioxidant agent against blood sugar levels and malondialdehyde (MDA) levels in male mice (Mus musculus) induced by Streptozotocin (STZ) to produce a diabetes mellitus model. The results of this study indicate that administration of curly red chili extract can lower blood sugar levels and reduce MDA levels, which indicates that curly red chili extract has therapeutic potential in overcoming the adverse effects of diabetes mellitus.

In STZ-induced mice, blood sugar levels increased significantly, which is typical of a diabetes mellitus model. Streptozotocin works by damaging pancreatic beta cells, which reduces insulin production, causing hyperglycemia (Venkatesh and Anbu, 2023). In this study, administration of ethanol extract of curly red chili peppers showed a significant decrease in blood sugar levels, with the greatest decrease in the group given the extract at a high dose (400 mg/kg BW). This suggests that curly red chili pepper extract has the potential to increase insulin sensitivity or stimulate increased insulin secretion, which can help lower blood sugar levels. The decrease in blood sugar levels seen in mice given curly red chili extract may be related to the ability of bioactive compounds in chili, especially

capsaicin, which is known to have hypoglycemic effects (Rahman, and Hossain, 2023). Capsaicin can modulate several metabolic pathways, including increasing glucose metabolism and improving insulin function. In addition, curly red chili extract can increase glucose uptake into cells and reduce insulin resistance, which may explain the significant decrease in blood sugar levels (Ahmed and Rehman, 2023).

Diabetes mellitus is characterized by increased production of reactive oxygen species (ROS), which causes lipid peroxidation and increases MDA levels, as a byproduct of the peroxidation process. In this study, STZ-induced mice showed significant increases in MDA levels, indicating excessive oxidative stress due to hyperglycemia (Gholami and Mohammadi, 2022). However, administration of curly red chili extract succeeded in significantly reducing MDA levels in all treatment groups, with the largest decrease in the group given a high dose (400 mg/kg BW). This decrease in MDA levels indicates that curly red chili extract has strong antioxidant activity, which can reduce oxidative stress in diabetic mice (Siddiqui and Naz, 2023). This antioxidant activity can be caused by bioactive compounds in curly red chili, such as flavonoids, vitamin C, and capsaicin, which are known to increase the activity of the body's antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), and reduce ROS production (Fahad and Tariq, 2023).

The decrease in blood sugar levels caused by curly red chili extract was also followed by a decrease in MDA levels, indicating that better management of blood sugar levels can reduce oxidative stress (Zhang and Yang, 2021). This supports the hypothesis that reducing hyperglycemia can reduce ROS production, which in turn reduces lipid peroxidation and MDA levels. Therefore, curly red chili extract not only reduces blood sugar levels but also protects the body from oxidative damage that often occurs in diabetes mellitus.

The results of this study indicate that curly red chili extract has potential as a therapeutic agent in the management of diabetes mellitus, both through hypoglycemic effects and through reducing oxidative stress (Elgawish and Abdelrahman, 2021). Given the close relationship between hyperglycemia and oxidative stress in diabetes, administration of curly red chili extract that reduces both parameters indicates that this extract can provide significant benefits in preventing or reducing diabetes complications.

Curly red chili extract, high dose (400 mg/kg BW), gave the most significant results in reducing blood sugar and MDA levels (Kaur and Jain, 2021). This suggests that the optimal dose that should be considered to obtain maximum benefits without the risk of side effects is a dose of 400 mg/kg BW. Further research is needed to explore more appropriate doses, deeper molecular mechanisms, and long-term safety of using curly red chili extract in the treatment of diabetes.

This study used an STZ-induced mouse model for diabetes mellitus, and although the results showed positive potential of curly red pepper extract, the application of these results to humans requires further research. Some limitations of this study include the use of only one type of animal model and limited dosage (Rojas and Rivas, 2019). Therefore, further research is needed to validate these results in humans through clinical trials and to assess potential side effects or drug interactions with other diabetes therapies.

CONCLUSION

This study shows that the ethanol extract of curly red chili (Capsicum annuum L.) has the potential as an antioxidant agent that can lower blood sugar levels and reduce malondialdehyde (MDA) levels in male mice induced by streptozotocin. These positive effects make curly red chili extract a promising candidate for additional therapy in the management of diabetes mellitus, especially through the mechanism of reducing oxidative stress and improving glucose metabolism. However, further research is needed to explore deeper mechanisms, optimal doses, and the safety of long-term use in humans.

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Author Contribution

All authors participated to all aspects of this work, including preparation, research, data collecting and analysis, manuscript drafting, and publication approval.

Competing Interest

There are no financial, personal, or professional conflicts of interest that may influence the research, its findings, authorship, or publication of this article.

Ethical Approval

This study received ethical approval from the Research Ethics Commission of the Faculty of Medicine, Universitas Airlangga with number 347/EC/KEPK/FKUA/2023.

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