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Research Article

WHITE CURCUMA EXTRACT (*CURCUMA ZEDOARIA* [CHRISTM.] ROSCOE) AMELIORATES INSULIN RESISTANCE BY MODULATING LIPID METABOLISM IN HIGH-FAT DIET-INDUCED WISTAR RATS

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ABSTRACT

Objectives: This study aims to examine the mechanism by which white turmeric extract inhibits insulin resistance in experimental animals.

Methods: Twenty-five male Wistar rats were divided into five groups: Normal control, high-fat diet (HFD), drug control (metformin), and two dose groups of white turmeric extract (200 mg/kg and 400 mg/kg). A HFD was administered for 10 days to induce insulin resistance, except in the normal control group. The drug control and two extract groups received metformin (45 mg/kg), and white turmeric extract (200 mg/kg and 400 mg/kg) for an additional 10 days. Insulin resistance was assessed using fasting blood glucose, insulin levels, homeostasis model assessment of insulin resistance (HOMA-IR) index, fat profiles, and tissue morphology of liver and brain organs.

Results: Rats given 400 mg/kg of white turmeric extract showed significantly lower fasting blood glucose (45.04±9.08 mg/dL), insulin levels (1.58±0.37 mU/L), and HOMA-IR index (0.17±0.02) compared to the HFD group (81.55±13.94 mg/dL, 2.28±0.20 mU/L, and 0.46±0.08, respectively). The extract improved fat profiles and caused morphological changes in liver and brain tissue, with liver cells appearing smaller and nerve cells showing longer axons.

Conclusion: White turmeric extract effectively inhibits insulin resistance by improving fat profiles.

Keywords: *Curcuma zedoaria*, Insulin resistance, Diabetes, Homeostasis model assessment of insulin resistance, Fat profile.

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INTRODUCTION

Diabetes mellitus remains a significant global health challenge due to its increasing prevalence each year. Chronic hyperglycemia, the hallmark of diabetes mellitus, is a major contributor to mortality worldwide, ranking as the sixth leading cause of death after ischemic heart disease, stroke, lower respiratory tract infections, chronic obstructive pulmonary disease, and lung cancer. In 2015, an estimated 415 million individuals worldwide were diagnosed with diabetes, with approximately 97% classified as type 2 diabetes, also referred to as non-insulin dependent diabetes mellitus. This figure is projected to escalate to 642 million by 2040 [1]. Reducing the incidence of diabetes and effectively managing its complications are critical public health priorities. One potential strategy to achieve this is by providing alternative treatments, as existing treatment modalities are often associated with adverse effects.

The impairment of insulin-mediated glucose uptake into cells (insulin resistance) is a key characteristic of type 2 diabetes. This condition is hypothesized to be associated with elevated levels of body fat, particularly free fatty acids. Three primary mechanisms have been proposed through which increased free fatty acid levels contribute to insulin resistance. First, increased levels of free fatty acids impair the PI-3 Kinase-Akt insulin signaling pathway, which is essential for facilitating glucose transporter translocation. This disruption leads to a reduction in cellular glucose uptake [2]. Second, elevated levels of free fatty acids create competition for energy substrates in oxidative metabolism, primarily by enhancing free fatty acid oxidation. Third, excessive free fatty acids contribute to mitochondrial dysfunction due to a reduction in mitochondrial components, particularly the enzyme pyruvate dehydrogenase. This impairment leads to decreased oxidative phosphorylation of glucose while simultaneously promoting *de novo* lipogenesis and gluconeogenesis [2].

Curcuma zedoaria (Christm.) Roscoe, commonly known as white turmeric, has demonstrated potential as an alternative therapeutic agent for the prevention and management of blood glucose levels in type 2 diabetes mellitus. This plant has long been utilized in traditional medicine for its diverse therapeutic properties, including its antibacterial, antifungal, antiamoebic, gastroprotective, hepatoprotective effects, and anticancer [3-8]. Additionally, the crude extract rhizome from this plant inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, suggesting a potential role in lipid metabolism regulation [9]. Several studies have supported its anti-diabetic properties. Research conducted by Rahmatullah *et al*. and Shoha *et al*. demonstrated that extracts from the rhizome and leaves of white turmeric exhibit significant hypoglycemic effects [10,11]. Additionally, a study by Handajani and Dhinintya reported that the essential oil extracted from white turmeric effectively reduced blood glucose levels in a streptozotocin-induced type 2 diabetes mellitus rat model at an intraperitoneal dose of 40 mg/kg [5]. Furthermore, Liu *et al*. revealed that crude extracts of white turmeric possess the ability to inhibit HMG-CoA reductase, a key enzyme in lipid metabolism, which may also influence insulin resistance [12]. From a taxonomic and phytochemical perspective, *Curcuma longa* L., which contains *curcumin* as its primary active compound, has been shown to ameliorate insulin resistance in a high-fat diet (HFD) induced obese mouse model, as assessed through the insulin sensitivity index [13]. These findings suggest that white turmeric holds considerable promise as an herbal-based therapeutic intervention for type 2 diabetes mellitus. Its beneficial effects may be exerted not only through direct hypoglycemic

mechanisms but also by modulating metabolic pathways implicated in insulin resistance. However, further research is required to elucidate the underlying molecular mechanisms and to evaluate its clinical potential in the management of diabetes in humans.

Based on these findings, this study aims to demonstrate that white turmeric extract can mitigate insulin resistance by improving lipid profiles in male Wistar rats subjected to a HFD. Therefore, *C. zedoaria* is not only a potential hypoglycemic agent but also a modulator of lipid metabolism that may contribute to enhancing insulin sensitivity. The findings of this study are expected to provide stronger scientific evidence supporting the potential of white turmeric as an herbal-based therapeutic approach for the prevention and management of type 2 diabetes mellitus.

METHODS

Materials

The materials used in this study included white turmeric rhizomes, ethanol, fat emulsion, and the following biochemical assay kits: Glucose Oxidase–Peroxidase Aminophenazone (GOD-PAP) kit (Dumolab®), Rat Insulin Enzyme-linked Immunosorbent Assay (ELISA) kit (Elabscience®), Cholesterol Oxidase–Peroxidase Aminophenazone (CHOD-PAP) kit (Dumolab®), high-density lipoprotein cholesterol (HDL-C) Precipitate kit (Dumolab®), and Triglyceride Glycerolphosphate Oxidase–Peroxidase Aminophenazone (GPO-PAP) kit (Dumolab®).

Preparation of white turmeric extract and phytochemical screening

The white turmeric used in this study was obtained from a demonstration garden in Cinanggela Village, Pacet District, Bandung Regency, West Java, Indonesia. Fresh rhizomes were collected, washed thoroughly with clean water, sliced into small pieces, and sun-dried until an optimal moisture content was achieved. The dried simplicia was then extracted using the maceration method with ethanol as the solvent. The resulting liquid extract was concentrated using a rotary evaporator to obtain a thick extract. A portion of the concentrated extract was subjected to phytochemical screening to identify its bioactive compound content. Alkaloids were detected using Dragendorff and Meyer reagents, while flavonoids were identified through the addition of magnesium powder and hydrochloric acid (HCl). Tannins were tested using a 1% gelatin solution, whereas phenolic compounds were identified using iron (III) chloride ($FeCl_3$) solution. Saponins and quinones were screened using a 5% potassium hydroxide (KOH) solution. In addition, the presence of monoterpenes, sesquiterpenes, steroids, and terpenoids was analyzed using the Liebermann-Burchard reagent. The majority of the concentrated extract was used for further *in vivo* testing on experimental animals to evaluate its biological effects in this study.

Preparation of fat emulsion

The fat emulsion was prepared in a fixed volume of 100 mL, containing 20 g of lard, 1 g of propylthiouracil, 5 g of cholesterol, 1 g of sodium glutamate, 10 g of sucrose, 20 mL of Tween 80, 30 mL of propylene glycol, and distilled water (aqua dest) to reach a total volume of 100 mL. The prepared fat emulsion was stored at a temperature of 4°C [14].

Experimental animal treatment

All procedures involving experimental animals in this study were approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran, no. 04/UN6.KEP/EC/2018. A total of 25 adult male Wistar rats, weighing between 200 and 250 g, were used as test subjects. The rats were housed in standard laboratory cages and acclimatized for 15 days under controlled environmental conditions, with access to standard chow and drinking water ad libitum. Following the acclimatization period, the rats were randomly assigned to five groups: A normal control group, a HFD group, a drug control group, and two treatment groups receiving *C. zedoaria* extract at different doses. The high-fat emulsion was administered to all groups for ten consecutive days, except for the normal control group. In addition to HFD induction, the drug control and treatment groups underwent intervention with specific compounds. The drug control group received metformin at a dose of 45 mg/kg, while the treatment groups were administered *C. zedoaria* extract at doses of 200 mg/kg and 400 mg/kg, respectively, for 10 consecutive days. Daily measurements of body weight (BW) and water intake were conducted to monitor the development of insulin resistance in the experimental animals. On the 11th day, the rats underwent fasting for 18–20 h, with continuous access to drinking water. Subsequently, biological samples were collected, and predetermined parameters were measured to evaluate the effects of the interventions.

Sample collection

The biological samples used in this study consisted of serum, liver, and brain tissues from experimental rats. Serum collection was performed following the euthanasia of the animals using the CO_2 inhalation method. Confirmation of death was ensured by the absence of respiratory movements and pupil dilation. Blood samples were collected immediately after euthanasia. A mid-sagittal transverse incision was made from the abdominal cavity to the thoracic cavity, exposing the heart for direct blood withdrawal. A total of 3 mL of blood was collected from the heart and transferred into centrifuge tubes, where it was allowed to clot at room temperature for 1 h. The samples were then centrifuged at 3000 rpm for 15 min. The resulting supernatant (serum) was carefully separated using a micropipette and stored in Eppendorf tubes for subsequent biochemical analysis according to predetermined parameters. For organ collection, a mid-sagittal transverse incision was made from the abdominal cavity to the thoracic cavity to extract the liver, which was then sectioned for further analysis. Additionally, a mid-sagittal incision was made in the cranial cavity to obtain brain tissue samples. Both liver and brain tissue specimens were preserved and processed for histological examination using light microscopy to assess morphological changes.

Measurement of blood biochemical parameters

Fasting blood glucose levels were measured using the enzymatic colorimetric GOD-PAP method, as previously described by Riasari *et al*. [15]. Serum insulin concentrations were determined using the Sandwich-ELISA method. Total cholesterol levels were analyzed using the enzymatic colorimetric CHOD-PAP method, whereas triglyceride levels were measured using the enzymatic colorimetric GPO-PAP method. HDL-C levels were assessed using the enzymatic colorimetric CHOD-PAP method, following the separation of HDL-C from other lipoproteins using a polyethylene glycol reagent, which precipitates all beta-lipoproteins (low-density lipoprotein [LDL] and very LDL). Meanwhile, LDL cholesterol (LDL-C) levels were calculated using the Friedewald equation.

Analysis of liver and brain tissue morphological changes

Liver and brain tissues were fixed using 2.5% glutaraldehyde in phosphate buffer for 4 h at room temperature. The tissues were then rinsed three times with phosphate buffer, each for 15 min. Subsequent fixation was performed using a 1% osmium tetroxide solution in phosphate buffer for 2 h at room temperature. Dehydration was carried out by immersing the tissues in a graded ethanol series with concentrations of 10%, 30%, 50%, 70%, 90%, and 100%, each for 60 min. The dehydrated tissues were then embedded in paraffin blocks. Tissue sections of 2 µm thickness were obtained using a microtome and mounted onto glass slides. The prepared tissue sections were stained with Hematoxylin and Eosin for histological analysis. Morphological observations were conducted using a light microscope at ×400 magnification. The observed structures were documented using an Optilab Viewer camera, and the images were analyzed for tissue diameter measurements using Image Raster software.

RESULTS AND DISCUSSION

Identification and phytochemical characterization of white turmeric

The *C. zedoaria* used in this study was collected from a demonstration garden in Cinanggela Village, Pacet District, Bandung Regency. The botanical identification of the plant was carried out at the School of

Life Sciences and Technology, Institut Teknologi Bandung, under the determination number 73/11.CO_2.2/PL/2018, to confirm that the plant used in this study was indeed *C. zedoaria*.The determination results confirmed that the plant was *C. zedoaria* (Christm.) Roscoe is commonly known in Indonesia as *Temu Putih* or *Konengtegal* (Sundanese). Further characterization of the test material was conducted through phytochemical screening to identify the secondary metabolites present in the white turmeric extract. Phytochemical screening serves as an essential step in identifying bioactive compounds responsible for pharmacological activity. The results of the phytochemical screening are presented in Table 1.

Phenotypic analysis of insulin resistance in an animal model of diabetes mellitus

The HFD used in this study was specifically formulated to induce insulin resistance in experimental animals. The dietary formulation consisted of 20 g of lard, 1 g of propylthiouracil, 5 g of cholesterol, 1 g of sodium glutamate, 5 g of sucrose, 5 g of saccharose, 20 mL of Tween 80, 30 mL of propylene glycol, and sufficient distilled water to reach a final volume of 100 mL. According to a study conducted by Ai *et al*., administration of this formula for 10 days can induce a diabetic phenotype, characterized by increased fluid intake, weight gain, and visceral fat accumulation in experimental animals [14].

The presence of lard and cholesterol in this formulation contributes to elevated levels of free fatty acids, which play a crucial role in the development of insulin resistance. The inclusion of propylthiouracil and sucrose is intended to accelerate the onset of hyperglycemia, while sodium glutamate is incorporated to stimulate insulin secretion from pancreatic beta cells. Collectively, this dietary composition is designed to establish an animal model of diabetes mellitus with insulin resistance, closely resembling the pathophysiological mechanisms observed in humans.

Phenotypic observations in this study revealed that administration of the HFD led to a significant increase in fluid intake among experimental rats; however, it did not markedly impact BW gain. Notably, when compared to the group receiving white turmeric extract, the group subjected to the HFD alone exhibited a higher percentage of weight gain. Treatment with white turmeric extract at both tested doses demonstrated a protective effect against the development of diabetes mellitus with insulin resistance, as indicated by phenotypic characteristics. Nevertheless, further confirmation of insulin resistance in this animal model is required through the analysis of blood biochemical parameters. The results of the phenotypic analysis of the diabetes mellitus animal model are presented in Table 2 below.

Results of insulin sensitivity analysis using the homeostasis model assessment of insulin resistance (HOMA-IR) index

Insulin resistance was assessed using the HOMA-IR index. The results demonstrated that a HFD effectively induced insulin resistance in the experimental animals. This was evidenced by elevated insulin levels and significantly higher HOMA-IR index values in the HFD group compared to the normal control group. Additionally, the drug control group (metformin) exhibited lower insulin levels and HOMA-IR index values than the HFD group, indicating the efficacy of metformin in improving insulin sensitivity. These findings confirm the successful establishment of insulin resistance using the induction method applied in this study.

Based on insulin level measurements and HOMA-IR index values, the administration of white turmeric ethanol extract at a dose of 400 mg/kg BW exhibited a protective effect against insulin resistance. This was demonstrated by significantly lower insulin levels and HOMA-IR index values compared to the HFD group. In contrast, the administration of white turmeric extract at a dose of 200 mg/kg BW did not clearly exhibit a protective effect against insulin resistance, as insulin levels remained comparable to those in the HFD group, although the HOMA-IR index was significantly reduced. The results of insulin level measurements and HOMA-IR index calculations are presented in Table 3 and Fig. 1.

Table 1: Phytochemical screening results of ethanol extract of white turmeric

Compound class	Ethanol extract of white turmeric
Alkaloids	+
Flavonoids	–
Tannins	–
Phenols	+
Saponins	+
Quinones	+
Monoterpenes and sesquiterpenes	+
Steroids and triterpenoids	–

Table 2: Average percentage of weight gain and fluid intake over 10 days of treatment

Assesment parameters	Treatment groups				
	Normal rats	High-fat diet rats	Drug control (metformin 45 mg/kg)	Ethanol extract of white turmeric doses 200 mg/kg	Ethanol extract of white turmeric doses 400 mg/kg
Average percentage of weight gain over 10 days of treatment (%)	1.18±1.42	−6.36±1.80	−3.61±4.92	−6.63±2.71	−10.86±4.83
Average fluid intake over 10 days of treatment (mL)	207.75	250.01	186.29	184.65	176.12

Table 3: Comparison of mean fasting blood glucose levels, insulin levels, and HOMA-IR index among treatment groups

Treatment groups	Assesment parameters		
	Average fasting blood glucose level (mg/dL)	Average insulin level (mU/L)	Average HOMA-IR index
Normal rats	53.52±29.32[b]	1.69±0.22[b]	0.23±0.13[b]
High fat diet rats	81.55±13.94[ac]	2.28±0.20[ac]	0.46±0.08[ac]
Drug control (metformin 45 mg/kg)	46.32±5.38[b]	1.57±0.46[b]	0.17±0.05[b]
Ethanol extract of white turmeric doses 200 mg/kg	63.82±14.55	2.13±0.27[ac]	0.34±0.08[abc]
Ethanol extract of white turmeric doses 400 mg/kg	45.04±9.08[b]	1.58±0.37[b]	0.17±0.02[b]

HOMA-IR: Homeostasis model assessment of insulin resistance. Mean difference significance; $p<0.05$, [a]Significantly different from the normal group of rats, [b]Significantly different from the high fat diet of rats, [c]Significantly different from the drug control of rats

Table 4: Comparison of lipid profiles among treatment groups

Treatment groups	Assesment parameters			
	Average tot-chol level (mg/dL)	Average HDL-chol level (mg/dL)	Average LDL-chol level (mg/dL)	Average triglycerides(mg/dL)
Normal rats	79.57 ± 7.67^{bc}	47.43 ± 5.51	18.83 ± 5.17^{bc}	66.56 ± 7.96^{b}
Hight-fat diet rats	212.76 ± 58.55^{ac}	64.29 ± 5.46	126.16 ± 49.87^{ac}	111.56 ± 21.78^{ac}
Drug control (Metformin 45 mg/kg)	161.58 ± 19.63^{ab}	60.86 ± 16.40	89.91 ± 5.40^{ab}	55.99 ± 13.81^{b}
Ethanol extract of white turmeric doses 200 mg/kg	197.28 ± 24.27^{a}	84.70 ± 19.48^{ac}	107.04 ± 3.81^{a}	58.40 ± 3.02^{b}
Ethanol extract of white turmeric doses 400 mg/kg	160.00 ± 16.50^{ab}	87.78 ± 8.77^{abc}	59.75 ± 8.39^{ab}	50.31 ± 14.05^{b}

HDL: High-density lipoprotein, LDL: Low-density lipoprotein. Mean difference significance; $p<0.05$, ^{a}Significantly different from the normal group of rats, ^{b}Significantly different from the high-fat diet of rats, ^{c}Significantly different from the drug control of rats

Insulin resistance can lead to a decreased uptake of glucose into tissues, ultimately resulting in hyperglycemia—one of the hallmark characteristics of diabetes mellitus. The findings of this study demonstrated that administering a HFD reduced insulin sensitivity at its receptors within the tissues. This was evidenced by significantly higher fasting blood glucose levels in the rats fed a HFD compared to the normal control group.

Conversely, the group of rats that received white turmeric extract at a dose of 400 mg/kg exhibited lower fasting blood glucose levels than the HFD group. This result further supports the notion that white turmeric extract at this dose effectively inhibits the development of insulin resistance. However, in the group administered the extract at a dose of 200 mg/kg, fasting blood glucose levels did not significantly differ from those of the HFD group. This suggests that white turmeric extract at this dose may not be sufficiently effective in preventing insulin resistance.

The observed improvement in insulin sensitivity following administration of *C. zedoaria* (white turmeric) extract is hypothesized to be primarily mediated by curcumin, a major bioactive compound known for its antidiabetic and insulin-sensitizing properties. This hypothesis is supported by the review conducted by Sharma *et al*., which highlights curcumin's potential in modulating glucose metabolism, enhancing insulin receptor signaling, and improving pancreatic β-cell function. The review also emphasizes curcumin's antioxidant and anti-inflammatory mechanisms as critical factors in mitigating insulin resistance, particularly in the context of metabolic disorders [16].

Furthermore, the hypoglycemic effect of *C. zedoaria* extract appears to be dose-dependent. Administration of a 400 mg/kg BW dose produced a significant reduction in fasting blood glucose levels when compared to the HFD control group, indicating a protective effect against insulin resistance. Conversely, treatment with a lower dose (200 mg/kg) did not result in a statistically significant difference, suggesting that subtherapeutic dosing may fail to elicit sufficient biological activity.

Lipid profile analysis among treatment groups

One of the primary factors contributing to insulin resistance is elevated levels of free fatty acids in the bloodstream. To evaluate whether the administration of white turmeric extract can mitigate insulin resistance through its hypolipidemic effects, lipid profile measurements were conducted in experimental animals. The results of these lipid profile measurements are presented in Table 4.

The results of lipid profile measurements demonstrated that a HFD induced hyperlipidemia in experimental animals. The total cholesterol, LDL-C, and triglyceride levels in the HFD group exceeded normal limits, with values of 212.76 mg/dL, 126.16 mg/dL, and 111.56 mg/dL, respectively. Meanwhile, HDL-C levels in this group did not differ significantly from those in the normal control group.

The administration of white turmeric ethanol extract at a dose of 400 mg/kg exhibited a notable hypolipidemic effect, potentially mitigating insulin resistance caused by elevated fat levels in the body. The hypolipidemic effect of white turmeric is presumed to be mediated through the inhibition of the HMG-CoA reductase enzyme, as previously demonstrated by Liu *et al*. [9]. At this dose, the extract effectively maintained lipid profile parameters within normal limits, including total cholesterol, LDL-C, and triglyceride levels. Additionally, white turmeric extract showed the potential to enhance HDL-C levels as a compensatory response to excessive fat intake.

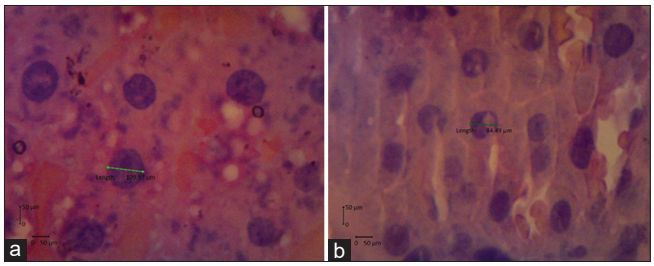

Fig. 1: Liver cells of the high-fat diet group (a) and the white turmeric extract 400 mg/kg group (b)

Conversely, the administration of white turmeric extract at a dose of 200 mg/kg was insufficient to regulate lipid profiles within normal ranges. Although total cholesterol and LDL-C levels in this group were lower than those observed in the HFD group, the differences were not statistically significant. Similarly, HDL-C levels, although elevated compared to the HFD group, did not exhibit a significant difference. The inability of the extract at this dose to significantly reduce total and LDL-C suggests that insulin resistance persists due to excessive fat accumulation.

These findings further support the potential of white turmeric as a hypolipidemic agent capable of mitigating the progression of insulin resistance, particularly at a dose of 400 mg/kg. However, further investigations are warranted to elucidate its precise mechanism of action and confirm its efficacy in significantly reducing lipid levels.

Morphological analysis of liver and brain cells

The morphological analysis of liver cells revealed that the liver cells in the HFD group were larger in size compared to those in the group administered white turmeric extract at a dose of 400 mg/kg. These findings were obtained by comparing the average cell diameter observed under a microscope at ×400 magnification. The increased cell size in the HFD group suggests excessive fat accumulation within liver cells. In contrast, the smaller liver cell size in the group treated with white turmeric extract at 400 mg/kg indicates a potential hypolipidemic effect, as observed in this study. The morphological observations of liver cells are presented in Fig. 1.

To further elucidate the mechanism underlying the inhibition of insulin resistance caused by excessive fatty acid intake, additional investigations are required. One potential mechanism involves the reduction of pyruvate dehydrogenase enzyme levels, a crucial mitochondrial component. Therefore, further confirmation through the

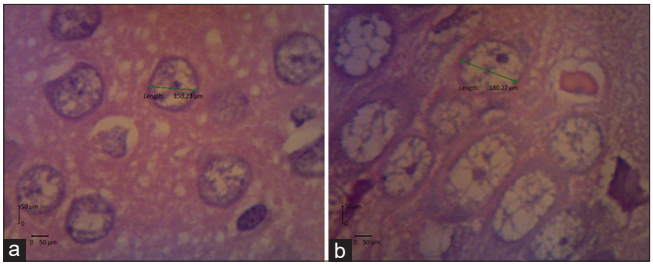

Fig. 2: Brain cells of the high-fat diet group (a) and the white turmeric extract 400 mg/kg group (b)

assessment of mitochondrial structure within liver cells is necessary to validate these findings.

Morphological differences were also observed in brain cells. The axons of brain cells in the HFD group were shorter compared to those in the group of rats administered white turmeric extract at a dose of 400 mg/kg. This finding suggests that a HFD may negatively affect neuronal structure, while white turmeric extract at the given dose may exert a protective effect on brain cell morphology. The observed morphological characteristics of brain cells are presented in Fig. 2 below.

CONCLUSION

The administration of a HFD formula successfully induced insulin resistance in male Wistar rats. The administration of white turmeric extract at a dose of 400 mg/kg demonstrated the ability to inhibit insulin resistance through its hypolipidemic effects, which contributed to the improvement of the lipid profile. However, its potency in preventing insulin resistance was still lower compared to metformin.

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AUTHORS' CONTRIBUTION

NIF conducted the research, performed data collection, and analyzed the experimental results. KA critically evaluated the findings, provided interpretations, and contributed to the refinement of the final analysis. Both authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST

There are no conflicts of interest in this text.

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