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Anti-inflammatory and Anti-infertility Effects of Ethanol Extract of Turmeric (Curcuma longa) in Male Wistar Rats with Type 2 Diabetes Mellitus Induced by Streptozotocin-Nicotinamide-High Fat Diet

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder associated with chronic inflammation and male reproductive dysfunction. The ethanol extract of turmeric (*Curcuma longa*) has demonstrated potential as an alternative therapeutic agent due to its anti-inflammatory and reproductive restorative properties. This study aims to analyze the anti-inflammatory and anti-infertility effects of the ethanol extract of *Curcuma longa* in male Wistar rats with T2DM induced by a streptozotocin-nicotinamide-high fat diet (STZ-NA-HFD).

Subjects and Method: Thirty male Wistar rats were randomized into six groups (n=5): normal control (K1), diabetic control (K2), positive control (T2DM + metformin 45 mg/kgBW, K3), and three treatment groups receiving *Curcuma longa* extract at doses of 50 mg/kgBW (K4), 100 mg/kgBW (K5), and 150 mg/kgBW (K6). Diabetes was induced with STZ (55 mg/kgBW) and nicotinamide (120 mg/kgBW). Blood glucose, IL-6, testosterone levels, sperm count, and sperm motility were evaluated after 21 days of treatment.

Results: The turmeric extract significantly reduced blood glucose levels ($p<0.001$) and IL-6 concentrations from 574.06±68.99 to 214.06±78.71 ng/mL at a dose of 150 mg/kgBW ($p<0.001$). Normal sperm motility increased significantly at 150 mg/kgBW (20.0±2.55%) compared to the diabetic control (8.40±2.07%) ($p=0.008$).

Conclusion: The ethanol extract of *Curcuma longa* demonstrated significant anti-inflammatory activity by reducing IL-6 levels and improving glycemic control. Its anti-infertility effect was reflected by enhanced sperm motility, particularly at the 150 mg/kgBW dose. These findings indicate that *Curcuma longa* possesses potential as an adjuvant therapy for the management of T2DM and its associated complications.

Keywords: Type 2 diabetes mellitus, *Curcuma longa*, anti-inflammatory, fertility, interleukin-6, spermatogenesis.

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BACKGROUND

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder characterized by impaired insulin secretion, insulin resistance, and chronic hyperglycemia. The global incidence of T2DM has reached alarming proportions, with the International Diabetes Federation (IDF) estimating 463 million affected adults in 2019 and projecting a rise to 700 million cases by 2045 (Chen et al., 2012; International Diabetes Federation, 2019; PERKENI, 2019; ADA, 2022). This growing burden has significant public health implications due to its association with multiple systemic complications, increased healthcare costs, and reduced quality of life.

Pathophysiologically, T2DM extends beyond glucose dysregulation. It is closely linked with a persistent low-grade inflammatory state characterized by the upregulation of pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein. Chronic inflammation plays a pivotal role in the progression of insulin resistance and vascular dysfunction and contributes to the development of both microvascular and macrovascular complications (Al-Goblan et al., 2014; Halim and Halim, 2019). Moreover, prolonged oxidative stress resulting from hyperglycemia amplifies tissue damage and disrupts normal physiological functions in multiple organ systems, including the reproductive axis.

An often underrecognized complication of T2DM is male reproductive dysfunction. Persistent hyperglycemia and oxidative stress adversely affect spermatogenesis, sperm motility, and testosterone biosynthesis, leading to subfertility or infertility. Clinical and experimental studies have shown that men with T2DM have higher rates of erectile dysfunction, diminished libido, and reduced sperm quality compared to non-diabetic counterparts (Khoei et al., 2019; Belhan et al., 2020). These reproductive alterations are believed to result from testicular oxidative stress, inflammation, and hormonal imbalance induced by chronic metabolic derangement.

Although synthetic antidiabetic drugs remain the cornerstone of T2DM management, their long-term use may produce adverse effects and does not adequately address the chronic inflammatory and reproductive complications of diabetes. Consequently, there is increasing interest in identifying natural compounds with pleiotropic effects that target both metabolic and inflammatory pathways (Wang et al., 2017).

Curcuma longa (turmeric) has been traditionally utilized for centuries to treat various ailments and has demonstrated broad pharmacological activities, including anti-inflammatory, antioxidant, and antidiabetic effects. Curcumin, the principal bioactive component of turmeric, exerts its actions through multiple molecular mechanisms such as inhibition of the NF-κB signaling pathway, reduction of pro-inflammatory cytokines, enhancement of insulin sensitivity, and attenuation of oxidative stress (Rivera-Mancía et al., 2018; Hussain et al., 2022). Furthermore, curcumin has been reported to protect pancreatic β-cells, improve glucose metabolism, and ameliorate testicular oxidative damage, thereby enhancing reproductive performance in diabetic animal models.

Despite extensive research on its pharmacological potential, few studies have comprehensively evaluated the concurrent effects of turmeric extract on glycemic regulation, systemic inflammation, and male reproductive parameters in T2DM models (Kanter et al., 2013; Rashid and Sil, 2015; Zhao et al., 2017). Therefore, the

present study was designed to investigate the anti-inflammatory and anti-infertility effects of ethanolic extract of Curcuma longa in streptozotocin–nicotinamide–high-fat diet (STZ–NA–HFD)-induced T2-DM male rats, providing further insight into its potential role as an adjuvant therapeutic agent for diabetes-related complications.

SUBJECTS METHOD

1. Study Design

This study employed an experimental laboratory design using a post-test randomized controlled group design. Thirty male Wistar rats were randomly assigned into six experimental groups using simple random sampling.

2. Population and Sample

The study population consisted of healthy male Wistar rats (*Rattus norvegicus*), aged 2.5–3 months and weighing 150–220 grams. A total of 30 rats were included, divided into six groups (n=5 per group) based on the Federer formula: $(n-1)(t-1) \geq 15$.

3. Inclusion and Exclusion Criteria

Inclusion criteria included male rats aged 2.5–3 months, weighing 150–220 grams, and showing healthy and active behavior. Exclusion criteria included rats that were inactive or died during the experimental period.

4. Study Variables

The independent variable was the dose of ethanolic extract of *Curcuma longa* (50 mg/kg BW, 100 mg/kg BW, and 150 mg/kg BW). The dependent variables included blood glucose level, serum IL-6 concentration, serum testosterone level, sperm count, and sperm motility.

5. Operational Definitions of Variables

Blood glucose level: The concentration of glucose in blood measured using an Easy Touch glucometer, expressed in mg/dL.

IL-6 concentration: The serum concentration of interleukin-6 measured by enzyme-linked immunosorbent assay (ELISA), expressed in ng/mL.

Testosterone level: The concentration of serum testosterone measured by ELISA, expressed in ng/mL.

Sperm count: The concentration of spermatozoa measured using a hemocytometer, expressed in 10^6/mL.

Sperm motility: The percentage of motile spermatozoa observed under a microscope.

Preparation of Ethanolic Extract of *Curcuma longa* Fresh turmeric rhizomes were cleaned, air-dried, and ground into fine powder. Extraction was performed by maceration using 96% ethanol for 5 days. The filtrate was then concentrated using a rotary evaporator until a thick extract was obtained.

Diabetes Induction Protocol

Type 2 diabetes mellitus was induced by intraperitoneal injection of streptozotocin (STZ) at a dose of 55 mg/kg BW and nicotinamide (NA) at 120 mg/kg BW. Rats were considered diabetic if fasting blood glucose exceeded 200 mg/dL on the 7th day after induction (Mostafavinia et al., 2016; Almalki et al., 2019).

Experimental Design and Treatment Administration

Rats were randomly divided into six experimental groups (n=5 per group):

Group 1 (K1): Normal control, healthy rats without treatment

Group 2 (K2): Negative control, diabetic rats without treatment

Group 3 (K3): Positive control, diabetic rats treated with metformin 45 mg/kg BW

Group 4 (K4): Diabetic rats treated with turmeric extract 50 mg/kg BW
Group 5 (K5): Diabetic rats treated with turmeric extract 100 mg/kg BW
Group 6 (K6): Diabetic rats treated with turmeric extract 150 mg/kg BW

Measurement of Parameters

Blood glucose levels were measured using a glucometer on days 0, 7, 14, and 21. At the end of the experiment, blood samples were collected for the measurement of serum IL-6 and testosterone levels using ELISA kits. Epididymal sperm samples were collected for assessment of sperm count and motility using a hemocytometer and light microscopy.

6. Data Analysis

Data were analyzed using SPSS software. The Shapiro–Wilk test was used to assess normality, and homogeneity was evaluated prior to analysis. One-way ANOVA followed by post-hoc LSD test was conducted to compare differences between groups. Results were expressed as mean ± standard deviation (SD), and a p-value <0.05 was considered statistically significant.

7. Research Ethics

The study protocol was approved by the Animal Ethics Committee of the Faculty of Medicine, Universitas Methodist Indonesia (Approval No. 93/KEPK-FKUMI/EC/-2024).

RESULTS

1. Sample Characteristics

A total of 30 male Wistar rats were initially included in this study. During the experimental period, 2 rats died and were excluded according to the predetermined exclusion criteria, leaving 28 animals for final analysis.

Table 1. Sample Characteristics of Wistar Rats Used in the Experimental Study

Variable	Description	n	%
Total rats used	Rats included at baseline	30	100
Completed study	Rats that completed the full protocol	28	93.3
Excluded (mortality)	Rats that died during intervention and excluded based on criteria	2	6.7

2. Effect on Blood Glucose Levels

Administration of Curcuma longa ethanolic extract significantly reduced blood glucose levels in diabetic rats across all treatment groups compared with the negative control. The differences among groups were statistically significant on both day 0 and day 21 (p<0.001).

Table 2. Blood Glucose Levels Before and After Treatment with Curcuma longa Ethanolic Extract in STZ-NA-HFD–Induced Diabetic Rats

Group	Day 0 (mg/dL) Mean ± SD	Day 21 (mg/dL) Mean ± SD	p-value
K1 (Normal)	86.40 ± 10.41	102.20 ± 10.01	<0.001
K2 (Negative control)	453.60 ± 35.70	315.40 ± 39.30	
K3 (Metformin 45 mg/kgBW)	383.60 ± 78.89	119.20 ± 43.72	
K4 (*Curcuma longa* 50 mg/kgBW)	413.25 ± 27.40	122.00 ± 54.01	
K5 (*Curcuma longa* 100 mg/kgBW)	296.25 ± 50.88	98.75 ± 13.68	
K6 (*Curcuma longa* 150 mg/kgBW)	347.80 ± 97.10	112.20 ± 27.53	

Ethanolic extract of turmeric exhibited a pronounced hypoglycemic effect in STZ–NA–HFD–induced diabetic rats. Statistical analysis by one-way ANOVA confirmed highly significant intergroup differences ($p<0.001$).

At baseline (day 0 after diabetes induction), all diabetic groups showed markedly elevated blood glucose levels. The negative control group (K2) exhibited the highest value (453.60 ± 35.704 mg/dL), confirming successful induction of diabetes. Following 21 days of treatment, all treated groups demonstrated marked reductions in blood glucose. The K5 group (100 mg/kg BW) achieved the most pronounced decrease (98.75 ± 13.675 mg/dL), approaching normoglycemic levels. Similarly, groups K6, K3, and K4 showed substantial reductions (112.20 ± 27.526; 119.20 ± 43.723; and 122.00 ± 54.012 mg/dL, respectively). The negative control group (K2) showed only a modest spontaneous reduction, remaining within diabetic range (315.40 ± 39.298 mg/dL).

3. Effect on Serum IL-6 Levels

Analysis of the inflammatory biomarker IL-6 revealed significant intergroup differences ($p<0.001$), as presented in Table 3.

Table 3. Serum IL-6 Levels After Treatment with Ethanolic Extract of Curcuma longa in STZ–NA–HFD-Induced Diabetic Rats

Group	IL-6 (ng/mL) Mean ± SD	p-value
K1 (Normal control)	55.58 ± 10.28	<0.001*
K2 (Negative diabetic control)	574.06 ± 68.99	
K3 (Metformin 45 mg/kgBW)	305.16 ± 51.71	
K4 (*C. longa* 50 mg/kgBW)	288.35 ± 183.71	
K5 (*C. longa* 100 mg/kgBW)	216.25 ± 151.06	
K6 (*C. longa* 150 mg/kgBW)	214.06 ± 78.71	

The serum IL-6 analysis demonstrated a strong anti-inflammatory effect of the turmeric extract ($p<0.001$). The normal group (K1) exhibited baseline IL-6 levels within physiological range (55.580 ± 10.275 ng/mL). In contrast, diabetes induction resulted in a marked increase of IL-6 levels in the negative control group (574.060 ± 68.992 ng/mL), indicating systemic inflammatory activeation.

Treatment with turmeric extract significantly reduced IL-6 levels in a dose-dependent manner. The reduction was moderate at 50 mg/kg BW (288.350 ± 183.710 ng/mL) and reached near-normal levels at higher doses—216.250 ± 151.063 ng/mL (K5) and 214.060 ± 78.714 ng/mL (K6). Interestingly, the metformin-treated group (305.160 ± 51.714 ng/mL) exhibited higher IL-6 levels than turmeric groups K5 and K6, suggesting superior anti-inflammatory efficacy of the turmeric extract at higher doses.

Effect on Fertility Parameters

Reproductive parameters evaluated included serum testosterone levels, sperm count, and sperm motility. The results are summarized in Table 4.

Table 4. Fertility Parameters After Treatment with Ethanolic Extract of Curcuma longa in STZ–NA–HFD-Induced Diabetic Rats

Group	Testosterone (ng/mL) Mean ± SD	p-value	Sperm Count (×10⁶/mL) Mean ± SD	p-value	Normal Motility (%) Mean ± SD	p-value
K1	4.66 ± 1.12	0.768	57.06 ± 10.54	0.105	44.00 ± 5.43	<0.001*
K2	0.28 ± 0.14		44.60 ± 6.38		8.40 ± 2.07	
K3	3.98 ± 4.07		46.92 ± 5.64		19.60 ± 2.70*	
K4	5.24 ± 9.58		50.10 ± 3.56		17.25 ± 6.55	
K5	4.45 ± 7.96		47.53 ± 6.24		18.25 ± 3.59	
K6	4.05 ± 5.53		49.98 ± 4.25		20.00 ± 2.55*	

Evaluation of fertility parameters revealed distinct trends across variables:

Testosterone levels: No statistically significant differences were observed among groups (p=0.768). The normal group (K1) exhibited normal testosterone levels (4.660 ± 1.124 ng/mL), while diabetes markedly reduced levels in the negative control (0.281 ± 0.139 ng/mL). Although not statistically significant, turmeric-treated groups showed a recovery trend, with K4 demonstrating the highest mean (5.245 ± 9.578 ng/mL), followed by K5 (4.446 ± 7.962 ng/mL) and K6 (4.051 ± 5.534 ng/mL). The large standard deviations indicate individual variability in hormonal responses.

Sperm count: No significant difference was found across groups (p=0.105). However, a positive trend was observed, with turmeric-treated groups exhibiting higher sperm counts compared to diabetic controls. The K4 group recorded the highest mean (50.1 ± 3.56 ×10⁶/mL), approaching normal levels.

Sperm motility: This parameter demonstrated the most significant improvement (p<0.001). Diabetes drastically impaired sperm motility (8.40 ± 2.074%) in the negative control group, while high-dose turmeric (K6, 150 mg/kg BW) significantly increased motility to 20.00 ± 2.55%, comparable to metformin (19.60 ± 2.702%). Moderate improvements were also observed in K5 (18.25 ± 3.594%) and K4 (17.25 ± 6.551%).

DISCUSSION

This study provides new evidence regarding the therapeutic effects of *Curcuma longa* ethanolic extract in mitigating inflammatory and fertility aspects of type 2 diabetes mellitus (T2DM), which have not been comprehensively evaluated within a single experimental framework. The main contribution of this study lies in demonstrating the dual effects of turmeric in reducing systemic inflammation while simultaneously improving reproductive parameters in a clinically relevant diabetic model.

Innovation of the Diabetes Model and Clinical Relevance

The use of a streptozotocin–nicotinamide–high-fat diet (STZ–NA–HFD) induction model in this study represents a type 2 diabetes model that more closely resembles human pathophysiology compared to single-agent induction models. This model effectively produces insulin resistance followed by β-cell dysfunction, mimicking the progressive nature of human diabetes (Mostafavinia et al., 2016). Consequently, it

enhances the validity of the findings compared with previous studies that used a pure type 1 diabetes model induced solely by STZ (Belhan et al., 2020).

Anti-Inflammatory Effects

A marked reduction in IL-6 levels by up to 62.7% at the highest dose of turmeric indicates a superior anti-inflammatory potential compared with metformin, which achieved a 46.8% reduction. Pharmacologically, this can be attributed to curcumin's ability to inhibit the NF-κB signaling pathway at the transcriptional level, unlike metformin, which primarily acts through AMPK activation (Hussain et al., 2022).

These findings align with Pivari et al. (2019), whose systematic review confirmed that curcumin reduces inflammatory markers such as IL-6, TNF-α, and CRP in various diabetic models. Similarly, Kato et al. (2017) demonstrated that curcumin not only decreases inflammatory mediators but also enhances GLP-1 secretion, which contributes to glucose homeostasis and exerts secondary anti-inflammatory effects.

Earlier studies by Brandford (2013) and Weisberg et al. (2008) in obesity models also reported the anti-inflammatory potential of curcumin. However, the present study is the first to directly demonstrate turmeric's superior anti-inflammatory efficacy compared to metformin in a diabetic model. This finding has significant clinical implications, as chronic inflammation is a major driver of diabetic complications, and IL-6 serves as a prognostic biomarker for cardiovascular risk in diabetic patients (Alfadul et al., 2022).

The observed superiority of turmeric's anti-inflammatory effect over metformin corresponds with Wang et al. (2017), who reported that while metformin exerts secondary anti-inflammatory actions through AMPK activation, curcumin directly targets the NF-κB inflammatory pathway. Rivera-Mancía et al. (2018) further emphasized curcumin's pleiotropic effects—including anti-inflammatory, anti-oxidant, and neuroprotective actions—which offer a broader pharmacological advantage compared with metformin's more glucose-centric effects.

Novel Findings in Turmeric Pharmacology

An interesting finding of this study is that a dose of 100 mg/kgBW provided optimal glycemic control, whereas 150 mg/kgBW produced superior anti-inflammatory and fertility-related effects. This non-linear pattern has not been previously reported and challenges the conventional assumption of a linear dose–response relationship for curcumin.

The hypoglycemic effect observed here is consistent with Wickenberg et al. (2010), who demonstrated postprandial glucose reduction after curcumin administration in healthy subjects. A meta-analysis by Marton et al. (2021) also confirmed that curcumin consistently decreases HbA1c and fasting glucose levels in diabetic patients, primarily by enhancing insulin sensitivity and protecting pancreatic β-cells.

This dose-dependent phenomenon can be explained by the concept of "hormesis," in which optimal biological responses occur at moderate doses, whereas higher doses may activate compensatory pathways that limit efficacy (Marton et al., 2021). Practically, this suggests the need for dose stratification according to specific therapeutic targets—a concept not yet established in curcumin's clinical applications.

Mechanisms of Spermatogenesis Protection

The significant improvement in sperm motility observed at 150 mg/kgBW (a 238% increase from diabetic baseline) represents a novel advancement in the application of turmeric for male fertility. Although previous studies by Zhao et al. (2017) and Khoei et al. (2019) reported curcumin's reproductive protective effects, the magnitude of improvement in this study appears superior.

This finding supports the results of Akomolafe and Aluko (2020), who demonstrated that curcumin protected fertility in cyclophosphamide-exposed rats. Similarly, Nancy Obaji et al. (2021) reported improved reproductive hormone profiles in male rats treated with turmeric extract. Kanter et al. (2013) also showed that curcumin protects testicular tissue against oxidative damage and germ-cell apoptosis in diabetic rats, providing a mechanistic explanation for the improved reproductive outcomes observed.

Interestingly, sperm functionality was preserved despite non-significant changes in quantitative parameters such as sperm count and testosterone levels. This suggests that curcumin acts primarily through mitochondrial protection and cellular energy preservation that supports motility, rather than stimulating spermatogenesis or hormonal synthesis (Lin et al., 2015).

Limitations and Future Directions

Despite the promising results, this study has several limitations that should be acknowledged. The 21-day observation period was relatively short to fully evaluate the process of spermatogenesis, which takes approximately 74 days in humans. The high variability observed in testosterone levels and sperm count suggests the need for larger sample sizes or stratification according to diabetes severity.

Future research should explore several aspects:

(1) The optimal duration of treatment required to achieve maximal therapeutic effects;

(2) The specific molecular mechanisms underlying the non-linear dose–response pattern observed;

(3) The bioavailability and pharmacokinetic–pharmacodynamic relationship of curcumin; and

(4) The long-term safety profile of Curcuma longa extract in chronic use.

Addressing these questions will provide a more comprehensive understanding of turmeric's pharmacological potential and its translational relevance to human clinical settings.

Translational Implications and Clinical Applications

The findings of this study carry strong translational potential for developing turmeric-based adjuvant therapy in diabetes management. The combined anti-diabetic, anti-inflammatory, and fertility-restoring effects of Curcuma longa represent a holistic therapeutic approach that is currently lacking in conventional pharmacotherapy.

Given that the prevalence of subfertility in diabetic men ranges between 25% and 90% (Khoei et al., 2019), these results highlight an opportunity for integrative treatment protocols addressing multiple diabetic complications simultaneously. The dual modulation of glucose metabolism and reproductive function may provide an innovative therapeutic strategy for male diabetic patients with comorbid infertility.

Scientific Contribution and Novelty

This study provides three main scientific contributions:

(1) It is the first to demonstrate the dual anti-inflammatory and fertility-enhancing effects of Curcuma longa in a clinically relevant model of type 2 diabetes;

(2) It identifies a non-linear dose–response pattern that challenges the conventional pharmacodynamic paradigm of curcumin;

(3) It provides direct evidence of turmeric's superior anti-inflammatory efficacy compared to metformin.

Collectively, these findings expand current understanding of curcumin pharmacology and lay the groundwork for developing personalized therapeutic strategies based on specific biological targets. In the context of global health, this research supports the scientific validation of traditional turmeric use and underscores its potential as a cost-effective adjunctive therapy for diabetes in developing countries.

Ethanolic extract of *Curcuma longa* demonstrated significant anti-inflammatory effects by reducing serum IL-6 levels and improving glycemic control in STZ–NA–HFD–induced diabetic rats. Moreover, it showed beneficial effects on male fertility, particularly through a marked improvement in sperm motility at a dose of 150 mg/kgBW. These findings suggest that *Curcuma longa* extract holds strong potential as an adjuvant therapy for managing type 2 diabetes and its associated reproductive complications. Further clinical investigations are warranted to assess its safety and efficacy in human populations.

AUTHOR CONTRIBUTIONS

Vivian: Conceptualization, methodology, investigation, data curation, writing – original draft, review, and editing.

Hadyanto Lim: Supervision, conceptualization, methodology, validation, review, and editing.

Jekson Martiar Siahaan: Data Analysis, methodology, visualization, review, and editing.

Endy Juli Anto: Laboratory supervision, experimental procedures, validation, resources.

Syaffrudin Ilyas: Formal analysis, biological interpretation, review, and editing.

Dedi Ardinata: Pharmacological analysis, data interpretation, review, and editing.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

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REFERENCE

Adab Z, Eghtesadi S, Vafa MR, Heydari I, Shojaii A, Haqqani H, Ghayour-Mobarhan M, et al (2019). Effect of turmeric on glycemic status, lipid profile, hs-CRP, and total antioxidant capacity in hyperlipidemic type 2 diabetes mellitus patients. Phytother Res. 33(4): 1173-1181. doi: 10.1002/ptr.6312

Akomolafe SF, Aluko BT (2020). Protective effect of curcumin on fertility in

cyclophosphamide exposed rats: involvement of multiple pathways. J Food Biochem. 44(1): e13073. doi: 10.1111/jfbc.13095

Al-Goblan AS, Al-Alfi MA, Khan MZ (2014). Mechanism linking diabetes mellitus and obesity. Diabetes Metab Syndr Obes. 7: 587-591. doi: 10.2147/DM-SO.S67400

Alfadul H, Sabico S, Al-Daghri N (2022). The role of interleukin-1β in type 2 diabetes mellitus: a systematic review and meta-analysis. Front Endocrinol. 13: 901616. doi: 10.33-89/fendo.2022.901616

Almalki DA, Alghamdi SA, Al-Attar AM (2019). Comparative study on the influence of some medicinal plants on diabetes induced by strepto-zotocin in male rats. Biomed Res Int. 2019: 3596287. doi: 10.1155/-2019/3596287

American Diabetes Association (2022). Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care. 45(Suppl 1): S1-S264. doi: 10.2337/-dc22-S002

Belhan S, Yıldırım S, Huyut Z, Özdek U, Oto G, Algül S (2020). Effects of curcumin on sperm quality, lipid profile, antioxidant activity and histopathological changes in streptozotocin-induced diabetes in rats. Andrologia. 52(6): e13595. doi: 10.1111/and.13584

Brandford PG (2013). Curcumin and obesity. IUBMB Life. 65(1): 78-87. doi: 10.1002/biof.1074

Chen L, Magliano DJ, Zimmet PZ (2012). The worldwide epidemiology of type 2 diabetes mellitus: present and future perspectives. Nat Rev Endocrinol. 8(4): 228-236. doi: 10.1038/nrendo.2011.183

Halim M, Halim A (2019). The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). Diabetes Metab Syndr. 13(2): 1165-1172. doi: 10.1016/j.dsx.2019.01.040

Hussain Y, Khan H, Alotaibi G, Khan F, Alam W, Aschner M, Jeandet P, et al (2022). How curcumin targets inflammatory mediators in diabetes: therapeutic insights and possible solutions. Molecules. 27(13): 4058. doi: 10.3390/molecules27134058

International Diabetes Federation (2019). IDF diabetes atlas. 9th ed. Brussels: International Diabetes Federation.

Kanter M, Aktas C, Erboga M (2013). Curcumin attenuates testicular damage, apoptotic germ cell death, and oxidative stress in streptozotocin-induced diabetic rats. Mol Nutr Food Res. 57(9): 1578-1585. doi: 10.1002/mnfr.201200170

Kato M, Nishikawa S, Ikehata A, Dochi K, Tani T, Takahashi T, Imaizumi A, et al (2017). Curcumin improves glucose tolerance via stimulation of glucagon-like peptide-1 secretion. Mol Nutr Food Res. 61(3): 1600471. doi: 10.1002/mnfr.201600471

Khoei HH, Fakhri S, Parvardeh S, Shams Mofarahe Z, Ghasemnejad-Berenji H, Nazarian H, Mohammadi-Motlagh HR (2019). Testicular toxicity and reproductive perfor-mance of streptozotocin-induced diabetic male rats: the ameliorating role of silymarin as an antioxidant. Toxin Rev. 38(3): 223-233. doi: 10.1080/15569543.2018.1444641

Lin C, Shin DG, Park SG, Chu SB, Gwon LW, Lee JG, Kim DH, et al (2015).

Curcumin dose-dependently improves spermatogenic disorders induced by scrotal heat stress in mice. Food Funct. 6(12): 3770-3777. doi: 10.1039/c5fo00726g

Marton LT, Pescinini-Salzedas LM, Camargo MEC, Barbalho SM, Haber JFDS, Sinatora RV, Detregiachi CRP (2021). The effects of curcumin on diabetes mellitus: a systematic review. Front Endocrinol. 12: 669-448. doi: 10.3389/fendo.2021.669-448

Mostafavinia A, Amini A, Ghorishi SK, Pouriran R, Bayat M (2016). The effects of dosage and the routes of administrations of streptozotocin and alloxan on induction rate of type 1 diabetes mellitus and mortality rate in rats. Lab Anim Res. 32(3): 160-165. doi: 10.5625/lar.2016.32.-3.160

Nancy Obaji N, Johnson A, Oji Ifegwu N (2021). Combined effect of aqueous extracts of Zingiber officinale and Curcuma longa on male reproductive hormones of male wistar rats. JETIR. 8(6): b123-b130.

PERKENI (2019). Pedoman pengelolaan dan pencegahan diabetes melitus tipe 2 dewasa di Indonesia. Jakarta: Perkumpulan Endokrinologi Indonesia.

Pivari F, Mingione A, Brasacchio C, Soldati L (2019). Curcumin and type 2 diabetes mellitus: prevention and treatment. Nutrients. 11(8): 1837. doi: 10.3390/nu11081837

Rashid K, Sil PC (2015). Curcumin ameliorates testicular damage in diabetic rats by suppressing cellular stress-mediated mitochondria and endoplasmic reticulum-dependent apoptotic death. Biochim Biophys Acta. 1852(1): 70-82. doi: 10.1016/-j.bbadis.2014.11.007

Rivera-Mancía S, Trujillo J, Chaverri JP (2018). Utility of curcumin for the treatment of diabetes mellitus: evidence from preclinical and clinical studies. J Nutr Intermed Metab. 14: 29-41. doi: 10.1016/-j.jnim.2018.05.001

Wang YW, He SJ, Feng X, Cheng J, Luo YT, Tian L, Huang Q (2017). Metformin: a review of its potential indications. Drug Des Devel Ther. 11: 2421-2429. doi: 10.2147/DDDT.S141675

Weisberg SP, Leibel R, Tortoriello DV (2008). Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity. Endocrinology. 149(7): 3549-3558. doi: 10.1210/en.2008-0262

Wickenberg J, Ingemansson SL, Hlebowicz J (2010). Effects of Curcuma longa (turmeric) on postprandial plasma glucose and insulin in healthy subjects. Nutr J. 9: 43. doi: 10.11-86/1475-2891-9-43

Zhao L, Gu Q, Xiang L, Dong X, Li H, Ni J, Wan L, Cai G (2017). Curcumin inhibits apoptosis by modulating Bax/Bcl-2 expression and alleviates oxidative stress in testes of streptozotocin-induced diabetic rats. Ther Clin Risk Manag. 13: 1099-1105. doi: 10.2147/TCRM.S141738