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Full Length Research Article

TURMERIC (*CURCUMA LONGA*) EXTRACT ENHANCES FIBROBLAST GROWTH FACTOR 21 (FGF21) SENSITIVITY AND MITIGATES SUPPRESSOR OF CYTOKINE SIGNALING PROTEIN-3 (SOCS-3)-INDUCED INSULIN RESISTANCE IN TYPE 2 DIABETIC RATS

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ABSTRACT
Type 2 diabetes mellitus (T2DM) is a disorder characterized by insulin resistance, hyperglycemia, and inflammation. Fibroblast growth factor 21 (FGF21) plays a crucial role in glucose and lipid metabolism but is often dysregulated in T2DM due to FGF21 resistance, linked to reduced β-Klotho expression. Additionally, unregulated blood glucose activates inflammatory pathways, increasing suppressor of cytokine signaling protein-3 (SOCS-3), which contributes to insulin resistance. This study investigates the potential of turmeric (*Curcuma longa*) extract in enhancing FGF21 sensitivity and mitigating SOCS-3-induced insulin resistance in T2DM. Thirty male Wistar rats were randomly assigned into five groups: normal control (NC), diabetic control (DC), diabetic rats treated with turmeric extract (100 mg/kg and 200 mg/kg), and diabetic rats treated with metformin (500 mg/kg). T2DM was induced by administering 10% fructose for 14 days, followed by streptozotocin (50 mg/kg) intraperitoneally. Turmeric extract exhibited a time-dependent hypoglycemic effect, significantly ($P < 0.05$) reducing blood glucose from the second week, with 200 mg/kg showing the greatest effect. Insulin levels increased significantly ($P < 0.05$), and HOMA-IR decreased in all treated groups, indicating improved insulin sensitivity. Gene expression analysis showed a significant ($P < 0.05$) upregulation of GLUT-4 and β-Klotho, along with downregulation of SOCS-3 and FGF21.Turmeric extract improves glucose metabolism through enhanced insulin sensitivity, GLUT-4 activation, SOCS-3 suppression, and restoration of FGF21 signaling via β-Klotho upregulation.

Keywords: Turmeric extract, Type 2 diabetes, FGF21 sensitivity, SOCS-3, Insulin resistance, β-Klotho, GLUT-4.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a multi-factorial metabolic disorder characterized by chronic hyperglycaemia, leading to impaired glucose, lipid, and protein metabolism. Persistent hyperglycaemia triggers oxidative stress and inflammation, which play central roles in the progression of insulin resistance and diabetes-related complications (Galicia-Garcia *et al.,* 2020; Oguntibeju, 2019). Inflammation causes the overexpression of Suppressor of Cytokine Signaling 3 (SOCS-3), which disrupts insulin signaling by binding to the insulin receptor and preventing insulin receptor substrate (IRS) activation. This interference truncates the insulin signaling pathway, exacerbating insulin resistance and metabolic dysfunction (Cao *et al.,* 2018; B. Emanuelli *et al.,* 2001).

One of the leading cause of hyperglycaemia in T2DM is the fibroblast growth factor 21 (FGF21), which is an important metabolic regulator involved in glucose and lipid homeostasis. Primarily secreted by the liver, it is also expressed in adipose tissue, muscle, and the pancreas, where it enhances energy balance by promoting lipolysis, glucose uptake, and mitochondrial function (BonDurant and Potthoff, 2018; Szczepańska and Gietka-Czernel, 2022). The FGF21 exerts its effects by binding to fibroblast growth factor receptor 1c (FGFR1c) in the presence of the co-receptor β-Klotho, which is critical for FGF21-mediated metabolic benefits (Kilkenny and Rocheleau, 2016; Salgado *et al.,* 2021). In T2DM, FGF21 levels are often elevated as a compensatory response to insulin resistance; however, FGF21 resistance characterized by reduced β-Klotho expression impairs its signaling, diminishing its metabolic effects. High glucose and lipid levels further suppress β-Klotho and also induce inflammation with rising level of SOCS-3, thereby exacerbating insulin resistance (Gu *et al.,* 2020; Li *et al.,* 2018).

Restoring β-Klotho expression has emerged as a potential strategy to overcome FGF21 resistance and improvement of metabolic health in T2DM through reducing inflammation and controlling the blood glucose level. Turmeric (*Curcuma longa*) extract, rich in bioactive compounds such as turmerone, zingiberene, and curcuminoids, has demonstrated antioxidant and anti-inflammatory properties, making it a promising candidate for addressing T2DM-associated metabolic dysfunction (Fuloria *et al.,* 2022; Kunnumakkara *et al.,* 2023; Orellana-Paucar, 2024). Research suggests that turmeric extract can enhance hepatic FGF21 expression, reduce oxidative stress, and mitigate inflammatory signaling, potentially reversing FGF21 resistance (Jin, 2019). By upregulating β-Klotho, turmeric extract may restore FGF21 sensitivity, enhance glucose metabolism, and counteract SOCS-3-induced insulin resistance (Gong *et al.,* 2016; Lin *et al.,* 2021).

This study aims to investigate the potential of turmeric extract in alleviating FGF21 resistance by enhancing β-Klotho expression, thereby improving glucose metabolism and mitigating SOCS-3-induced insulin resistance. Understanding this mechanism could

provide valuable insights into novel therapeutic strategies for managing T2DM and its complications.

MATERIALS AND METHODS

Chemicals and Reagents

Enzyme-linked immunosorbent assay (ELISA) kits for insulin were purchased from Wuhan Fine Biotech Co., Ltd., China. Streptozotocin, Tween 80, acetone, corn oil, fructose, citric acid monohydrate ($C_6H_8O_7 \cdot H_2O$), and sodium citrate dihydrate ($Na_3C_6H_5O_7 \cdot 2H_2O$) were obtained from Bridge Biotech Ltd., Ilorin, Kwara State. Metformin was procured from Dialogue Pharmacy, Kaduna State. Primers for SOCS-3, GLUT-4, FGF21, β-Klotho, and β-actin genes, along with the RNA extraction kit and all polymerase chain reaction (PCR) reagents, were sourced from Inqaba Biotec West Africa Ltd., Ibadan, Nigeria.

Sample Collection and Preparation

Fresh turmeric (*Curcuma longa*) was purchased from Central Market, Kaduna State, Nigeria and authenticated by a specialist at the Department of Biological Science, Kaduna State University, assigned a voucher number BSH/1242. The rhizomes were thoroughly washed, cut into smaller pieces, and air-dried in the Biochemistry Laboratory at Kaduna State University (KASU) for 10 days. The dried turmeric was finely ground using a mortar and pestle to obtain a uniform powder.

Extraction of Turmeric (*Curcuma longa)*

Turmeric powder was subjected to Soxhlet extraction using acetone as a solvent at 60°C for 8 hours. The acetone was subsequently removed from the extract using a rotary evaporator (Stuart RE300) under vacuum at 35°C. The resulting residue was dried, weighed and stored at 4^{o}C for further analysis.

Extract Preparation for Administration

The turmeric extract, containing both curcuminoids and essential oils, is highly hydrophobic, making it difficult to dissolve in conventional aqueous solutions. To enhance solubility and ensure uniform dispersion, Tween 80 (a nonionic surfactant) was first added to the extract at a ratio of 3:1 (Tween 80: Extract, w/w) which facilitates solubilization and stabilizes the emulsion, prevents phase separation. After thorough mixing, corn oil was incorporated at the desired concentration to serve as a carrier, forming a stock solution. Corn oil enhances the bioavailability of curcuminoids by improving their solubilization in lipid-based systems and promotes efficient absorption of the extract into the biological system (Sholihat *et al.,* 2020).

Experimental Animals

Thirty (30) male Wistar rats, weighing 150-250 g, were procured from the Faculty of Veterinary Medicine, Ahmadu Bello University (ABU), Zaria, Nigeria. The rats were housed under standard laboratory conditions, maintained at room temperature with a 12-hour light–dark cycle, and provided with commercial rat feed and drinking water ad libitum. All procedures followed the guidelines established by the Animal Research Ethics Committee of KASU.

Animal Grouping and Induction of Type 2 Diabetes

After a one-week adaptation period, the rats were randomly divided into five groups (n = 6 per group) as follows:

1. NC: Normal Control
2. DC: Diabetic Control
3. C100: Diabetic rats treated with 100 mg/kg body weight turmeric extract.
4. C200: Diabetic rats treated with 200 mg/kg body weight turmeric extract.
5. DMET: Diabetic rats treated with 500 mg/kg body weight metformin.

To induce insulin resistance, all groups except the NC group were supplied with 10% fructose ad libitum for 14 days, while the NC group received normal drinking water. After the fructose-loading period, streptozotocin (STZ) (50 mg/kg body weight, dissolved in citrate buffer, pH 4.5) was administered intraperitoneally to induce partial pancreatic β-cell destruction.

One week post-STZ injection, non-fasting blood glucose (NFBG) levels were measured using a glucometer from tail vein blood. The Wister rats with NFBG > 300 mg/dL were classified as diabetic and included in the study, while those with NFBG < 300 mg/dL were excluded (Wilson & Islam, 2012). All animals received their respective treatments daily via oral administration for three weeks, while the NC group received only the vehicle (corn oil). Weekly blood glucose level was also measured.

Collection of Blood and Organ Samples

At the end of the experimental period, the Wister rats were sacrificed via cervical dislocation. Blood samples were collected via cardiac puncture and immediately centrifuged at 3000 rpm for 10 minutes to obtain serum, which was stored at −20°C for further analysis. Liver and skeletal muscle tissues were carefully harvested, preserved in liquid nitrogen, and stored at −70°C until RNA extraction.

Analytical methods

The serum insulin level was measured at the end of the experimental period by an ELISA method using rat ELISA kit as described by the manufacturer. Homeostatic model assessment for insulin resistance (HOMA-IR) was also calculated from fasting serum insulin and fasting blood glucose concentrations using the following formula:

$$\text{HOMA} - \text{IR} = \frac{\text{Serum insulin in } \frac{\text{U}}{\text{L}} \text{ X Blood glucose in mmol/L}}{22.5}$$

GLUT-4, SOCS-3, FGF21 and β-Klotho gene expression studies

Tissue RNA extraction

Total RNA was extracted from skeletal muscle tissue and liver using an RNA extraction kit following the manufacturer's protocol (Inqaba Biotec West Africa Ltd., Ibadan, Nigeria). Briefly, 140 µL of the sample was mixed with 560 µL of AVL working solution, vortexed for 15 seconds, incubated at room temperature for 10 minutes, and centrifuged briefly. An equal volume of absolute ethanol (560 µL) was added, vortexed, and centrifuged before loading 630 µL of the mixture onto a spin column for purification. The column was sequentially washed with 500 µL of AW1 buffer (containing chaotropic salts) and AW2 buffer (containing ethanol), centrifuged at 8,000 rpm and 14,000 rpm, respectively. To remove residual ethanol, an additional centrifugation step was performed, followed by elution with 60 µL of AVE elution buffer (containing 10

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mM Tris). The purified RNA was stored at −20°C for cDNA synthesis (Bako *et al.,* 2019).

Reverse transcription and quantitative polymerase chain reaction

Reverse transcription was carried out using a PCR tube preloaded with reverse transcriptase. Each reaction contained 15 µL of extracted RNA, 2 µL each of forward and reverse primers, and 3 µL of deionized water. The reaction was subjected to the following thermal cycling conditions: 95°C for 5 minutes (denaturation), followed by 42°C for 60 minutes (reverse transcription). For quantitative PCR (qPCR), 16 µL of PCR master mix (containing DNA polymerase, dNTPs, and SYBR Green) was added to the reaction tube, along with 2 µL of synthesized cDNA. The qPCR was conducted using an RT-PCR machine (Rotor-Gene Q, Qiagen) under the following conditions: 95°C for 10 minutes (pre-denaturation), 95°C for 10 seconds (denaturation), 50°C for 15 seconds (annealing), and 72°C for 20 minutes (extension) for 40 cycles. A melting curve analysis was performed from 65–95°C in 5°C increments every 5 seconds. Gene expression levels of GLUT-4, SOCS-3, FGF21, and β-Klotho were normalized to the β-actin reference gene, and relative expression in treated groups was determined using the Comparative Ct (ΔΔCt) method. The primer sequences used for amplification were as follows:

β-actin (F: 5'-CCCGCGAGTACAACCTTCTT-3'-, R: 3'-AACACAGCCTGGATGGCTAC-5'), GLUT-4 (F: 5'-GCACAGCCAGGACATTGTTG-3', R: 3'-CCCCCTCAGCAGCGAGTGA-5'), SOCS-3 (F: 5'-ACCAGCGCCACTTCTTCACA-3', R: 3'-GTGGAGCATCATACTGGTCC-5'). FGF21 (F: 5'-TGGCACCTGAGGCATTGTT-3', R: 3'-AAGAGCACCCCAAAAGACCAC-5') B-Klotho (F: 5'-CAGAGAAGGAGGAGGTGAGG-3', R: 3'-CAGCACCTGCCTTAAGTTG-5'

Statistical analysis

All data obtained during the study were expressed as mean ± SD. Statistical analysis was performed using SPSS for Windows, version 22 (IBM Corporation, NY, USA). Group comparisons were conducted using Tukey's HSD multiple range post-hoc test. A P-value < 0.05 was considered statistically significant.

RESULTS

The following results shows the effect of Turmeric (*Curcuma longa*) extract in enhancing FGF21 Sensitivity and reducing SOCS-3-induced insulin resistance in type 2 diabetic rats. In the first week of treatment, there was a significant ($P < 0.05$) increase in blood glucose levels in all treated groups compared to the diabetic control, suggesting that the extract did not exert an immediate hypoglycemic effect. However, from the second week onwards, a notable decrease in blood glucose levels was observed in the C200 group (200 mg/kg turmeric extract), with a more pronounced effect by the third week, where all treated groups (C100, C200, and DMET) exhibited a significant ($P < 0.05$) reduction compared to the diabetic control (Fig. 1). Further analysis of insulin levels and insulin resistance (HOMA-IR) (Fig. 2 & 3) showed that all turmeric-treated groups (C100 and C200) exhibited a significant ($P < 0.05$) increase in insulin levels, alongside a significant ($P < 0.05$) reduction in insulin resistance (HOMA-IR) values compared to the diabetic control. The gene expression analysis (Fig. 4&5) revealed a significant ($P < 0.05$) upregulation of GLUT-4 and β-Klotho genes, alongside a marked suppression of SOCS-3 and FGF21 expression in the turmeric-treated groups.

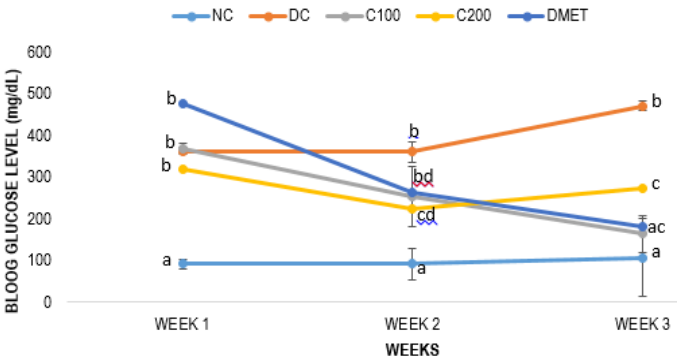

Fig. 1. Effect of turmeric extract on weekly blood glucose level of type 2 diabetic rats. The results are expressed as the Mean±SD. Different alphabets over the lines indicate significant difference (Tukey's-HSD multiple range post hoc test, P<0.05). NC=normal control, DC=diabetic control, C100=diabetic rats treated with 100mg/kg BW of concentration of turmeric extract, C200=diabetic rats treated with 200mg/kg BW of concentration of turmeric extract, DMET=diabetic rats treated with 500mg/kg BW of metformin

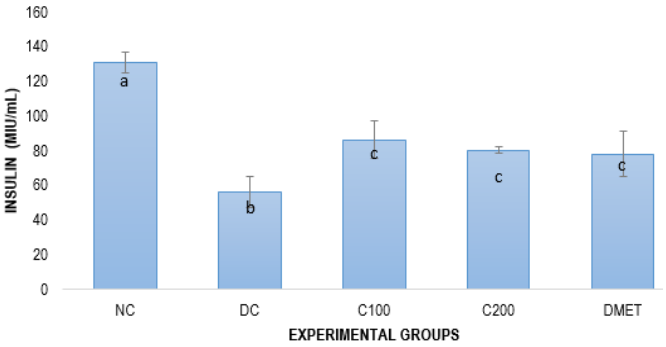

Fig. 2. Effect of turmeric extract on insulin level of type 2 diabetic rats. The results are expressed as the Mean±SD. Different alphabets over the bars indicate significant difference (Tukey's-HSD multiple range post hoc test, P<0.05). NC=normal control, DC=diabetic control, C100=diabetic rats treated with 100mg/kg BW of concentration of turmeric extract, C200=diabetic rats treated with 200mg/kg BW of concentration of turmeric extract, DMET=diabetic rats treated with 500mg/kg BW of metformin.

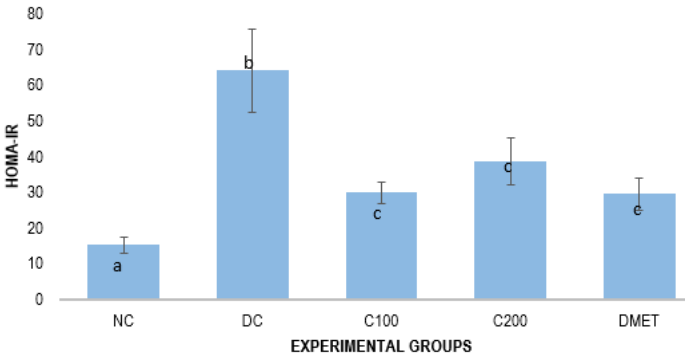

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Fig. 3. Effect of turmeric extract on HOMA-IR of type 2 diabetic rats. The results are expressed as the Mean±SD. Different alphabets over the bars indicate significant difference (Tukey's-HSD multiple range post hoc test, P<0.05). NC=normal control, DC=diabetic control, C100=diabetic rats treated with 100mg/kg BW of concentration of turmeric extract, C200=diabetic rats treated with 200mg/kg BW of concentration of turmeric extract, DMET=diabetic rats treated with 500mg/kg BW of metformin.

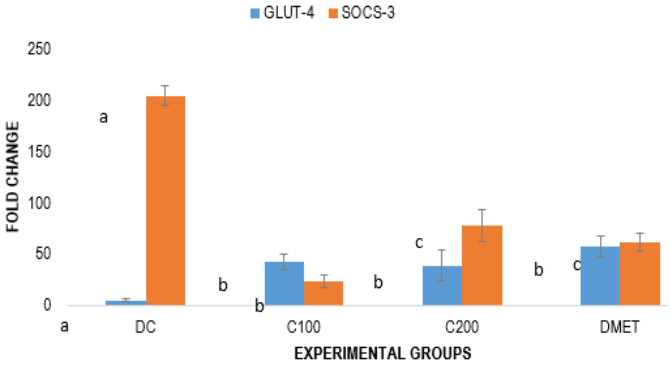

Fig. 4. The relative fold expression of GLUT-4 and SOCS-3 genes in type 2 diabetic rats treated with turmeric extract. The results are expressed as the Mean±SD. Different alphabets over the bars indicate significant difference (Tukey's-HSD multiple range post hoc test, P<0.05). NC=normal control, DC=diabetic control, C100=diabetic rats treated with 100mg/kg BW of concentration of turmeric extract, C200=diabetic rats treated with 200mg/kg BW of concentration of turmeric extract, DMET=diabetic rats treated with 500mg/kg BW of metformin.

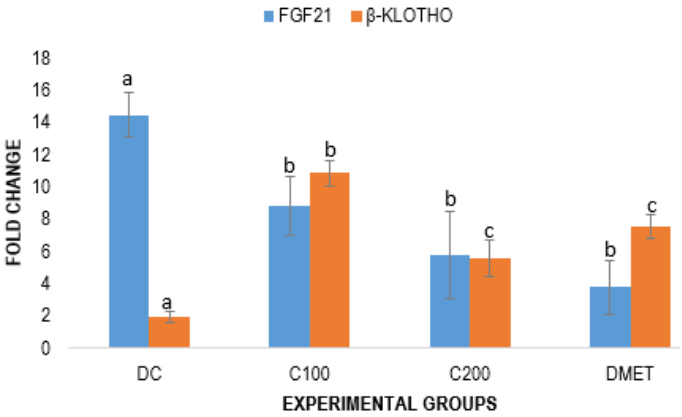

Fig. 5. The relative fold expression of FGF21 and β-klotho genes in type 2 diabetic rats treated with turmeric extract. The results are expressed as the Mean±SD. Different alphabets over the bars indicate significant difference (Tukey's-HSD multiple range post hoc test, P<0.05). NC=normal control, DC=diabetic control, C100=diabetic rats treated with 100mg/kg BW of concentration of turmeric extract, C200=diabetic rats treated with 200mg/kg BW of concentration of turmeric extract, DMET=diabetic rats treated with 500mg/kg BW of metformin.

DISCUSSION

Type 2 diabetes mellitus (T2DM) is characterized by chronic hyperglycaemia, insulin resistance, and impaired glucose metabolism, with inflammatory pathways playing a crucial role in disease progression (Hameed *et al.,* 2015; Zhao *et al.,* 2023). The results of this study demonstrated that turmeric extract significantly enhances insulin sensitivity, reduces insulin resistance, and modulates key metabolic pathways involved in glucose homeostasis in type 2 diabetic Wister rats. The observed progressive reduction in blood glucose levels following turmeric administration suggests that the extract may improve glycemic control through its anti-inflammatory effects that decrease insulin resistance and improve glucose uptake. This is consistent with previous findings, which indicate that curcumin and other bioactive compounds in turmeric exert hypoglycaemic effects by targeting inflammatory cytokines and oxidative stress pathways (El-Saadony *et al., 2022;* Rapti *et al.,* 2024).

One of the most striking findings in this study that explain the mechanism of blood glucose reduction is the significant increase in GLUT-4 expression in turmeric-treated groups. The GLUT-4, a glucose transporter primarily found in skeletal muscle and adipose tissue, plays a pivotal role in insulin-mediated glucose uptake (Wang *et al.*, 2020). The upregulation of GLUT-4 suggests that turmeric extract enhances insulin-stimulated glucose transport, thereby improving glycaemic control and insulin responsiveness. This is supported by earlier studies demonstrating that polyphenolic compounds in turmeric can activate AMPK and PPARγ signaling pathways, leading to enhanced GLUT-4 translocation (Den Hartogh *et al.,* 2020; Wang *et al.,* 2020). Additionally, the downregulation of SOCS-3 in this study further reinforces the role of turmeric in improving insulin sensitivity and decreasing insulin resistance. The SOCS-3 is a negative regulator of insulin signaling that inhibits IRS-1/2 phosphorylation, thereby contributing to insulin resistance (Emanuelli *et al.,* 2001). The observed reduction in SOCS-3 expression in turmeric-treated groups suggests that the extract restores insulin receptor function by relieving SOCS-3-mediated inhibition, facilitating improved glucose metabolism.

A key finding of this study is the modulation of FGF21 and β-Klotho expression following turmeric administration. The FGF21, a metabolic hormone crucial for lipid and glucose homeostasis, is often elevated in T2DM as a compensatory response to insulin resistance (Xie and Leung, 2017; Yang *et al.,* 2023). However, despite high circulating levels, many diabetic patients exhibit FGF21 resistance, primarily due to reduced β-Klotho expression, the essential co-receptor required for FGF21 action (So *et al.,* 2013). The significant increase in β-Klotho expression caused by decreased blood glucose and lipid levels, observed in turmeric-treated groups suggests that turmeric extract may enhance FGF21 signaling sensitivity, thereby counteracting FGF21 resistance and restoring metabolic balance. Interestingly, the concurrent reduction in FGF21 expression in the treated groups may indicate an improvement in insulin sensitivity and glucose metabolism, reducing the need for FGF21 overproduction as a compensatory mechanism. This aligns with findings from previous studies where natural polyphenols were shown to upregulate β-Klotho expression and restore FGF21 functionality in metabolic disorders (Zeng *et al.*, 2016).

Overall, these findings suggest that turmeric extract exerts its anti-diabetic effects through multiple mechanisms, including enhancing insulin sensitivity, improving glucose uptake via GLUT-4 upregulation, and mitigating FGF21 resistance through β-Klotho enhancement. The dose-dependent effect observed in this study

further suggests that higher doses of turmeric extract (200 mg/kg) may provide greater metabolic benefits.

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Conflict of Interest
There is no conflict of interest.

Author's Contribution
H.Y. Bako and R. Auta conceptualized the study, while the experimental design was developed by H.Y. Bako, Z.K. Mohammed and J.S. Mohammed. B.M. Ladan and A.O. Irene conducted the experiments, and H.Y. Bako and A. Yakubu performed the data analysis. H.Y. Bako drafted the manuscript, which was reviewed by Z.K. Mohammed, R. Auta and J.S. Mohammed.

Declaration of generative AI and AI-assisted technologies in the writing process
During the preparation of this work the authors used CHATGPT in order to improve language and readability. After using this tool, the authors reviewed the content as needed and take full responsibility for the content of the publication.

REFERENCES

BonDurant, L. D., & Potthoff, M. J. (2018). Fibroblast Growth Factor 21: A Versatile Regulator of Metabolic Homeostasis. *Annu Rev Nutr*, *38*, 173-196. https://doi.org/10.1146/annurev-nutr-071816-064800

Cao, L., Wang, Z., & Wan, W. (2018). Suppressor of Cytokine Signaling 3: Emerging Role Linking Central Insulin Resistance and Alzheimer's Disease [Mini Review]. *Frontiers in Neuroscience*, *12*. https://doi.org/10.3389/fnins.2018.00417

Den Hartogh, D. J., Gabriel, A., & Tsiani, E. (2020). Antidiabetic Properties of Curcumin I: Evidence from In Vitro Studies. *Nutrients*, *12*(1). https://doi.org/10.3390/nu12010118

El-Saadony, M. T., Yang, T., Korma, S. A., Sitohy, M., Abd El-Mageed, T. A., Selim, S., Al Jaouni, S. K., Salem, H. M., Mahmmod, Y., Soliman, S. M., Mo'men, S. A. A., Mosa, W. F. A., El-Wafai, N. A., Abou-Aly, H. E., Sitohy, B., Abd El-Hack, M. E., El-Tarabily, K. A., & Saad, A. M. (2022). Impacts of turmeric and its principal bioactive curcumin on human health: Pharmaceutical, medicinal, and food applications: A comprehensive review. *Front Nutr*, *9*, 1040259. https://doi.org/10.3389/fnut.2022.1040259

Emanuelli, B., Peraldi, P., Filloux, C., Chavey, C., Freidinger, K., Hilton, D. J., Hotamisligil, G. S., & Van Obberghen, E. (2001). SOCS-3 inhibits insulin signaling and is up-regulated in response to tumor necrosis factor-alpha in the adipose tissue of obese mice. *J Biol Chem*, *276*(51), 47944-47949. https://doi.org/10.1074/jbc.M104602200

Fuloria, S., Mehta, J., Chandel, A., Sekar, M., Rani, N., Begum, M. Y., Subramaniyan, V., Chidambaram, K., Thangavelu, L., Nordin, R., Wu, Y. S., Sathasivam, K. V., Lum, P. T., Meenakshi, D. U., Kumarasamy, V., Azad, A. K., & Fuloria, N. K. (2022). A Comprehensive Review on the Therapeutic Potential of Curcuma longa Linn. in Relation to its Major Active Constituent Curcumin. *Front Pharmacol*, *13*, 820806. https://doi.org/10.3389/fphar.2022.820806

Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of Type 2 Diabetes Mellitus. *Int J Mol Sci*, *21*(17). https://doi.org/10.3390/ijms21176275

Gong, Q., Hu, Z., Zhang, F., Cui, A., Chen, X., Jiang, H., Gao, J., Chen, X., Han, Y., Liang, Q., Ye, D., Shi, L., Chin, Y. E., Wang, Y., Xiao, H., Guo, F., Liu, Y., Zang, M., Xu, A., & Li, Y. (2016). Fibroblast growth factor 21 improves hepatic insulin sensitivity by inhibiting mammalian target of rapamycin complex 1 in mice. *Hepatology*, *64*(2), 425-438. https://doi.org/10.1002/hep.28523

Gu, H., Jiang, W., You, N., Huang, X., Li, Y., Peng, X., Dong, R., Wang, Z., Zhu, Y., Wu, K., Li, J., & Zheng, L. (2020). Soluble Klotho Improves Hepatic Glucose and Lipid Homeostasis in Type 2 Diabetes. *Molecular Therapy - Methods & Clinical Development*, *18*, 811-823. https://doi.org/https://doi.org/10.1016/j.omtm.2020.08.002

Hameed, I., Masoodi, S. R., Mir, S. A., Nabi, M., Ghazanfar, K., & Ganai, B. A. (2015). Type 2 diabetes mellitus: From a metabolic disorder to an inflammatory condition. *World J Diabetes*, *6*(4), 598-612. https://doi.org/10.4239/wjd.v6.i4.598

Jin, T. (2019). Mechanisms underlying the metabolic beneficial effect of curcumin intervention: Beyond anti-inflammation and anti-oxidative stress. *Obesity Medicine*, *13*, 1-5. https://doi.org/https://doi.org/10.1016/j.obmed.2018.11.002

Kilkenny, D. M., & Rocheleau, J. V. (2016). The FGF21 Receptor Signaling Complex: Klothoβ, FGFR1c, and Other Regulatory Interactions. *Vitam Horm*, *101*, 17-58. https://doi.org/10.1016/bs.vh.2016.02.008

Kunnumakkara, A. B., Hegde, M., Parama, D., Girisa, S., Kumar, A., Daimary, U. D., Garodia, P., Yenisetti, S. C., Oommen, O. V., & Aggarwal, B. B. (2023). Role of Turmeric and Curcumin in Prevention and Treatment of Chronic Diseases: Lessons Learned from Clinical Trials. *ACS Pharmacol Transl Sci*, *6*(4), 447-518. https://doi.org/10.1021/acsptsci.2c00012

Li, H., Wu, G., Fang, Q., Zhang, M., Hui, X., Sheng, B., Wu, L., Bao, Y., Li, P., Xu, A., & Jia, W. (2018). Fibroblast growth factor 21 increases insulin sensitivity through specific expansion of subcutaneous fat. *Nature Communications*, *9*(1), 272. https://doi.org/10.1038/s41467-017-02677-9

Lin, W., Zhang, T., Zhou, Y., Zheng, J., & Lin, Z. (2021). Advances in Biological Functions and Clinical Studies of FGF21. *Diabetes Metab Syndr Obes*, *14*, 3281-3290. https://doi.org/10.2147/dmso.S317096

Oguntibeju, O. O. (2019). Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. *Int J Physiol Pathophysiol Pharmacol*, *11*(3), 45-63.

Orellana-Paucar, A. M. (2024). Turmeric Essential Oil Constituents as Potential Drug Candidates: A Comprehensive Overview of Their Individual Bioactivities. *Molecules*, *29*(17), 4210. https://www.mdpi.com/1420-3049/29/17/4210

Rapti, E., Adamantidi, T., Efthymiopoulos, P., Kyzas, G. Z., &

Tsoupras, A. (2024). Potential Applications of the Anti-Inflammatory, Antithrombotic and Antioxidant Health-Promoting Properties of Curcumin: A Critical Review. *Nutraceuticals*, *4*(4), 562-595. https://www.mdpi.com/1661-3821/4/4/31

Salgado, J. V., Goes, M. A., & Salgado Filho, N. (2021). FGF21 and Chronic Kidney Disease. *Metabolism*, *118*, 154738. https://doi.org/https://doi.org/10.1016/j.metabol.2021.154738

Sholihat, S. I., Indahyanti, E., Lestari, M. L. A. D., & Ningsih, Z. (2020). Preparation of Curcumin Nanoemulsion in Soybean Oil – Tween 80 System by Wet Ball Milling Method. *IOP Conference Series: Materials Science and Engineering*, *833*(1), 012044. https://doi.org/10.1088/1757-899X/833/1/012044

So, W. Y., Cheng, Q., Chen, L., Evans-Molina, C., Xu, A., Lam, K. S., & Leung, P. S. (2013). High glucose represses β-klotho expression and impairs fibroblast growth factor 21 action in mouse pancreatic islets: involvement of peroxisome proliferator-activated receptor γ signaling. *Diabetes*, *62*(11), 3751-3759. https://doi.org/10.2337/db13-0645

Szczepańska, E., & Gietka-Czernel, M. (2022). FGF21: A Novel Regulator of Glucose and Lipid Metabolism and Whole-Body Energy Balance. *Horm Metab Res*, *54*(4), 203-211. https://doi.org/10.1055/a-1778-4159

Wang, T., Wang, J., Hu, X., Huang, X. J., & Chen, G. X. (2020). Current understanding of glucose transporter 4 expression and functional mechanisms. *World J Biol Chem*, *11*(3), 76-98. https://doi.org/10.4331/wjbc.v11.i3.76

Wilson, R. D., & Islam, M. S. (2012). Fructose-fed streptozotocin-injected rat: an alternative model for type 2 diabetes. *Pharmacol Rep*, *64*(1), 129-139. https://doi.org/10.1016/s1734-1140(12)70739-9

Xie, T., & Leung, P. S. (2017). Fibroblast growth factor 21: a regulator of metabolic disease and health span. *Am J Physiol Endocrinol Metab*, *313*(3), E292-e302. https://doi.org/10.1152/ajpendo.00101.2017

Yang, M., Liu, C., Jiang, N., Liu, Y., Luo, S., Li, C., Zhao, H., Han, Y., Chen, W., Li, L., Xiao, L., & Sun, L. (2023). Fibroblast growth factor 21 in metabolic syndrome. *Front Endocrinol (Lausanne)*, *14*, 1220426. https://doi.org/10.3389/fendo.2023.1220426

Zeng, K., Tian, L., Patel, R., Shao, W., Song, Z., Liu, L., Manuel, J., Ma, X., McGilvray, I., Cummins, C. L., Weng, J., & Jin, T. (2016). Diet Polyphenol Curcumin Stimulates Hepatic Fgf21 Production and Restores Its Sensitivity in High-Fat-Diet–Fed Male Mice. *Endocrinology*, *158*(2), 277-292. https://doi.org/10.1210/en.2016-1596

Zhao, X., An, X., Yang, C., Sun, W., Ji, H., & Lian, F. (2023). The crucial role and mechanism of insulin resistance in metabolic disease [Review]. *Frontiers in Endocrinology*, *14*. https://doi.org/10.3389/fendo.2023.1149239