FUDMA Journal of Sciences (FJS)
ISSN online: 2616-1370
ISSN print: 2645 - 2944
Vol. 9 No. 12, December (Special Issue), 2025, pp 241 – 246
DOI: https://doi.org/10.33003/fjs-2025-0912-4119

HEPATOPROTECTIVE AND NEPHROPROTECTIVE EFFECTS OF TOFACITINIB AND ASPIRIN AS ANTI-INFLAMMATORY DRUGS TARGETING JAK-STAT AND NF-κB SIGNALING PATHWAYS IN TYPE 2 DIABETES-INDUCED RATS

[*1,2]Hauwa'u Yakubu Bako, [1]Mohammed Auwal Ibrahim and [1]Sani Ibrahim

[1]Department of Biochemistry, Ahmadu Bello University, Zaria, Nigeria.
[2]Department of Biochemistry, Kaduna State University, Kaduna, Nigeria.

*Corresponding authors' email: hauwa.yakubu@kasu.edu.ng Phone: +2347033446762

ABSTRACT

Chronic inflammation contributes to hepatic and renal complications in type 2 diabetes, largely through dysregulation of the JAK–STAT and NF-κB signaling pathways. This study evaluated the hepatoprotective and nephroprotective effects of tofacitinib (JAK–STAT inhibitor) and aspirin (NF-κB inhibitor) in streptozotocin-induced type 2 diabetic rats. Type 2 diabetes was induced using streptozotocin. Diabetic rats were treated orally with tofacitinib (10 or 20 mg/kg), aspirin (100 or 200 mg/kg), or combination therapy for 9 weeks. Serum ALT, AST, creatinine, and urea levels were quantified, and liver and kidney tissues were examined histologically. Statistical significance was set at $P < 0.05$. Diabetic controls showed substantial increases in ALT (74.56 ± 4.71 U/L), AST (181.30 ± 16.91 U/L), creatinine (45.33 ± 2.17 mg/dL), and urea (198.25 ± 6.49 mg/dL). Tofacitinib significantly reduced ALT to 32.32 ± 4.22 and 33.07 ± 4.06 U/L, AST to 79.80 ± 7.38 and 74.67 ± 6.37 U/L, creatinine to 17.25 ± 1.26 and 10.38 ± 1.02 mg/dL, and urea to 91.07 ± 9.48 and 61.36 ± 5.99 mg/dL at 10 and 20 mg/kg, respectively ($P < 0.05$). Aspirin at 100 mg/kg produced comparable improvements, while 200 mg/kg aspirin and combination regimens failed to significantly improve biomarkers ($P > 0.05$). Histopathology confirmed reduced hepatocyte degeneration and glomerular injury in effective treatment groups. In conclusion, tofacitinib and low-dose aspirin independently confer significant hepatoprotective and nephroprotective effects in type 2 diabetic rats, whereas combined therapy provides no added benefit. Targeted inhibition of inflammatory pathways may offer a promising therapeutic strategy for diabetes-associated organ injury. Limitations include use of an animal model, and absence of mechanistic molecular assays, which may limit direct clinical translation.

Keywords: Complications, Hepatotoxicity, Inflammation, Nephrotoxicity, Type 2 Diabetes

INTRODUCTION

Diabetes is a major global health concern and is currently the eighth leading cause of death and disability worldwide. The International Diabetes Federation (IDF) estimates that 537 million adults aged 20–79 years are living with the disease (Sun et al., 2022). This number is projected to rise to 643 million by 2030 and 783 million by 2045 (Sun et al., 2022), and may reach 1.3 billion by 2050 (Chan et al., 2021; Magliano et al., 2021). Diabetes causes approximately 1.5 million deaths annually and imposes substantial economic burden. In Africa, an estimated 24 million people were living with diabetes in 2021, with projections suggesting an increase to 55 million by 2045.

Type 2 diabetes is a complex metabolic disease characterized by insulin resistance and progressive β-cell dysfunction (Wesolowska-Andersen et al., 2022). Chronic low-grade inflammation plays a major role in worsening insulin resistance and promoting β-cell damage, ultimately predisposing individuals to severe complications (Cerf, 2013). These complications include nephropathy, neuropathy, retinopathy, and cardiovascular disease, resulting from metabolic derangements that affect organs such as the liver and kidneys (Cade, 2008).

In T2D, impaired glucose utilization increases lipolysis in adipose tissue, leading to accumulation of fatty acids in the liver, oxidative stress, and activation of inflammatory pathways that damage hepatocytes. Similarly, hyperglycemia in the kidney activates the polyol and hexosamine pathways, generating free radicals that promote inflammation and structural injury to renal cells (Wu et al., 2023). Several studies have attempted to mitigate these complications by suppressing oxidative stress and inflammation (Adelakun et al., 2024; Arigela et al., 2021; Zhu et al., 2021).

Two key inflammatory pathways involved in this process are the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway and the nuclear factor-kappa B (NF-κB) pathway. Activation of these pathways increases the production of proinflammatory cytokines and free radicals, contributing to insulin resistance and organ damage. Bako et al. (2019) demonstrated that inhibiting both JAK–STAT and NF-κB in type 2 diabetic rats significantly reduced proinflammatory cytokines and insulin resistance.

However, while previous studies explored systemic inflammation, less is known about how these pathway inhibitors influence organ-specific complications, particularly liver and kidney injury. This study therefore investigates the effects of targeting inflammation using tofacitinib (a JAK inhibitor) and aspirin (an NF-κB inhibitor) on hepatic and renal complications in type 2 diabetic rats, providing new insight beyond earlier work.

MATERIALS AND METHODS

Chemicals and Reagents

Citric acid, sodium hydroxide, fructose, methylcellulose, metformin (reference standard), aspirin, and diagnostic kits for aspartate transaminase (AST), alanine transaminase (ALT), urea, and creatinine (Randox) were used. Histology supplies (10% neutral buffered formalin, ethanol, paraffin, hematoxylin, eosin) were obtained locally from Royal Surgical Limited, Kaduna, Nigeria. Streptozotocin (STZ) and tofacitinib were procured from Beijing Mesochem Technology, China.

Animals and Ethical Approval
Adult male Wistar rats (200–250 g) were obtained from the Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria, Nigeria. Animals were housed under standard laboratory conditions (12 h light/dark cycle), with free access to commercial rat chow and water. The study protocol was approved by the Animal Research Ethics Committee of Ahmadu Bello University (Approval No. ABUCAUC/2019/24). All procedures followed institutional and international guidelines for animal care and use.

Experimental Design, group Labels and Sample Size
To allow for attrition we procured animals in excess of the final planned sample. After acclimatization, animals that met inclusion criteria following diabetes induction were randomized into ten groups (final planned n = 8 rats per group; total randomized N = 80):
NC — Normal control (vehicle)
DC — Diabetic control (vehicle)
DT10 — Diabetic + tofacitinib 10 mg/kg
DT20 — Diabetic + tofacitinib 20 mg/kg
DA100 — Diabetic + aspirin 100 mg/kg
DA200 — Diabetic + aspirin 200 mg/kg
DA1T1 — Diabetic + aspirin 100 mg/kg + tofacitinib 10 mg/kg (combination low dose)
DA2T2 — Diabetic + aspirin 200 mg/kg + tofacitinib 20 mg/kg (combination high dose)
A2T2NR — Non-diabetic + aspirin 200 mg/kg + tofacitinib 20 mg/kg (non-diabetic treatment control)
DMET — Diabetic + metformin 850 mg/kg (positive control)
Doses were selected from published preclinical studies showing pharmacologic activity and tolerability in rodents. Tofacitinib was used at 10 and 20 mg/kg to represent a low and a higher active range reported in several rodent models. These doses are pharmacokinetically justified and have been used to modulate JAK–STAT signaling in rats (Lee and Kim, 2019; Bako et al., 2019).
Aspirin doses (100 and 200 mg/kg) were selected to span an anti-inflammatory range commonly used in rat studies that demonstrate effects on inflammatory endpoints; 100 mg/kg is widely reported as an effective anti-inflammatory/antioxidant dose in rodents while 200 mg/kg represents a higher exposure for dose-response assessment (Bako et al., 2019).
Metformin (DMET) was included as a standard positive control. The chosen metformin dose (850 mg/kg) follows precedent in some preclinical studies using high-dose metformin as a comparator in rodent efficacy studies and as used previously in local studies; it therefore serves to benchmark the hepatic and renal readouts against a commonly used oral hypoglycaemic agent (Zehad et al., 2017; Bako et al., 2019).

Diabetes Induction and Inclusion Criteria
Following one week acclimatization, rats (except NC and A2T2NR) received a 10% fructose solution ad libitum for 14 days to induce insulin resistance. Thereafter partial β-cell damage was induced with a single intraperitoneal dose of STZ (40 mg/kg in citrate buffer, pH 4.5). Blood glucose was measured one week after STZ administration using a glucometer; only animals with fasting blood glucose >300 mg/dL were enrolled as diabetic and randomized into groups (Islam, 2011).

Randomization and Blinding
Randomization to groups was performed using a computer-generated random sequence (random.org). Allocation was performed by a technician not involved in endpoint assessments. Investigators performing biochemical assays and histopathological scoring were blinded to group identity. Histology slides were coded so the pathologist was unaware of treatment allocation during semi-quantitative scoring.

Drug preparation and Administration
All test drugs and metformin were suspended in 0.5% methylcellulose and administered orally once daily for nine weeks. Vehicle (0.5% methylcellulose) was given to NC and DC as appropriate.

Outcome Measures (Blood and Tissue Collection)
At study end, animals were anesthetized and euthanized according to institutional guidelines. Blood was collected by cardiac puncture, centrifuged at 3,000 rpm for 10 minutes and serum stored at −30°C until biochemical assays. ALT and AST (U/L), urea and creatinine (mg/dL) were measured using Randox kits following manufacturer protocols. Liver and kidney specimens were fixed in 10% neutral buffered formalin for histology.

Histopathology
Processing followed Palipoch and Punsawad (2013). Fixed tissues were processed through graded ethanols, embedded in paraffin, sectioned (5 µm), stained with hematoxylin and eosin (H&E), and examined under light microscopy. Semi-quantitative scoring categorized lesions as: 0 (normal), 1 (mild, <25% affected), 2 (moderate, 25–50% affected) and 3 (severe, >50% affected). Histological evaluation was performed by a board-certified pathologist blinded to group allocation.

Handling of Exclusions and Outliers
Predefined inclusion/exclusion: animals failing to reach the diabetes threshold (>300 mg/dL) following STZ were excluded prior to randomization. All animals procured and screened are accounted for in the Results (procurement → exclusions → randomization). During the treatment phase, any unexpected deaths, moribund animals or protocol deviations were recorded. Outliers in biochemical data were assessed using Grubbs' test ($\alpha = 0.05$). Outliers identified were examined for technical errors (e.g., hemolysis, assay failure). If a technical cause was confirmed, the sample was excluded and replacement values were not imputed; analyses were performed both with and without outliers to confirm robustness.

Sample Size and Power Analysis
Sample size (n = 8 per group) was determined a priori using power calculations (G*Power). The calculation assumed a two-sided $\alpha = 0.05$ and 80% power to detect an effect size (Cohen's d) of ~1.0 (approximately a 25–30% change in primary biochemical endpoints such as ALT or AST), based on variability reported in comparable preclinical studies; n = 8 per group was therefore selected to balance statistical power and ethical use of animals.

Statistical Analysis
Data are expressed as mean ± SEM. Statistical analyses were conducted in SPSS v22 (IBM). Group comparisons were performed by one-way ANOVA followed by Tukey's HSD post-hoc test for pairwise comparisons. A P-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION
This study investigated the effects of tofacitinib and aspirin on liver and kidney function in type 2 diabetic rats. As

presented in Table 1, treatment with either drug alone resulted in a significant ($P < 0.05$) reduction in serum ALT and AST levels when compared with the diabetic control group. However, the combination therapy groups did not show significant improvement in ALT and AST levels relative to the diabetic control rats.

Creatinine concentration was significantly reduced ($P < 0.05$) in all treatment groups, indicating improved renal function. In contrast, urea levels remained elevated in the groups treated with 200 mg/kg aspirin alone (DA200) and the combination of 200 mg/kg aspirin and 20 mg/kg tofacitinib (DA2T2), with no significant reduction when compared to the diabetic control group.

The histopathological examination of the liver and kidney (Figures 1 and 2) further supported the biochemical findings.

Liver Histopathology (Figure 1)

The normal control (NC) group displayed normal hepatocyte architecture, intact sinusoidal orientation, and a clearly defined central vein (CV). The diabetic control (DC) group showed marked hepatocyte disorientation, loss of sinusoidal structure, and severe infiltration around the CV.

Rats treated with 10 mg/kg tofacitinib (DT10) showed near-normal hepatocyte arrangement with mild sinusoidal congestion and slight infiltration of the CV. Treatment with 20 mg/kg (DT20) produced normal hepatocyte orientation with minor degeneration and slight central vein congestion. Aspirin at 100 mg/kg (DA100) resulted in moderate hepatocyte degeneration, sinusoidal congestion, and infiltration of the CV. At 200 mg/kg (DA200), moderate hepatocyte distortion and congestion were observed.

Combination therapy groups (DA1T1 and DA2T2) showed various degrees of hepatocyte degeneration, sinusoidal disorientation, and CV congestion, with DA2T2 presenting the most pronounced infiltration.

Kidney Histopathology (Figure 2)

The NC group showed normal glomerular architecture and intact collecting ducts. The DC group exhibited highly atrophic and degenerated glomeruli with marked cellular infiltration of the collecting ducts.

Treatment with 10 mg/kg tofacitinib (DT10) preserved normal glomeruli but showed severe infiltration of the collecting ducts. The 20 mg/kg dose (DT20) preserved both glomerular integrity and collecting duct structure. Aspirin at 100 mg/kg (DA100) caused glomerular degeneration with normal collecting ducts, whereas 200 mg/kg (DA200) maintained some normal glomeruli but also presented pronounced degeneration and infiltration.

Combination therapy (DA1T1 and DA2T2) showed mixed features, including atrophic glomeruli and persistent cellular infiltration of the collecting ducts, with DA2T2 showing more severe lesions.

Table 1: Effect of Tofacitinib and Aspirin on Liver and Kidney Function Parameters in Type 2 Diabetic Rats

Group	ALT (U/L)	AST (U/L)	Creatinine (mg/dL)	Urea (mg/dL)
NC	10.16 ± 2.08^{a}	25.38 ± 2.63^{a}	2.15 ± 0.77^{a}	17.43 ± 1.54^{a}
DC	74.56 ± 4.71^{b}	181.30 ± 16.91^{b}	45.33 ± 2.17^{b}	198.25 ± 6.49^{b}
DT10	32.32 ± 4.22^{ac}	79.80 ± 7.38^{ac}	17.25 ± 1.26^{c}	91.07 ± 9.48^{c}
DT20	33.07 ± 4.06^{a}	74.67 ± 6.37^{a}	10.38 ± 1.02^{bcd}	61.36 ± 5.99^{ac}
DA100	43.47 ± 4.30^{cd}	106.17 ± 16.26^{cd}	23.27 ± 2.76^{ce}	120.19 ± 10.56^{cd}
DA200	44.80 ± 5.57^{cd}	100.10 ± 9.94^{c}	34.53 ± 2.12^{e}	159.47 ± 14.49^{bd}
DA1T1	53.76 ± 6.45^{bc}	140.70 ± 17.34^{bd}	26.67 ± 0.96^{e}	128.97 ± 11.69^{ce}
DA2T2	58.40 ± 9.30^{bc}	147.00 ± 15.18^{bd}	36.56 ± 2.11^{e}	166.66 ± 12.78^{be}
A2T2NR	20.80 ± 3.53^{a}	53.08 ± 3.43^{a}	3.37 ± 0.27^{ad}	25.78 ± 1.63^{a}
DMET	22.40 ± 4.56^{a}	56.58 ± 2.92^{a}	12.20 ± 1.06^{c}	55.19 ± 7.15^{ac}

Values are expressed as Mean ± SE (n = 8). Different superscript letters within each column indicate statistically significant differences (Tukey's HSD post-hoc test, $P < 0.05$). NC: Normal control DC: Diabetic control DT10, DT20: Diabetic rats treated with 10 or 20 mg/kg tofacitinib DA100, DA200: Diabetic rats treated with 100 or 200 mg/kg aspirin DA1T1, DA2T2: Combination therapy groups (aspirin + tofacitinib) A2T2NR: Non-diabetic rats treated with high-dose combination DMET: Diabetic rats treated with metformin

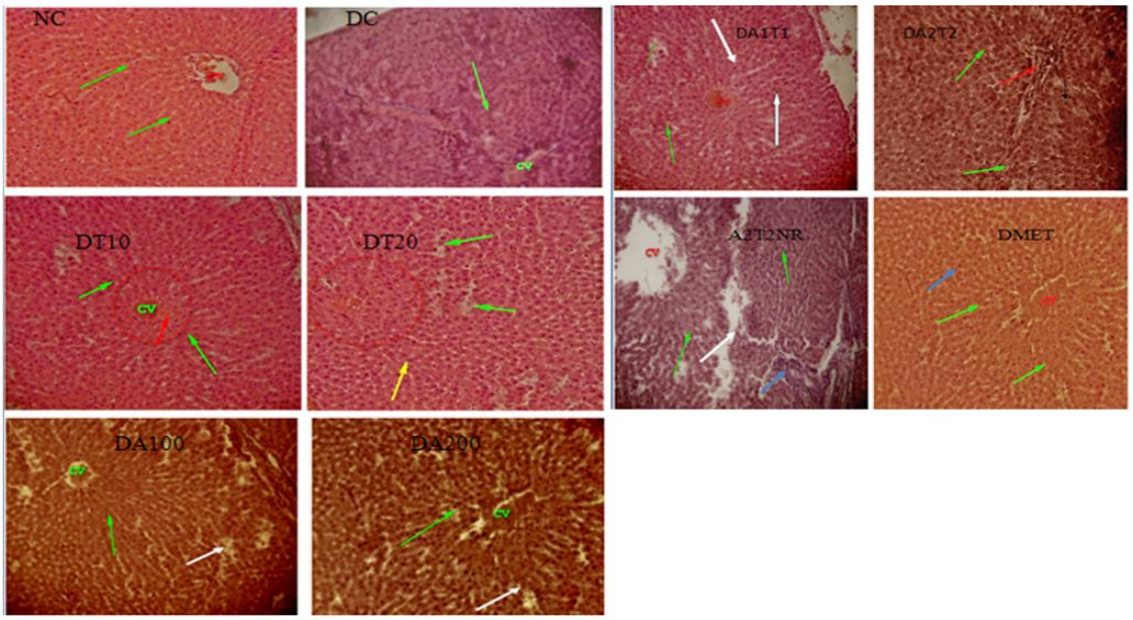

Figure 1: Photomicrograph of H&E-Stained Liver Sections (H&E, x150) from Diabetes-Induced Rats after Treatment with Varying doses of Tofacitinib, Aspirin, and their Combination. NC: Normal Control, DC: Diabetic Control, DT10, DT20: Diabetic Rats Treated with 10 or 20 mg/kg Tofacitinib, DA100, DA200: Diabetic Rats Treated with 100 or 200 mg/kg Aspirin, DA1T1, DA2T2: Combination Therapy groups (Aspirin + Tofacitinib), A2T2NR: Non-Diabetic Rats Treated with High-dose Combination, DMET: Diabetic Rats Treated with Metformin

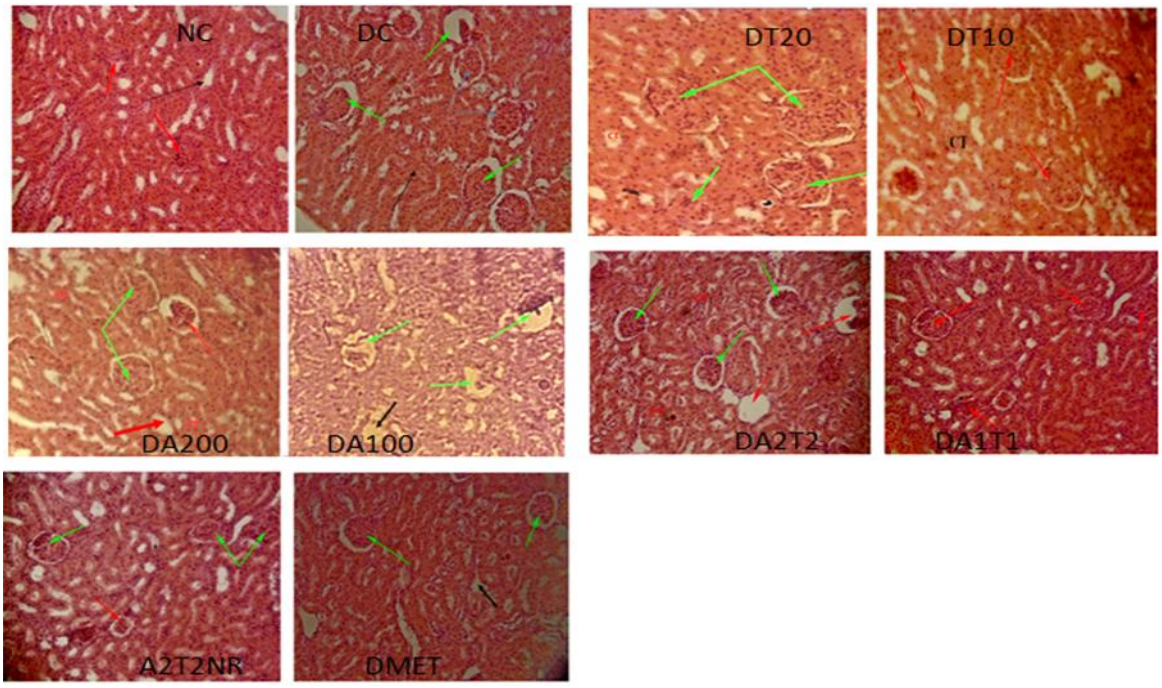

Figure 2: Photomicrograph of H&E-stained Kidney Sections (H&E, x150) from Diabetes-Induced Rats after Treatment with Varying doses of Tofacitinib, Aspirin, and their Combination. NC: Normal Control, DC: Diabetic Control, DT10, DT20: Diabetic Rats Treated with 10 or 20 mg/kg Tofacitinib, DA100, DA200: Diabetic Rats Treated with 100 or 200 mg/kg Aspirin, DA1T1, DA2T2: Combination Therapy Groups (Aspirin + Tofacitinib), A2T2NR: Non-diabetic Rats Treated with High-dose Combination, DMET: Diabetic Rats Treated with Metformin

Discussion

The present study investigated the hepatoprotective and nephroprotective potential of modulating inflammation through the inhibition of JAK-STAT and NF-κB signaling pathways using tofacitinib and aspirin in a rat model of type 2 diabetes. These pathways are central mediators of the inflammatory response. Chronic hyperglycemia in diabetes is known to trigger persistent low-grade inflammation, leading to increased production and release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). This inflammatory milieu promotes macrophage infiltration into target organs, contributing to progressive liver and kidney tissue damage.

Hepatic and renal dysfunction, as evidenced by elevated levels of liver enzymes such as ALT, AST, and markers of renal impairment like creatinine and urea, are well-

documented complications in type 2 diabetes (Adiga & Malawadi, 2016). Our findings demonstrated that treatment with tofacitinib and aspirin significantly reduced the levels of ALT, AST, urea and creatinine in diabetic rats, suggesting a protective effect of these anti-inflammatory drugs against diabetes-induced liver and kidney damage. The observed reductions in these biomarkers indicate that both tofacitinib and aspirin effectively mitigate the hepatotoxic and nephrotoxic effects caused by type 2 diabetes, likely by attenuating the underlying inflammatory processes. These results align with previous studies that have reported similar protective effects of anti-inflammatory therapies in diabetic models (Bako et al., 2019; Balague et al., 2012; Wang et al., 2019; Isaacs et al., 2014).

The histopathological analysis further corroborates the biochemical findings, showing that treatment with tofacitinib and aspirin resulted in less severe hepatic and renal lesions compared to the diabetic control group. Specifically, the liver sections from treated rats displayed improved hepatocyte orientation and reduced cellular infiltration, while the kidney sections showed preservation of glomerular structure and reduced atrophy. These histological improvements were most pronounced in the groups treated with tofacitinib or aspirin alone, whereas the combination therapy did not provide additional benefits and, in some cases, failed to significantly reduce urea levels. In some cases, combined treatment failed to significantly improve urea levels. This may reflect pharmacodynamic overlap, where both drugs converge on similar inflammatory pathways, limiting incremental benefit. The possibility of drug–drug interaction or excessive immunosuppression cannot be excluded and warrants further investigation.

The observed hepatoprotective and nephroprotective effects of aspirin are consistent with the literature, where long-term, high-dose aspirin therapy has been shown to preserve liver function and prevent renal impairment, possibly due to its antioxidant properties (Ashoori et al., 2015; Li et al., 2017). Similarly, the protective effects of tofacitinib, a JAK inhibitor, on organ function in inflammatory conditions have been documented, with studies showing its ability to reduce inflammation and protect against tissue damage (Kremer et al., 2015; Zhang et al., 2022).

CONCLUSION

In conclusion, targeting inflammation by inhibiting both JAK-STAT and NF-κB signaling pathways plays a significant role in managing liver and kidney complications associated with type 2 diabetes. However, the current findings show that selective inhibition of the JAK-STAT pathway alone—particularly at a moderate dose of tofacitinib (10 mg/kg)—provides more promising protection against inflammation-induced hepatic and renal damage. This suggests that focused and dose-optimized regulation of inflammatory pathways may offer a more efficient therapeutic strategy than broad multi-pathway inhibition. From a broader clinical and public health perspective, these results highlight the potential for targeted anti-inflammatory therapies to reduce the burden of diabetes-related organ damage, which remains a major cause of morbidity, healthcare expenditure, and reduced quality of life globally. Optimizing such therapies could contribute to earlier, more effective intervention strategies—especially in low-resource settings where diabetes complications are often detected late and treatment options are limited. Despite these important insights, the study is limited by its reliance on an animal model, short treatment duration, and the evaluation of only one therapeutic agent and selected doses. Future research should focus on long-term safety and efficacy, expanded dose ranges, potential synergistic effects with other anti-inflammatory or antidiabetic agents, and ultimately, human clinical trials to confirm translational value and support evidence-based public health recommendations.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the Tertiary Education Trust Fund (TETFund) and Kaduna State University for granting a PhD study sponsorship to the first author. Special thanks are extended to Prof. Yusuf Yakubu of Usmanu Danfodiyo University, Sokoto, and Mrs. Rabiat Idrees of Kaduna State University for their invaluable technical support. We also appreciate the Department of Biochemistry, Ahmadu Bello University, Zaria, for granting access to laboratory facilities that were instrumental to the success of this study.

AUTHOR CONTRIBUTIONS

HYB and MAI conceptualized and designed the study. The experimental procedures were carried out by HYB and MAI, while MSI conducted the data analysis. HYB prepared the initial draft of the manuscript, and MAI critically reviewed and revised it. All authors read and approved the final version of the manuscript.

REFERENCES

Adelakun, S. A., Akomaye, A. J., Omotoso, O. D., & Arowosegbe, O. A. (2024). Anti-hepatopathy and anti-nephropathy activities of *Taraxacum officinale* in a rat model of streptozotocin diabetes-induced hepatorenal toxicity and dyslipidemia via attenuation of oxidative stress, inflammation, apoptosis, electrolyte imbalances, and mitochondrial dysfunction. *Aspects of Molecular Medicine, 3*, 100034. https://doi.org/10.1016/j.amolm.2024.100034

Adiga, U. S., & Malawadi, B. N. (2016). Association of diabetic nephropathy and liver disorders. *Journal of Clinical and Diagnostic Research, 10*(10), BC05–BC07. https://doi.org/10.7860/JCDR/2016/21672.8728

Arigela, C. S., Nelli, G., Gan, S. H., Sirajudeen, K. N. S., Krishnan, K., Abdul Rahman, N., & Pasupuleti, V. R. (2021). Bitter gourd honey ameliorates hepatic and renal diabetic complications in type 2 diabetes rat models by antioxidant, anti-inflammatory, and anti-apoptotic mechanisms. *Foods, 10*(11), 2872. https://doi.org/10.3390/foods10112872

Ashoori, M., Bathaie, S. Z., & Heidarzadeh, H. (2015). Long-term, high-dose aspirin therapy increases the specific activity of complex III of the mitochondrial respiratory chain in the kidney of diabetic rats. *Physiology and Pharmacology, 19*, 158–167.

Bako, H. Y., Ibrahim, M. A., Isah, M. S., & Ibrahim, S. (2019). Inhibition of JAK-STAT and NF-κB signalling systems could be a novel therapeutic target against insulin resistance and type 2 diabetes. *Life Sciences, 239*, 117045. https://doi.org/10.1016/j.lfs.2019.117045

Cade, W. T. (2008). Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Physical Therapy, 88*(11), 1322–1335. https://doi.org/10.2522/ptj.20080008

Cerf, M. E. (2013). Beta cell dysfunction and insulin resistance. *Frontiers in Endocrinology, 4*, 37. https://doi.org/10.3389/fendo.2013.00037

Chan, J. C. N., Lim, L. L., Wareham, N. J., Shaw, J. E., Orchard, T. J., Zhang, P., ... Gregg, E. W. (2021). The Lancet Commission on diabetes: Using data to transform diabetes care and patient lives. *The Lancet*, *396*(10267), 2019–2082. https://doi.org/10.1016/S0140-6736(20)32374-6

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. *International Journal of Molecular Sciences*, *21*(17), 6275. https://doi.org/10.3390/ijms21176275

Isaacs, J. D., Zuckerman, A., Krishnaswami, S., Nduaka, C., Lan, S., Hutmacher, M. M., ... Riese, R. (2014). Changes in serum creatinine in patients with active rheumatoid arthritis treated with tofacitinib: Results from clinical trials. *Arthritis Research & Therapy*, *16*(4), R158. https://doi.org/10.1186/ar4673

Islam, M. S. (2011). Fasting blood glucose and diagnosis of type 2 diabetes. *Diabetes Research and Clinical Practice*, *91*(1), e26–e27. https://doi.org/10.1016/j.diabres.2010.09.035

Kremer, J. M., Kivitz, A. J., Simon-Campos, J. A., Nasonov, E. L., Tony, H. P., Lee, S. K., ... Isaacs, J. D. (2015). Evaluation of the effect of tofacitinib on measured glomerular filtration rate in patients with active rheumatoid arthritis: Results from a randomized controlled trial. *Arthritis Research & Therapy*, *17*(1), 95. https://doi.org/10.1186/s13075-015-0612-7

Kumar Bhatt, L., & Addepalli, V. (2011). Minocycline with aspirin: An approach to attenuate diabetic nephropathy in rats. *Renal Failure*, *33*(1), 72–78. https://doi.org/10.3109/0886022X.2010.528117

Lee, J. S., & Kim, S. H. (2019). Dose-dependent pharmacokinetics of tofacitinib in rats: Influence of hepatic and intestinal first-pass metabolism. Pharmaceutics, 11(7), 318. https://doi.org/10.3390/pharmaceutics11070318

Li, C. J., Yang, Z. H., Shi, X. L., & Liu, D. L. (2017). Effects of aspirin and enoxaparin in a rat model of liver fibrosis. *World Journal of Gastroenterology*, *23*(35), 6412–6419. https://doi.org/10.3748/wjg.v23.i35.6412

Magliano, D. J., Boyko, E. J., & International Diabetes Federation Diabetes Atlas committee. (2021). *IDF Diabetes Atlas*. International Diabetes Federation.

Palipoch, S., & Punsawad, C. (2013). Biochemical and histological study of rat liver and kidney injury induced by cisplatin. *Journal of Toxicologic Pathology*, *26*(3), 293–299. https://doi.org/10.1293/tox.26.293

Phaniendra, A., Jestadi, D. B., & Periyasamy, L. (2015). Free radicals: Properties, sources, targets, and their implication in various diseases. *Indian Journal of Clinical Biochemistry*, *30*(1), 11–26. https://doi.org/10.1007/s12291-014-0446-0

Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, B. B., ... Mbanya, J. C. (2022). IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Research and Clinical Practice*, *183*, 109119. https://doi.org/10.1016/j.diabres.2021.109119

Vos, T., Lim, S. S., Abbafati, C., Abbas, K. M., Abbasi, M., Abbasi-Kangevari, M., ... Abdelalim, A. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, *396*(10258), 1204–1222.

Wang, H., Feng, X., Han, P., Lei, Y., Xia, Y., Tian, D., & Yan, W. (2019). The JAK inhibitor tofacitinib ameliorates immune-mediated liver injury in mice. *Molecular Medicine Reports*, *20*(6), 4883–4892. https://doi.org/10.3892/mmr.2019.10750

Wesolowska-Andersen, A., Brorsson, C. A., Bizzotto, R., Mari, A., Tura, A., Koivula, R., ... Brunak, S. (2022). Four groups of type 2 diabetes contribute to the etiological and clinical heterogeneity in newly diagnosed individuals: An IMI DIRECT study. *Cell Reports Medicine*, *3*(1), 100477. https://doi.org/10.1016/j.xcrm.2021.100477

World Health Organization. (2024). *Health topic: Diabetes*. https://www.who.int/health-topics/diabetes

Wu, T., Ding, L., Andoh, V., Zhang, J., & Chen, L. (2023). Mechanisms of hyperglycemia-induced renal cell injury in diabetic nephropathy disease: An update. *Life*, *13*(2), 539. https://doi.org/10.3390/life13020539

Zehad, A., Islam, G. J., Rashid, M., Juthy, N. J., & Zannah, S. (2017). *Antidiabetic and antihyperlipidemic activities of methanolic leaf extract of* Stephania japonica *in alloxan induced diabetic rats*. **Pharmacology & Pharmacy, 8**(4), 147–158. https://doi.org/10.4236/pp.2017.84008

Zhang, X., Lin, L., Li, L., Hu, K., Shao, R., Li, P., ... Yang, Y. (2022). Janus kinase inhibitor tofacitinib alleviates acute hepatitis induced by lipopolysaccharide/D-galactosamine in mice. *Molecular Biology Reports*, *50*, 1–9. https://doi.org/10.1007/s11033-022-08086-6

Zhu, Y., Su, Y., Zhang, J., Zhang, Y., Li, Y., Han, Y., ... Li, W. (2021). Astragaloside IV alleviates liver injury in type 2 diabetes due to promotion of AMPK/mTOR-mediated autophagy. *Molecular Medicine Reports*, *23*(6), 437. https://doi.org/10.3892/mmr.2021.12076