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Therapeutic Efficacy of 11-Keto-β-Boswellic Acid and 5-Chloro-8-Hydroxyquinoline in Ameliorating Spleen Dysfunction in Streptozotocin-Induced Diabetic Mice

Eficacia Terapéutica del Ácido 11-Ceto-β-Boswélico y 5-Cloro-8-Hidroxiquinolina para Mejorar la Disfunción del Bazo en Ratones Diabéticos Inducidos por Estreptozotocina

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SUMMARY: Diabetes mellitus (DM) causes immune dysfunction and spleen damage. This study investigated the therapeutic effects of 11-keto-β-boswellic acid (KBA) isolated and semi-synthesized from Boswellia sacra resin and commercially sourced 5-chloro-8-hydroxyquinoline (CHQ) on spleen injury in streptozotocin-induced diabetic mice. Twenty-four female CD1 mice were divided into control, diabetic, diabetic + CHQ, and diabetic + KBA groups. KBA (25 mg/kg/day) or CHQ (25 mg/kg/day) was administered intraperitoneally for four weeks. Spleen tissues were examined histologically with hematoxylin–eosin staining and morphometric analysis. Diabetic mice showed noticeable capsular thickening, disruption of white pulp architecture, lymphocyte depletion, and red pulp congestion. Both treatments significantly improved splenic structure; however, KBA treatment produced near-normal restoration of white and red pulp morphology, reduced inflammation, and lowered siderophage accumulation compared with CHQ. Laboratory-isolated KBA demonstrated superior protection against diabetes-induced splenic dysfunction, highlighting its potential as a novel therapeutic approach for immune complications associated with diabetes. Further studies are warranted to define the underlying molecular mechanisms.

KEY WORDS: 11-Keto-β-boswellic acid; 5-Chloro-8-hydroxyquinoline; Spleen; Diabetes mellitus; Histopathology.

INTRODUCTION

Diabetes mellitus (DM) is a persistent metabolic condition characterized by insufficient insulin production, reduced insulin sensitivity, or both, resulting in hyperglycemia (George *et al*., 2010). Globally, DM ranks among the top five causes of mortality. According to the World Health Organization (WHO) and the International Diabetes Federation (IDF), the global diabetes burden has continued to rise, reaching approximately 589 million adults (aged 20–79 years) in 2024, compared to about 200 million cases in 1990, and accounting for around 3.4 million deaths worldwide (World Health Organization, 2024).

Elevated blood glucose contributes to ~11 % of cardiovascular mortality (Organization, 2024). In Oman, the escalating prevalence of diabetes poses a critical public-health challenge. Current estimates indicate that ~15.7 % of Omani adults have diabetes and are projected to reach ~23.8 % by 2050 (Al-Mawali *et al*., 2021). The number of diagnosed cases in Oman increased from ~128,769 in 2015 to 149,195 in 2020 and is expected to rise to ~352,000 by 2050 (Yousif *et al*., 2021). Uncontrolled diabetes can lead to severe complications, affecting multiple organs, including the nervous and vascular systems (Li *et al*., 2023). It may result in vision loss, renal failure, myocardial infarction, and limb amputations (Hippisley-Cox & Coupland, 2016). The pathogenesis of DM involves multiple mechanisms, such as autoimmune-mediated β-cell destruction and diminished insulin action in target tissues. This dysfunction arises due to either inadequate insulin

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secretion or impaired tissue sensitivity, leading to disruptions in complex insulin signaling cascades (Lebovitz, 2001). DM is primarily classified into Type 1 (T1DM) and Type 2 (T2DM) based on etiology. T1DM, constitutes approximately 10 % of all diagnosed diabetes cases (Genuth *et al*., 2018). Environmental triggers such as chemical toxins, viral infections, or autoimmune responses can damage pancreatic b-cells, leading to insulin deficiency and T1DM development (Genuth *et al*., 2018). Chronic hyperglycemia, a defining feature of diabetes, causes structural and functional damage to multiple organs, leading to systemic complications. Persistent hyperglycemia also compromises lymphocyte function and promotes oxidative stress, resulting in immune dysregulation (Boynes, 1991). Consequently, lymphoid organs, especially the spleen, are particularly affected (Alblihd *et al*., 2023). Moreover, by employing histopathological evidence, we aimed to correlate the observed histological recovery with the pharmacological actions of the investigated compounds.

Phytochemicals derived from medicinal plants have been reported to show broad-spectrum bioactivity and favorable safety profiles, offering promising therapeutic potential against chronic diseases (Hossain *et al*., 2025). Among these, pentacyclic triterpene molecules such as boswellic acids from *Boswellia* species have demonstrated significant antidiabetic effects (Roy *et al*., 2019). Clinical trials reported improved blood glucose, HbA1c, and lipid profiles in type 2 diabetes patients treated with *Boswellia serrata* resin (Ammon, 2019). Herbal formulations containing *Boswellia* resin have likewise shown antidiabetic activity (al-Awadi *et al*., 1991). Furthermore, 8-hydroxyquinoline (8HQ) and its derivatives possess antidiabetic, anticancer, antimicrobial, and antioxidant properties (Abbas *et al*., 2017). Quinoline analogs exhibit strong antiglycation and antioxidant effects *in vitro* with proven non-toxicity (Prachayasittikul *et al*., 2013). The growing popularity of natural medications, particularly in developing countries, is attributed to their safety and minimal adverse effects (Abugomaa & Elbadawy, 2020). Recent studies highlight the therapeutic potential of flavonoids and other natural compounds as cost-effective alternatives for diabetes management (Nasrollahi *et al*., 2022). KBA, the principal bioactive pentacyclic triterpenoid of *Boswellia* resin, is a critical mediator of frankincense's pharmacological effects (Ni *et al*., 2012). Numerous studies describe its anti-inflammatory (Shehata *et al*., 2011), anticancer, and immunomodulatory activities(Prachayasittikul *et al*., 2013) and its benefits in chronic inflammatory disorders such as osteoarthritis, inflammatory bowel disease, and respiratory ailments (Lim *et al*., 2025). Importantly, recent work has demonstrated KBA's protective effects in diabetes models (Khan *et al*., 2022), highlighting its relevance to the present study. CHQ, a quinoline derivative, substituted with a hydroxyl group at C-8 and a chlorine atom at C-5, has emerged as a compound of significant pharmacological interest due to its broad-spectrum biological activities, including antibacterial, anticancer, and anti-inflammatory effects. Furthermore, CHQ is a versatile synthetic intermediate in medicinal chemistry. Developing a diabetic mouse model is essential for understanding the pathophysiological mechanisms of DM and for evaluating potential therapeutic strategies derived from medicinal plants (Ebaid, 2014). In this study, 5-chloro-8-hydroxyquinoline (CHQ) was obtained commercially, whereas 11-keto-b-boswellic acid was extracted and semi-synthesized in our own laboratory from *Boswellia sacra* resin at the Natural and Medical Sciences Research Centre of the University of Nizwa. This study is the first to evaluate and compare the histological effects of laboratory-isolated KBA and commercially sourced CHQ (Fig. 1) on spleen tissue altered by streptozotocin-induced diabetes in mice (Rehman *et al*., 2023).

MATERIAL AND METHOD

Previous studies by our group involved the systematic isolation of secondary metabolites from *Boswellia sacra* resin and the chemical modification of boswellic acid structures, were evaluated for their potential to address a range of biological disorders (Al-Harrasi *et al*., 2017). To assess the antidiabetic effects in mice model, KBA was extracted and

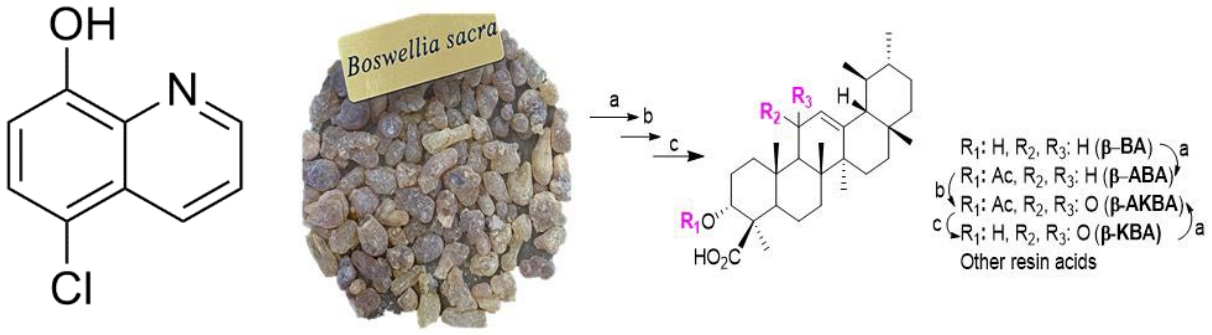


Fig. 1. Chemical structures and synthetic route of the investigated compounds: (A) 5-Chloro-8-hydroxyquinoline (commercially sourced) and (B) large-scale production of 11-Keto-β-boswellic acid (β-KBA). Reagents and conditions: (a) Ac_2O/Py/DMAP, CH_2Cl_2, room temperature, 6 h; (b) NBS/$CaCO_3$/H_2O/hn, dioxane, room temperature, 10 h; (c) 0.5 N KOH in iPrOH, reflux, 10 h.

semi-synthesized in our laboratory from *Boswellia sacra* resin, using previously validated protocols (Shamraiz *et al.*, 2020). Additionally, CHQ was obtained from our in-house compound library (originally purchased from Sigma-Aldrich). Streptozotocin (STZ) powder, used to induce diabetes, was purchased from Sigma-Aldrich (St. Louis, MO, USA)

Ethical Approval

All animal procedures were conducted in accordance with the ethical principles and institutional guidelines of the University of Nizwa for the care and use of laboratory animals and were approved by the University Animal Ethics Committee.

Animal Model

Twenty-four female CD1 mice (25–30 g, aged 10–12 weeks) were selected to minimize hormonal variability and to maintain consistency with previous STZ-induced diabetes studies. The animals were divided into two primary groups: a healthy control group (n = 6) and a streptozotocin-induced diabetic group (n = 18). Mice were housed under a 12-hour light/dark cycle in a controlled environment with regulated temperature and humidity, and were given free access to food and water.

Experimental Design.

Following a one-week acclimatization period, the mice were randomly assigned to four experimental groups (n = 6 each) (n = 6 each) to minimize selection bias. Group 1: healthy controls receiving standard chow and water, Group 2: diabetic controls established by intraperitoneal (IP) injection of streptozotocin (180 mg/kg) dissolved in 10 mM citrate buffer (pH 4.5), Group 3: diabetic mice treated daily with CHQ (25 mg/kg, IP), Group 4: diabetic mice treated daily with KBA (25 mg/kg, IP). Glycemia was assessed at 72 h and again between days 3–6 after STZ injection using blood from the lateral tail vein (On Call Plus glucometer, ACON Laboratories, Germany). Mice with blood glucose ≥ 300 mg/dL and symptoms such as polydipsia and polyuria were considered diabetic. After 4 weeks of treatment, animals were euthanized under 5 % isoflurane anesthesia by decapitation, and spleens were collected in 10 % neutral buffered formalin.

Histology.

Spleen specimens were fixed in 10 % neutral buffered formalin for 24 h, dehydrated in graded ethanol, cleared in xylene, and embedded in paraffin. Sections (4 μm) were cut using a rotary microtome and stained with hematoxylin and eosin (H&E) for histological examination and semi-morphometric scoring.

RESULTS

Histopathological Assessment

Microscopic analysis of H&E-stained spleen sections revealed that the control group (Fig. 2A) demonstrated normal capsular thickness and well-preserved tissue architecture. In contrast, diabetic mice (Fig. 2B) displayed a significant increase in capsular thickness compared to controls. Administration of CHQ (Fig. 2C) resulted in a modest reduction in capsular thickness, whereas treatment with KBA (Fig. 2D) demonstrated noticeable restoration and structural improvement. Histological examination of control spleens showed intact microarchitecture, featuring demarcated periarteriolar lymphoid sheaths (PALS), germinal centers with densely packed lymphocytes, follicular arteries encircled by concentric lymphocyte layers, and well-defined mantle-marginal zone complexes. The white and red pulp compartments maintained sharply distinct histological boundaries (Fig. 3A). In contrast, diabetic mice (Fig. 3B) demonstrated disrupted white pulp architecture, lymphocyte depletion, and a loss of structural integrity. These animals also showed increased arterial wall thickness, necrosis, and a significant reduction in mature lymphocytes within the germinal center. Treatment with CHQ and KBA (Figs. 3C-D) resulted in significant improvements ($p < 0.05$), characterized by enhanced lymphocyte distribution and restoration of the normal balance between white and red pulp. Statistical analyses confirmed that diabetes induced severe depletion, degeneration, and necrosis of white pulp lymphocytes, whereas CHQ and KBA administration significantly mitigated these pathological alterations, nearly restoring normal tissue integrity and leading to a near recovery of the normal immunologic function of the spleen $p < 0.05$ (one-way ANOVA followed by Tukey's post hoc test).

The red pulp morphology of the control spleen demonstrated well-organized lymphoid cells, plasma cells, reticular fibers, splenic cords, and sinusoids (Fig. 4A). In diabetic mice, the red pulp displayed congestions, degenerative changes, hemosiderin accumulation (a marker of splenic injury), and a predominance of siderophages (hemosiderin-laden macrophages), along with reduced lymphocyte counts (Fig. 4B). Notably, in animals treated with CHQ and KBA (Figs. 4C-D), red pulp restoration was evident, with reduced hemosiderin deposits and improved tissue structure. Morphometric scoring showed considerable reductions in lesion severity in both treatment groups ($p < 0.05$), with KBA demonstrating the greatest improvement. KBA effect produced near-normal restoration of white and red pulp morphology, reduced inflammation, and lowered siderophage accumulation compared with CHQ (Figs. 2D-4D).

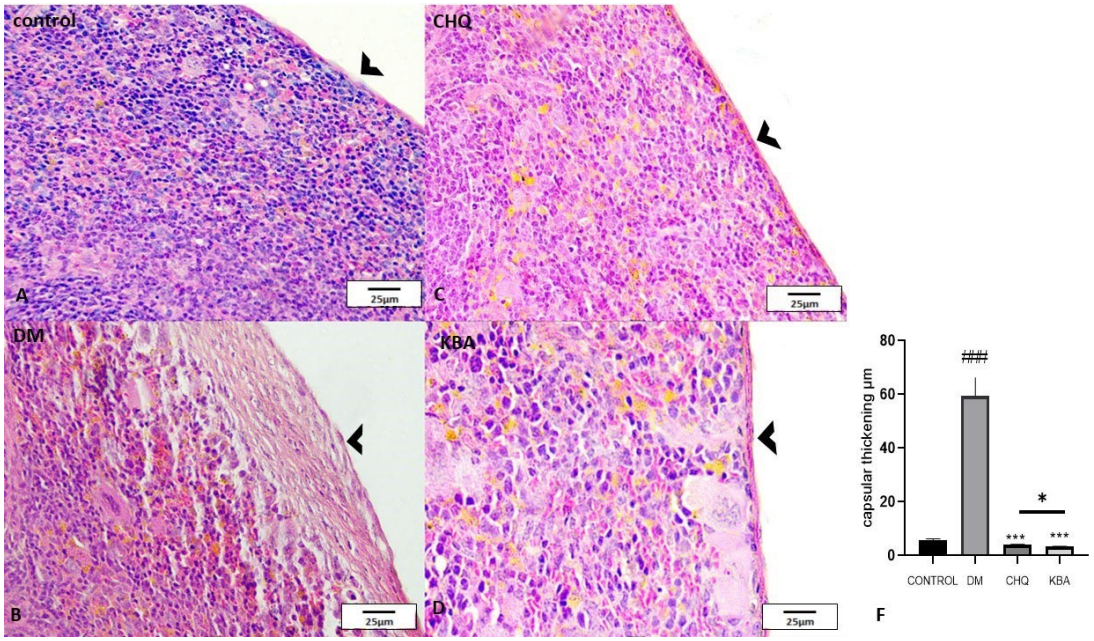


Fig. 2. Histopathological analysis of splenic capsular thickness in hematoxylin–eosin–stained spleen tissue sections: (A) Control group showing normal capsular structure (Δ); (B) untreated DM group exhibiting marked capsular thickening (Δ); (C) DM + CHQ group showing a moderate reduction in capsular thickness (Δ); (D) DM + KBA group showing nearly normal capsule dimensions (Δ). (F) Quantitative analysis of mean capsule thickness in different groups. *P < 0.05 compared with the DM group. Control, healthy animals; DM, diabetic animals; DM + CHQ, diabetic animals treated with CHQ (5-chloro-8-hydroxyquinoline); DM + KBA, diabetic animals treated with 11-keto-β-boswellic acid. Data are expressed as mean ± SEM. 10× magnification, scale bar = 25 µm.

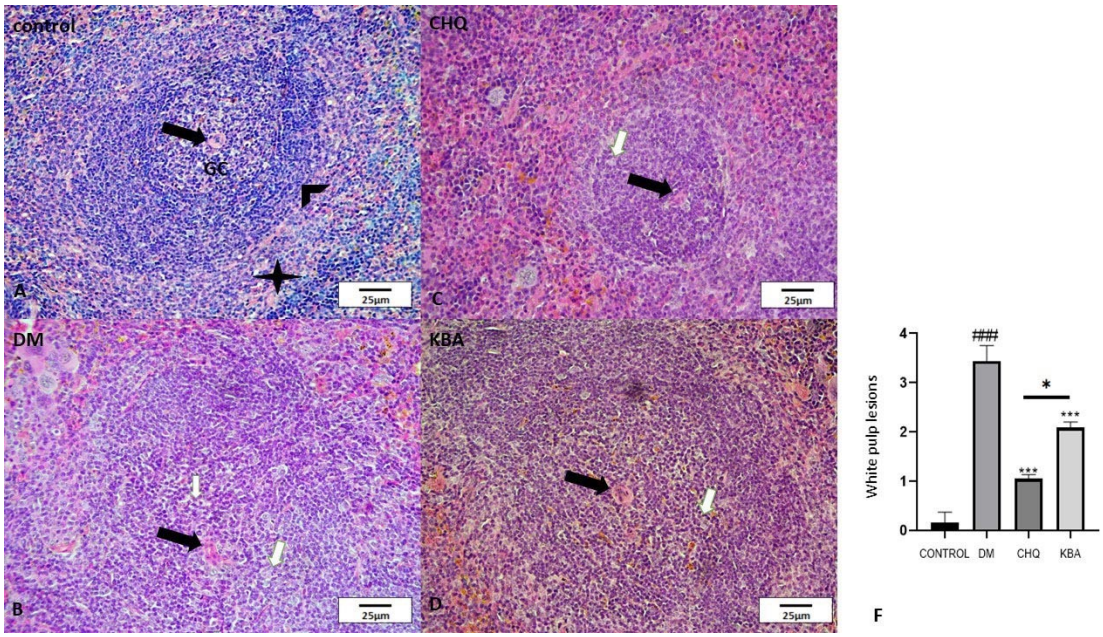
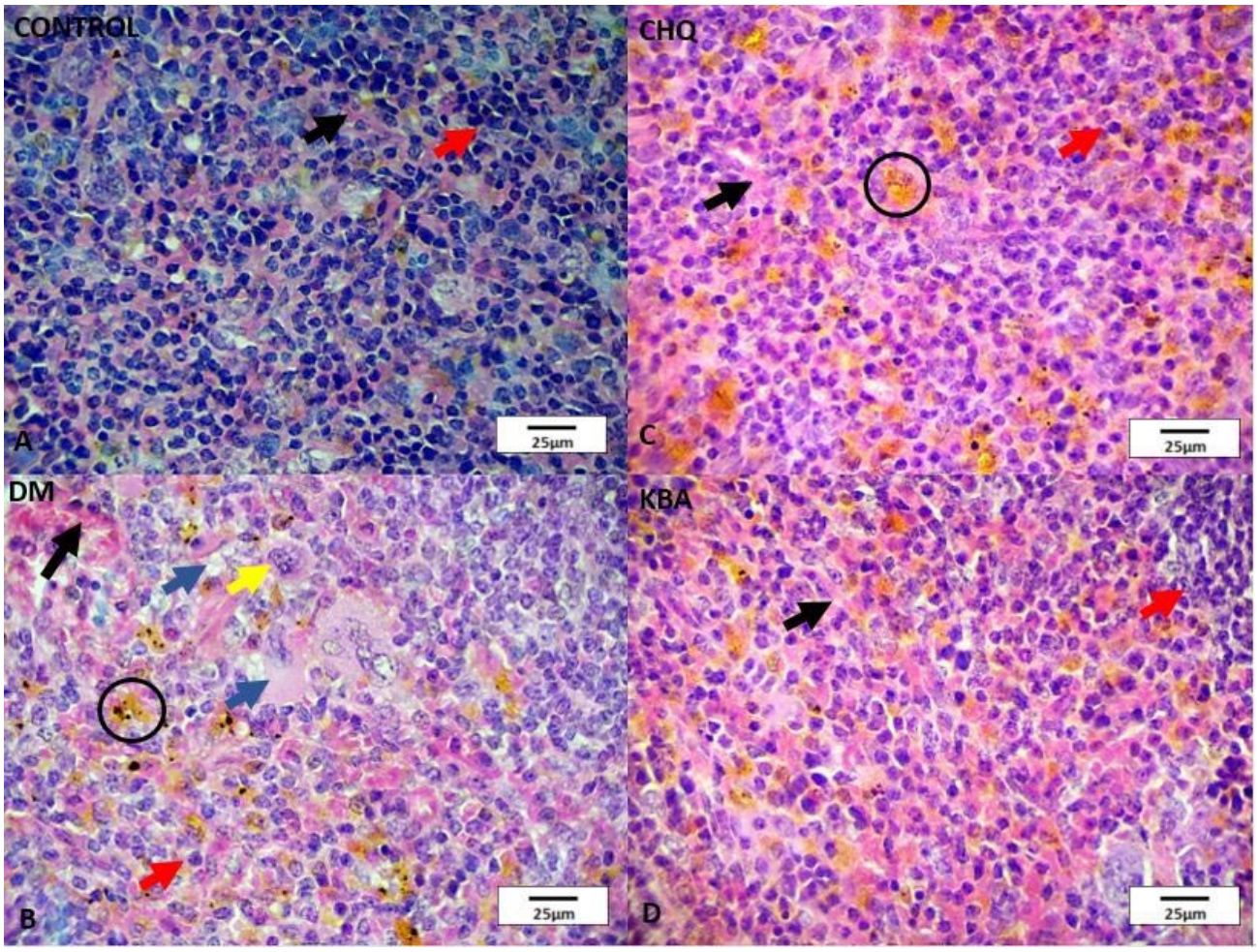


Fig. 3. Hematoxylin and eosin (H&E) staining of spleen tissue sections. (A) Control group showing a normal white pulp architecture with a well-defined central artery (→), densely packed lymphocytes in the germinal center (GC), and a distinct mantle zone (→) surrounded by the marginal zone (H). (B) Untreated DM group exhibiting central artery thickening (→), necrotic changes, and marked lymphocytic reduction in the germinal center (*). (C) DM + CHQ-treated group showing mild central artery thickening (→) and moderate lymphocytic depletion in the germinal center (⇒). (D) DM + KBA-treated group showing an improved white pulp structure with only mild lymphocytic reduction in the germinal center (⇒). (F) Quantitative analysis of white pulp lesions across groups. *P < 0.05 compared with the DM group. Control, healthy animals; DM, diabetic animals; DM + CHQ, diabetic animals treated with CHQ (5-chloro-8-hydroxyquinoline); DM + KBA, diabetic animals treated with 11-keto-β-boswellic acid. Data are expressed as mean ± SEM. 40× magnification, scale bar = 25 µm.



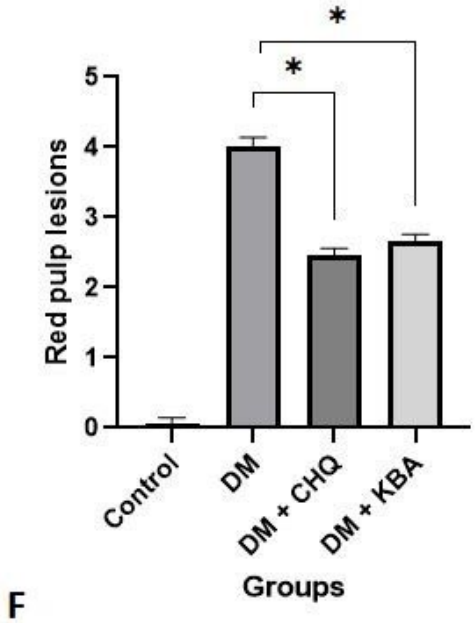


Fig. 4. Hematoxylin and eosin (H&E) staining of spleen tissue sections (red pulp). (A) Control group showing normal red pulp histology with preserved lymphoid cellular density (red arrow), intact splenic cords, and patent sinusoids (→). (B) Untreated DM group exhibiting marked sinusoidal congestion (→), necrotic changes, and lymphoid depletion (blue arrow), accompanied by numerous siderophages (O) and megakaryocytes (yellow arrow). (C) DM + CHQ-treated group and (D) DM + KBA-treated group showing restored red pulp morphology with repopulated lymphocytes (red arrow), organized splenic cords, and normalized sinusoidal architecture (→). (F) Quantitative analysis of red pulp lesions across groups. *P < 0.05 compared with the DM group. Control, healthy animals; DM, diabetic animals; DM + CHQ, diabetic animals treated with CHQ (5-chloro-8-hydroxyquinoline); DM + KBA, diabetic animals treated with 11-keto-β-boswellic acid. Data are expressed as mean ± SEM. 40× magnification, scale bar = 25 µm.

DISCUSSION

Diabetes mellitus is characterized by persistent hyperglycemia, hypoinsulinemia, and progressive weight loss. STZ, a well-established diabetogenic agent, selectively targets pancreatic b-cells, leading to impaired insulin production and subsequent hyperglycemia. Extensive research has explored the mechanisms of STZ-induced b-cell damage and potential protective strategies (Kim *et al*., 2020). These structural alterations and their clinical implications are summarized in Figure 5.

STZ induces apoptosis in b-cells, reducing insulin secretion and causing hyperglycemia (Akwu *et al*., 2024). One primary pathway involves oxidative stress and inflammation, evidenced by increased reactive oxygen species (ROS) and elevated pro-inflammatory cytokines (Liu *et al*., 2021). Despite extensive research, no definitive treatment exists for T1DM and adult-onset autoimmune diabetes (Rehman *et al*., 2023). Recent investigations highlight the antidiabetic properties of boswellic acids, particularly KBA, bioactive compounds derived from frankincense (Ammon, 2019). These acids exhibit anti-inflammatory effects that influence immune mechanisms implicated in both T1DM and T2DM (Gomaa *et al*., 2021). Recent studies confirm KBA's protective effects in experimental diabetes (Khan *et al*., 2022), providing important context for the present work, which is the first to examine KBA's effects on diabetic spleen pathology. Among boswellic acid derivatives, α- and β-boswellic acids and their acetylated forms show limited efficacy, whereas KBA and 3-O-acetyl-11-keto-β-boswellic acid (AKBA) display significant antidiabetic potential (Solanki *et al*., 2024).

Histopathological evaluation revealed significant structural alterations in the spleen of STZ-induced diabetic mice, including thickening of the splenic capsule and disruption of the white pulp architecture (Figs. 2B and 3B). These fibrotic alterations were likely mediated by persistent activation of pro-fibrotic signaling cascades, which are strongly implicated in diabetes-related tissue remodeling (Wu *et al*., 2020). The white pulp, normally composed of a central follicular artery surrounded by dense lymphocytic aggregates, exhibited severe disorganization and fragmentation of the periarteriolar lymphoid sheath (PALS) (Fig. 3B). Lymphocyte depletion, particularly at the periphery of the follicles, was accompanied by noticeable necrotic changes within the germinal centers, suggesting impaired immunologic function. The marginal zone, which serves as the transition between white and red pulp, became indistinct.

Treatment with CHQ and KBA produced noticeable histological improvement, as evidenced by the restoration of lymphoid follicle architecture and reappearance of distinct germinal centers (Figs. 3C-D). The splenic capsule also demonstrated partial and near-complete normalization in CHQ- and KBA-treated groups, respectively (Figs. 2C-D).

The red pulp, responsible for blood filtration and erythrocyte turnover, showed noticeable congestion, degenerative changes, and hemosiderin deposition (Fig. 4B). The presence of siderophages, macrophages laden with hemosiderin granules, indicated excessive erythrocyte destruction and tissue injury. In addition, the detection of megakaryocytes within the red pulp suggests compensatory extramedullary hematopoiesis, reflecting the spleen's maladaptive response to diabetic stress. Collectively, these alterations were statistically significant ($p < 0.05$, one-way ANOVA followed by Tukey's post hoc test), underscoring the detrimental effects of chronic hyperglycemia and inflammation on spleen morphology and immune function.

Administration of KBA and CHQ independently resulted in notable improvements in spleen morphology. In the KBA-treated group, the splenic capsule returned to

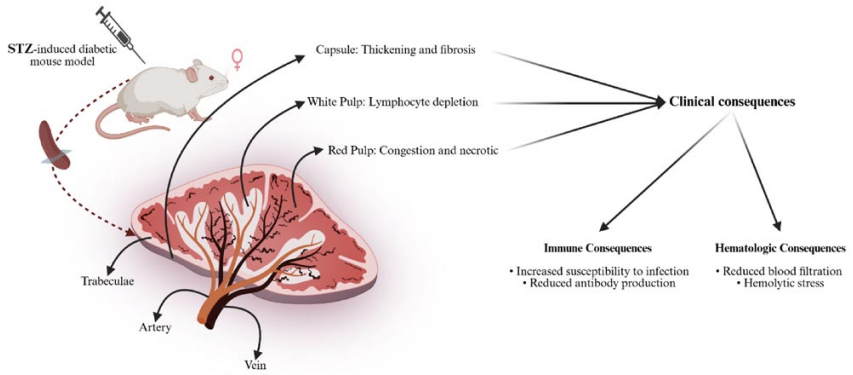


Fig. 5. Schematic representation of splenic pathological changes in STZ-induced diabetic mice. The diagram illustrates diabetes-related alterations in the spleen, including capsular thickening and fibrosis, lymphocyte depletion and necrosis in the white pulp, and congestion/necrosis in the red pulp. These histopathological changes collectively contribute to the observed clinical consequences, namely: (i) immune dysfunction (increased susceptibility to infection and reduced antibody production) and (ii) hematologic impairment (reduced blood filtration and hemolytic stress).

near-normal thickness, and the white pulp regained its structural integrity (Figs. 2D and 3D). Lymphoid follicles were well-organized, with dense lymphocyte populations and intact arteriolar sheaths (Fig. 3D). Necrotic changes in the germinal centers were absent, and the marginal zone was clearly defined, indicating functional restoration of immunological components. The red pulp demonstrated significant repair, with reduced congestion, fewer siderophages, and diminished hemosiderin deposition (Fig. 4D). These observations suggest not only the resolution of inflammation but also the regeneration of splenic tissue, highlighting KBA's potential role in modulating immune function. KBA has also been shown to block lymphocyte migration to pancreatic islets, thereby mitigating autoimmune-mediated diabetic pathology. By limiting immune-mediated β-cell destruction, KBA may serve as a protective agent for pancreatic islets, presenting a promising therapeutic strategy for diabetes prevention (Shehata *et al*., 2017).

Although modest therapeutic enhancements were noted with CHQ administration, its effects were less pronounced than those observed with KBA. The splenic capsule demonstrated modest thinning, while the white pulp showed partial recovery with increased lymphocyte density (Figs. 2C and 3C). The germinal centers, although present, were slightly reduced in size (Fig. 3C). The red pulp demonstrated decreased congestion and degeneration, with fewer siderophages and less hemosiderin accumulation (Fig. 4C). These findings suggest that CHQ exerts a protective effect on the spleen, likely by modulating oxidative stress and immune responses (Chen *et al*., 2025). CHQ (Clioquinol), a derivative of 8-hydroxyquinoline, is known for its antimicrobial, antifungal, anticancer, and neuroprotective properties. Research indicates that CHQ influences inflammatory mechanisms, particularly through the calpain-calpastatin signaling pathway (Chashoo *et al*., 2011). However, alternative studies suggest that 8-hydroxyquinoline derivatives do not significantly impact inflammatory cartilage metabolism (Suwanjang *et al*., 2016). Clinically, CHQ has demonstrated efficacy in treating bacterial, fungal, and protozoal infections, and it is used topically for dermatomycoses, particularly in supportive infections (Ammon, 2019). The present study highlighted the distinct therapeutic effects of KBA and CHQ in mitigating diabetes-induced splenic dysfunction. KBA, a natural triterpenoid, demonstrated significant anti-inflammatory properties by inhibiting pro-inflammatory cytokines and oxidative stress (Moudgil & Venkatesha, 2022), thus promoting immune homeostasis and facilitating spleen tissue regeneration. In contrast, CHQ functioned as an immune modulator, conferring moderate protective effects on splenic morphology. The observed improvements in spleen architecture, particularly the restoration of white-pulp structure and red-pulp function, indicate the potential of both compounds in preserving immune system integrity under diabetic conditions. This analysis suggests that both CHQ and KBA exhibit protective effects on splenic architecture, attenuating diabetes-induced damage and promoting structural restoration. KBA, however, showed superior efficacy in restoring spleen histology compared to CHQ, suggesting greater therapeutic potential. KBA treatment produced near-normal restoration of white and red pulp morphology, reduced inflammation, and lowered siderophage accumulation compared with CHQ (Figs. 2D and 4D). While both compounds demonstrated activity, their precise molecular mechanisms require further elucidation. To the best of our knowledge, this study represents one of the first direct comparative evaluations of laboratory-isolated KBA and commercially sourced CHQ in diabetic splenic pathology. Investigation of combination therapy may uncover synergistic effects that could optimize treatment outcomes. Future studies should prioritize strategy optimization to fully exploit these compounds' potential in managing diabetes-associated immune dysfunction. The noticeable restoration of splenic capsule and lymphoid architecture after KBA treatment aligns with suppression of NF-κB-mediated inflammation and activation of the Nrf2–AMPK antioxidant pathway (Moudgil & Venkatesha, 2022). Additionally, reduced capsular fibrosis is consistent with the inhibition of TGF-b1 signaling (Ali & Mansour, 2011). Collectively, these converging mechanisms provide a mechanistic basis for the histological improvements observed in current diabetic mouse model.

CONCLUSION

In conclusion, both KBA and CHQ demonstrated therapeutic effects against diabetes-induced spleen dysfunction and supported immune homeostasis in diabetic mice. CHQ provided moderate protection, however, KBA extracted and semi-synthesized in our laboratory, showed superior efficacy in spleen tissue regeneration, likely due to its robust anti-inflammatory activity. Future investigations should (1) elucidate the precise molecular mechanisms underlying these effects and (2) evaluate potential synergistic benefits of combined KBA and CHQ therapy for diabetes-related immune dysregulation.

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RESUMEN: La diabetes mellitus (DM) causa disfunción inmunitaria y daño esplénico. Este estudio investigó los efectos terapéuticos del ácido 11-ceto-β-boswélico (KBA), aislado y semisintetizado a partir de la resina de *Boswellia sacra*, y de la 5-cloro-8-hidroxiquinolina (CHQ) de origen comercial sobre el daño esplénico en ratones diabéticos inducidos por estreptozotocina. Veinticuatro ratones hembra CD1 se dividieron en grupos control, diabético, diabético + CHQ y diabético + KBA. Se administró KBA (25 mg/kg/día) o CHQ (25 mg/kg/día) por vía intraperitoneal durante cuatro semanas. Los tejidos del bazo se examinaron histológicamente mediante tinción con hematoxilina-eosina y análisis morfométrico. Los ratones diabéticos mostraron un notable engrosamiento capsular, alteración de la arquitectura de la pulpa blanca, depleción de linfocitos y congestión de la pulpa roja. Ambos tratamientos mejoraron significativamente la estructura esplénica; sin embargo, el tratamiento con KBA produjo una restauración casi normal de la morfología de la pulpa blanca y roja, redujo la inflamación y disminuyó la acumulación de siderófagos en comparación con CHQ. El KBA aislado en laboratorio demostró una protección superior contra la disfunción esplénica inducida por la diabetes, lo que resalta su potencial como un nuevo enfoque terapéutico para las complicaciones inmunitarias asociadas a la diabetes. Se justifican estudios adicionales para definir los mecanismos moleculares subyacentes.

PALABRAS CLAVE: Ácido 11-ceto-β-boswélico; 5-cloro-8-hidroxiquinolina; Bazo; Diabetes mellitus; Histopatología.

REFERENCES

Abbas, G.; Albroumi, M.; Rehman, N.; Hussain, H. & Al-Harrasi, A. Evaluation of essential oils from *Boswellia sacra* and Teucrium mascatense against acetylcholinesterase and urease enzymes. Int. J. Phytomedicine, 8(4):500-5, 2017.

Abugomaa, A. & Elbadawy, M. Olive leaf extract modulates glycerol-induced kidney and liver damage in rats. *Environ. Sci. Pollut. Res. Int., 27(17)*:22100-11, 2020.

Akwu, B. P.; Ajibade, A. J.; Abijo, A. Z. & Adeeyo, O. A. The beneficial role of combinatorial Spondias mombin and metformin treatments in streptozotocin-induced pancreatic damage. *Food Chem. Adv., 4*:100670, 2024.

al-Awadi, F.; Fatania, H. & Shamte, U. The effect of a plant mixture extract on liver gluconeogenesis in streptozotocin-induced diabetic rats. *Diabetes Res., 18(4)*:163-8, 1991.

Al-Harrasi, A.; Rehman, N. U.; Mabood, F.; Albroumi, M.; Ali, L.; Hussain, J.; Hussain, H.; Csuk, R.; Khan, A. L.; Alam, T.; *et al*. Application of NIRS coupled with PLS regression as a rapid, non-destructive alternative method for quantification of KBA in *Boswellia sacra*. Spectrochim. *Acta A Mol. Biomol. Spectrosc., 184*:277-85, 2017.

Al-Mawali, A.; Al-Harrasi, A.; Jayapal, S. K.; Morsi, M.; Pinto, A. D.; Al-Shekaili, W.; Al-Kharusi, H.; Al-Balushi, Z. & Idikula, J. Prevalence and risk factors of diabetes in a large community-based study in the Sultanate of Oman: STEPS survey 2017. *BMC Endocr. Disord., 21(1)*:42, 2021.

Alblihd, M. A.; Alsharif, K. F.; Hamad, A. A.; Ali, F. A. Z.; Hussein, M. T.; Alhegaili, A. S.; Hassan, M. A.; Al-Amer, O. M.; Albezrah, N. K. A.; Almalki, A. A.; *et al*. Okra [Abelmoschus esculentus (L.) Moench] improved blood glucose and restored histopathological alterations in splenic tissues in a rat model with streptozotocin-induced type 1 diabetes through CD8+ T cells and NF-kb expression. *Front. Vet. Sci., 10*:1268968, 2023.

Ali, E. N. & Mansour, S. Z. Boswellic acids extract attenuates pulmonary fibrosis induced by bleomycin and oxidative stress from gamma irradiation in rats. *Chin. Med., 6*:36, 2011.

Ammon, H. P. T. Boswellic extracts and 11-keto-b-boswellic acids prevent type 1 and type 2 diabetes mellitus by suppressing the expression of proinflammatory cytokines. *Phytomedicine, 63*:153002, 2019.

Boynes, J. Role of oxidative stress in development of complications in diabetes. *Diabetes, 40(4)*:405-11, 1991.

Chashoo, G.; Singh, S. K.; Sharma, P. R.; Mondhe, D. M.; Hamid, A.; Saxena, A.; Andotra, S. S.; Shah, B. A.; Qazi, N. A.; Taneja, S. C.; *et al*. A propionyloxy derivative of 11-keto-b-boswellic acid induces apoptosis in HL-60 cells mediated through topoisomerase I & II inhibition. *Chem. Biol. Interact., 189(1-2)*:60-71, 2011.

Chen, P.; Wang, Y.; Tang, H.; Zhou, C.; Liu, Z.; Gao, S.; Wang, T.; Xu, Y. & Ji, S. L. New applications of clioquinol in the treatment of inflammatory disease by directly targeting arginine 335 of NLRP3. *J. Pharm. Anal., 15(1)*:101069, 2025.

Ebaid, H. Promotion of immune and glycaemic functions in streptozotocin-induced diabetic rats treated with undenatured camel milk whey proteins. *Nutr. Metab. (Lond.), 11*:31, 2014.

Genuth, S. M.; Palmer, J. P. & Nathan, D. M. *Classification and diagnosis of diabetes*. En: Cowie, C. C.; Casagrande, S. S.; Menke, A.; Cissell, M. A.; Eberhardt, M. S.; Meigs, J. B.; Gregg, E. W.; Knowler, W. C.; Barrett-Connor, E.; Becker, D. J.; Brancati, F. L.; Boyko, E. J.; Herman, W. H.; Howard, B. V.; Narayan, K. M. V.; Rewers, M. & Fradkin, J. E. (Eds.). Diabetes in America. 3rd ed. Bethesda (MD), National Institute of Diabetes and Digestive and Kidney Diseases, 2018.

George, B.; Cebioglu, M. & Yeghiazaryan, K. Inadequate diabetic care: global figures cry for preventive measures and personalized treatment. *EPMA J., 1(1)*:13-8, 2010.

Gomaa, A. A.; Farghaly, H. A.; Abdel-Wadood, Y. A. & Gomaa, G. A. Potential therapeutic effects of boswellic acids/*Boswellia* serrata extract in the prevention and therapy of type 2 diabetes and Alzheimer's disease. *Naunyn Schmiedebergs Arch. Pharmacol., 394(11)*:2167-85, 2021.

Hippisley-Cox, J. & Coupland, C. Diabetes treatments and risk of amputation, blindness, severe kidney failure, hyperglycaemia, and hypoglycaemia: open cohort study in primary care. *BMJ, 352*:i1450, 2016.

Hossain, M. S.; Wazed, M. A.; Asha, S.; Amin, M. R. & Shimul, I. M. Dietary phytochemicals in health and disease: mechanisms, clinical evidence, and applications—a comprehensive review. *Food Sci. Nutr., 13(3)*:e70101, 2025.

Khan, A.; Khan, I.; Halim, S. A.; Rehman, N. U.; Karim, N.; Ahmad, W.; Khan, M.; Csuk, R. & Al-Harrasi, A. Anti-diabetic potential of b-boswellic acid and 11-keto-b-boswellic acid: mechanistic insights from computational and biochemical approaches. *Biomed. Pharmacother., 147*:112669, 2022.

Kim, H. J.; Kim, D.; Yoon, H.; Choi, C. S.; Oh, Y. S. & Jun, H. S. Prevention of oxidative stress-induced pancreatic beta cell damage by Broussonetia kazinoki fruit extract via the ERK-Nox4 pathway. *Antioxidants (Basel), 9(5)*:406, 2020.

Lebovitz, H. E. Diagnosis, classification, and pathogenesis of diabetes mellitus. *J. Clin. Psychiatry, 62 Suppl. 27*:5-9, 2001.

Li, Y.; Liu, Y.; Liu, S.; Gao, M.; Wang, W.; Chen, K.; Huang, L. & Liu, Y. Diabetic vascular diseases: molecular mechanisms and therapeutic strategies. *Signal Transduct. Target. Ther., 8(1)*:152, 2023.

Lim, K. M.; Song, J. H.; Lim, E. Y.; Kim, G. D.; Lee, S. Y.; Lee, S. H.; Lee, D. K.; Cho, Y. B. & Shin, H. S. Immunomodulatory effects of herbal extract mixture of *Boswellia* serrata, Commiphora myrrha, and propolis in a forced swimming-induced mouse model of immune dysfunction. *Appl. Food Res., 5(1)*:100662, 2025.

Liu, H.; Wang, L.; Li, F.; Jiang, Y.; Guan, H.; Wang, D.; Sun-Waterhouse, D.; Wu, M. & Li, D. The synergistic protection of EGCG and quercetin against streptozotocin-induced NIT-1 pancreatic b cell damage via upregulation of BCL-2 expression by miR-16-5p. *J. Nutr. Biochem., 96*:108748, 2021.

Moudgil, K. D. & Venkatesha, S. H. The anti-inflammatory and immunomodulatory activities of natural products to control autoimmune inflammation. *Int. J. Mol. Sci., 24(1)*:95, 2022.

Nasrollahi, Z.; Shahanipour, K.; Monajemi, R. & Ahadi, A. M. Abelmoschus esculentus improved blood glucose, lipid profile, and down-regulated PPAR-a and PTP1B gene expression in diabetic rats. *J. Food Biochem., 46(7)*:e14097, 2022.

Ni, X.; Suhail, M. M.; Yang, Q.; Cao, A.; Fung, K. M.; Postier, R. G.; Woolley, C.; Young, G.; Zhang, J. & Lin, H. K. Frankincense essential oil prepared from hydrodistillation of *Boswellia sacra* gum resins induces human pancreatic cancer cell death in cultures and in a xenograft murine model. *BMC Complement. Altern. Med., 12*:253, 2012.

Prachayasittikul, V.; Prachayasittikul, S.; Ruchirawat, S. & Prachayasittikul, V. 8-Hydroxyquinolines: a review of their metal chelating properties and medicinal applications. *Drug Des. Devel. Ther., 7*:1157-78, 2013.

Rehman, N. U.; Ullah, S.; Alam, T.; Halim, S. A.; Mohanta, T. K.; Khan, A.; Anwar, M. U.; Csuk, R.; Avula, S. K. & Al-Harrasi, A. Discovery of new boswellic acid hybrid 1H-1,2,3-triazoles for diabetic management: *in vitro* and in silico studies. *Pharmaceuticals (Basel), 16(2)*:229, 2023.

Roy, N. K.; Parama, D.; Banik, K.; Bordoloi, D.; Devi, A. K.; Thakur, K. K.; Padmavathi, G.; Shakibaei, M.; Fan, L.; Sethi, G.; *et al*. An update on pharmacological potential of boswellic acids against chronic diseases. *Int. J. Mol. Sci., 20(17)*:4101, 2019.

Shamraiz, U.; Hussain, H.; Ur Rehman, N.; Al-Shidhani, S.; Saeed, A.; Khan, H. Y.; Khan, A.; Fischer, L.; Csuk, R.; Badshah, A.; *et al*. Synthesis of new boswellic acid derivatives as potential antiproliferative agents. *Nat. Prod. Res., 34(13)*:1845-52, 2020.

Shehata, A. M.; Quintanilla-Fend, L.; Bettio, S.; Kamyabi-Moghaddam, Z.; Kohlhofer, U. A.; Scherbaum, W. A. & Ammon, H. P. T. 11-keto-b-boswellic acid inhibits lymphocyte (CD3) infiltration into pancreatic islets of young non-obese diabetic (NOD) mice. *Horm. Metab. Res., 49(9)*:693-700, 2017.

Shehata, A. M.; Quintanilla-Fend, L.; Bettio, S.; Singh, C. & Ammon, H. Prevention of multiple low-dose streptozotocin-induced diabetes in mice by an extract from gum resin of *Boswellia* serrata. *Phytomedicine, 18(12)*:1037-44, 2011.

Solanki, N.; Gupta, G.; Chellappan, D. K.; Singh, S. K.; Gulati, M.; Paudel, K. R.; Hansbro, P. M.; Dua, K.; Bhan, S.; Saini, M.; *et al*. Boswellic acids: a critical appraisal of their therapeutic and nutritional benefits in chronic inflammatory diseases. *Endocr. Metab. Immune Disord. Drug Targets, 24(1)*:116-29, 2024.

Suwanjang, W.; Prachayasittikul, S. & Prachayasittikul, V. Effect of 8-hydroxyquinoline and derivatives on human neuroblastoma SH-SY5Y cells under high glucose. *PeerJ, 4*:e2389, 2016.

World Health Organization. *Diabetes*. Geneva, World Health Organization, 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes

Wu, Y.; Jia, G.; Wang, B.; Xiong, J.; Xu, J.; Zheng, P.; Yuan, Y.; Li, Y.; Jiang, T.; Al Mamun, A.; *et al*. Fibroblast growth factor 1 ameliorates diabetes-induced splenomegaly via suppressing inflammation and oxidative stress. *Biochem. Biophys. Res. Commun., 528(2)*:249-55, 2020.

Yousif, J. H.; Khan, F. R.; Zia, K. & Saadi, N. A. Analytical data review to determine the factors impacting risk of diabetes in North Al-Batinah Region, Oman. *Int. J. Environ. Res. Public Health, 18(10)*:5323, 2021.

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