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Regulation of Macrophage Metabolism by Traditional Plant-Based Extracts Under High-Glucose and Inflammatory Stress: An in vitro study

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تنظيم عملية التمثيل الغذائي للبلعميات باستخدام المستخلصات النباتية التقليدية تحت ارتفاع مستوى الجلوكوز والإجهاد الالتهابي: دراسة معملية

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Abstract:

Background: Chronic inflammation associated with diabetes often lead to abnormal lipid levels and oxidative stress, both of which play a key role in the progression of metabolic syndrome. Researchers continue to investigate medications aimed at preventing or managing diabetes-related complications. This study investigated the therapeutic potential of three herbal extracts by assessing their impact on macrophage oxidative bioactive marker expression in metabolic disorders and comparing the results with those of conventional Western medicine. **Method**: In this study, the following inhibited concentrations were applied to treat LPS-stimulated inflammation in high-glucose mimic cell cultures: Artemisia afra (200 µg/ml), Cinnamon verum (250 µg/ml), Fenugreek (2500 µg/ml), and metformin (200 µg/ml). **Results**: LPL is significantly overexpressed, while SOD-2 activity is suppressed in the presence of high glucose, both with and without stimulation by LPS-activated macrophage cells. *A. afra* and *C. verum* extracts promoted cell growth under high glucose conditions more effectively than *Fenugreek* and *metformin*. *Cinnamon verum* significantly enhances the antioxidant enzyme SOD-2 and effectively downregulates the LPL enzyme under high glucose conditions, both in the presence and absence of stimulation. Compared to *Artemisia afra, fenugreek*, or *metformin.* **In conclusion:** These herbs help regulate metabolic markers in diabetic patients may help prevent diabetes progression, treat atherosclerosis, and manage chronic inflammation while supporting glucose control. Future investigations are essential to identify and understand the bioactive molecules in these herbal therapies involved in this protocol.

Keywords: Diabetes mellitus, High glucose, Metabolic syndrome, Artemisia afra, Cinnamon verum, Fenugreek., Inflammation.

الملخص:

الخلفية: غالبًا ما يؤدي الالتهاب المزمن المرتبط بمرض السكري إلى مستويات غير طبيعية من الدهون والإجهاد التأكسدي، وكلاهما يلعب دورًا رئيسيًا في تطور متلازمة التمثيل الغذائي. يواصل الباحثون البحث في الأدوية التي تهدف إلى منع أو إدارة المضاعفات المرتبطة بمرض السكري. بحثت هذه الدراسة في الإمكانات العلاجية لثلاثة مستخلصات عشبية من خلال تقييم تأثيرها على العلامة الحيوية المؤكسدة للخلايا البلعمية في الاضطرابات الأيضية ومقارنة النتائج مع نتائج الطب الغربي التقليدي. **الطريقة**: في هذه الدراسة، تم تطبيق التركيزات المثبطة التالية لعلاج الالتهاب المحفز بواسطة LPS في مزارع الخلايا المقلدة عالية الجلوكوز: Artemisia afra (200 ميكروغرام / مل)، Cinnamon verum (250 ميكروغرام / مل)، Fenugreek (2500 ميكروغرام / مل)، وMetformin (200 ميكروغرام / مل). **النتائج**: تم التعبير عن LPL بشكل مفرط بشكل ملحوظ، بينما تم قمع نشاط SOD-2 في وجود نسبة عالية من الجلوكوز، سواء مع أو بدون تحفيز من قبل الخلايا البلعمية المنشطة بواسطة LPS. عززت مستخلصات الشيح الأفرا والقرفة فيروم نمو الخلايا في ظل ارتفاع مستوى الجلوكوز بشكل أكثر فعالية من الحلبة والميتفورمين. يعزز مستخلص القرفة فيروم بشكل ملحوظ إنزيم SOD-2 المضاد للأكسدة، ويُخفّض بشكل فعال إنزيم LPL في ظل ارتفاع مستوى الجلوكوز، سواءً بوجود التحفيز أو غيابه. بالمقارنة مع الشيح الأفرا أو الحلبة أو الميتفورمين. **الخلاصة**: أثبتت الدراسة أن هذه الأعشاب تساعدعلى تنظيم المؤشرات الأيضية لدى مرضى السكري، وقد تُساعد في منع تطور داء السكري، وعلاج تصلب الشرايين، وإدارة الالتهابات المزمنة، مع دعم ضبط مستوى الجلوكوز. المستقبلية ضرورية لتحديد وفهم الجزيئات النشطة بيولوجيًا في هذه العلاجات العشبية المشاركة في هذا البروتوكول.

الكلمات المفتاحية :داء السكري، ارتفاع نسبة الجلوكوز، متلازمة التمثيل الغذائي، الشيح الأفرا، القرفة فيروم، الحلبة، الالتهاب.

Introduction

Metabolic disorders are defined by elevated blood sugar levels, abnormal lipid profiles, high blood pressure, and weakened bone density. [1,2] Dyslipidaemia and hyperglycaemia are components of the common pathological condition known as metabolic syndrome in diabetes mellitus. [3] Cholesterol and triglycerides are carried alongside proteins and removed from circulation by lipoprotein lipase (LPL). This enzyme is essential for lipid transport from the liver to peripheral tissues and for reverse cholesterol transport. [4,5] Type 2 diabetes mellitus (T2DM) is frequently linked to metabolic stress resulting from an excess of lipoproteins and free radical species. [6]

Accumulated lipids within macrophages serve as precursors to foam cells in the sub-endothelial layer, contributing to the formation of atherosclerotic lesions. [7,8] LPL in macrophages plays a crucial role in increasing the risk of atherosclerosis by serving as a molecular link between lipoproteins and cell surface receptors. [9,10] The increased lipid buildup and oxidation trigger an inflammatory reaction in the arterial wall, leading to the formation of foam cells. [11,12] The regulation of LPL can reduce inflammatory cytokine expression and alter the lipid composition and foam plaque formation in macrophages. [13]

LPL is encoded by the same gene, but its expression, regulation, and function vary significantly across different cell types. In macrophages, LPL primarily

facilitates lipid uptake in immune cells, a process often linked to pathological conditions like atherosclerosis. In skeletal muscle, LPL plays a key role in providing energy for muscle contraction, especially during extended exercise or fasting. Meanwhile, in adipose tissue, LPL activity increases to store surplus dietary fat, enabling adipocytes to absorb and re-esterify it into triglycerides for long-term storage. [14]

Oxidative low-density lipoprotein (Ox-LDL), formed from excess circulating LDL in diabetic individuals, promotes adipocyte proliferation by enhancing macrophage infiltration. [15] These mechanisms that enhance macrophage expression of LPL lead to the buildup of free fatty acids (FFA) in both adipocyte and non-adipocyte tissues.[16] Additionally, changes in Ox-LDL production result in reduced adipokine levels, including the release of antioxidant mediators that suppress reactive oxygen species (ROS) synthesis.[17] A recent study reported that elevated Ox-LDL levels in individuals with hyperlipidemia may result from a reduced antioxidant capacity, including diminished activity of the superoxide dismutase-2 (SOD-2) enzyme. [18]

Elevated ROS levels lead to heightened oxidative stress (OS) as antioxidants, including catalase and SOD-2, fail to effectively neutralize ROS. [19] Additionally, hyperglycemia contributes to OS induction, promotes pro-inflammatory markers, and reduces the expression of the SOD-2 enzyme. [20,21] Consequently, targeting the regulation of LPL and SOD-2 could serve as a potential approach for addressing microvascular complications in T2DM. [22]

The physicochemical properties, chemical compositions, and biological activities of *artemisia afra*, *Cinnamon verum*, and *fenugreek* suggest their potential as pharmacological agents for industrial applications in treating diabetes mellitus and its associated complications. [23, 24, 25] The chemical composition of *fenugreek* seeds reveals that hexadecanoic acid is present in the highest concentration at 31.06%. This compound has demonstrated potential for anti-inflammatory and anti-diabetic activities. [26] In the case of *C. verum* extract, the primary bioactive component is cinnamaldehyde, which constitutes 89.31% of the extract. This compound may help lower levels of low-density lipoprotein (LDL) and triglycerides (TG). [27, 28] Additionally, the major compounds found in *A. afra* are artemisia ketone (36.05%) and 1,8-cineole (18.15%). Both of these phytochemical substances have shown potential for anti-inflammatory, antioxidant, and anti-diabetic activities. [29]

Controlling hyperglycemia is a key priority in managing T2DM and its associated complications, with an emphasis on reducing hyperlipidemia and oxidative stress-induced chronic inflammation. This study investigated the

expression levels of macrophage bioactive markers associated with metabolic disorders contributing to the pathogenesis of T2DM and examines the therapeutic potential of herbal remedies in modulating their activity.

Materials and Methods

Materials

Dulbecco's Modified Eagle's Medium (DMEM) was sourced from Lanza (Belgium), and Minimum Essential Medium (MEM), high D-glucose, 10% Bovine Serum Albumin (BSA), and metformin solution were obtained from Sigma-Aldrich (Germany). The mouse macrophage cell line came from Thermo Fisher Scientific (USA). The XTT labeling reagent was purchased from Roche Diagnostic GmbH (Germany), and Lipopolysaccharide (LPS) derived from Escherichia coli 0111: B4 was obtained from Amersham Biosciences (UK Ltd). Human/Mouse SOD-2 ELISA kits and p-Nitrophenyl-palmitate were also sourced from Sigma-Aldrich (Germany). Ethanolic extracts of Artemisia afra, Cinnamon verum, and Fenugreek were prepared using 70% ethanol.

Methods

Assay of Cell viability

Macrophage cells were cultured in DMEM with 10% heat-inactivated FBS, 0.2 mM L-glutamine, 1% antibiotic-antimycotic solution, and 1% gentamycin, incubated at 37°C with 5% CO2 until 70–80% confluence. [30] They were then seeded into a 96-well plate at 1×10^5 cells per well and grown to 50–60% confluence before switching to MEM medium with the same supplements. The cells were divided into two groups: –LPS and +LPS, under low glucose (5 mM) and high glucose (25 mM) conditions. After 24 hours of incubation, the supernatant was removed, and cells were treated with A. afra, metformin, C. verum, or fenugreek extracts in 0.5% FBS-MEM. XTT reagent (50 µl) was added, and cell viability was measured at 450 nm using an ELISA plate reader initially and every 10 minutes for 40 minutes. [31]

Assay of Lipoprotein lipase

The expression of LPL in macrophages stimulated by high glucose (HG) and LPS was analyzed using a colorimetric assay. Activation of LPL was achieved using p-nitrophenyl-palmitate (p-NP palmitate) as the substrate. The substrate stock solution consisted of 30 mM p-NP palmitate dissolved in 10 ml of 2-isopropanol. The buffer was prepared by combining 602 mg of a Tris derivative, 100 mg of Arabic gum, and 400 µl of Triton X-100, and adjusting the pH to 8 with HCl. The reaction mixture was prepared by mixing 135 µL of

a 1:10 dilution of the substrate stock with the buffer and 15 µL of cell extract, followed by incubation at 37°C. Lipase activity was determined by measuring the release of p-nitrophenol at 410 nm. [32]

Assay of Superoxide Dismutase Enzyme Activities

To examine the regulation of macrophage SOD-2 expression, the macrophage cell line was exposed to HG conditions combined with LPS stimulation. Four distinct measurements of macrophage cell lysates associated with HG and LPS were treated with ethanol extracts of herbal agents and analyzed following the manufacturer's guidelines. [33]

Statistical analysis

Statistical analysis was conducted using ANOVA through Sigma Plot software. Data are expressed as means ± standard, with statistical significance defined at $P < 0.01$. The majority of experiments were carried out in triplicate.

Results

Effects of Artemisia afra and Metformin on the Viability of Macrophage Cells.

The cytotoxic effects of *A. afra* and *metformin* on macrophage cells were assessed using an XTT assay. The results indicated that ethanol extracts of *A. afra* and *metformin* solution showed no toxicity on macrophage cell viability at a concentration of 200 µg/mL. Additionally, *A. afra* demonstrated enhanced cell growth under 5- and 25-mM glucose conditions, both with and without LPS stimulation, compared to *metformin* (Figure 1 (a and b)).

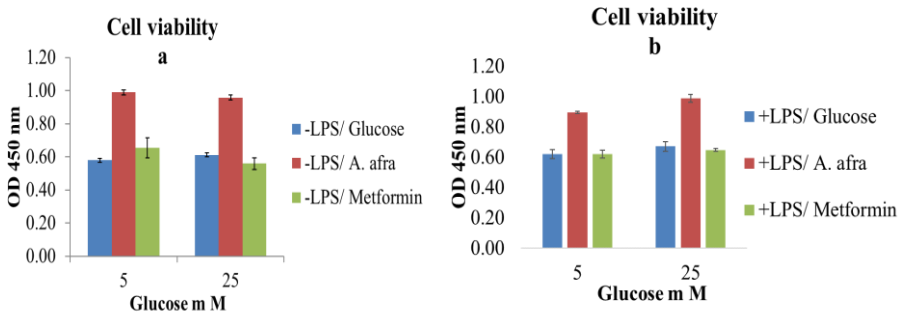

Figure 1. *A. afra* promotes cell growth in both 5 mM and 25 mM glucose conditions, regardless of LPS stimulation, whereas *metformin* has no impact on macrophage cell viability (a and b).

Regulation of macrophage cell lipoprotein lipase activity by Artemisia afra and metformin.

LPL enzyme activity plays a critical role in lipid metabolism. To investigate its behaviour, the effects of HG on LPS-induced macrophage cell expression were analyzed, along with an assessment of whether *A. afra* or *metformin* could regulate LPL, a key factor in early foam cell formation. The findings revealed that HG, both with and without LPS, significantly elevated LPL expression compared to low glucose (LG) under similar conditions ($P < 0.001$). Additionally, the study demonstrated that *A. afra* extract and *metformin* solution at concentrations of 200 µg/ml effectively downregulated LPL activity, as depicted in Figure 2 (a and b).

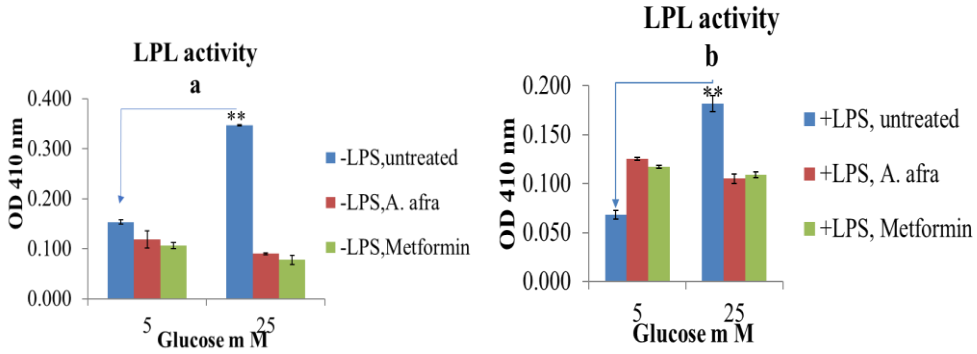

Figure 2. *A. afra* and *metformin* extracts significantly deceased LPL activity in macrophages under HG conditions with LPS, normalizing activity compared to LG-stimulated and unstimulated cells (a and b).

Regulation of SOD-2 activity in macrophage cells by Artemisia afra and metformin

The SOD-2, a key defence mechanism against oxidative stress (OS), was assessed to determine the antioxidative effects of *A. afra* and *metformin* in regulating oxidation factors. The findings revealed a statistically significant reduction in SOD-2 levels caused by HG, both with and without LPS stimulation ($P < 0.001$). In HG conditions without LPS, *A. afra* and *metformin* significantly upregulated SOD-2 expression ($P < 0.001$), as illustrated in Figure 3 (a). There was no significant effect of *A. afra* or *metformin* on macrophage cell SOD-2 expression under HG conditions with LPS stimulation, as illustrated in Figure 3 (b).

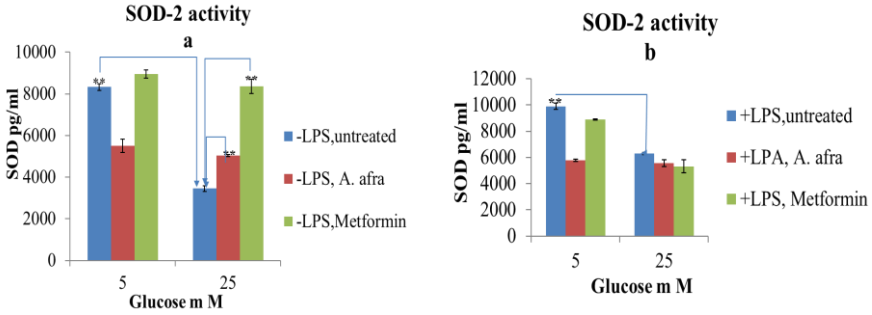

Figure 3. A. afra and metformin extracts increased SOD-2 expression in macrophage cells under high glucose (HG) conditions ($P < 0.001$), but only without LPS stimulation. No changes were seen with LPS stimulation.

Effects of *Cinnamon verum* and *fenugreek* on viability of Macrophage cell

We first evaluated the impact of treatments on macrophage cell viability. Cells were exposed to LG and HG conditions and incubated at 37°C for 24 hours, followed by treatment with 250 µg/ml and 2500 µg/ml concentrations of *C. verum* and *fenugreek* extracts, respectively, for an additional 24 hours. The findings revealed enhanced cell growth induced by *C. verum* under both LG and HG conditions, with or without LPS stimulation (Figure 4 (a and b)). Similarly, *fenugreek* extract demonstrated increased cell growth in HG conditions with LPS stimulation (Figure 4 (b)).

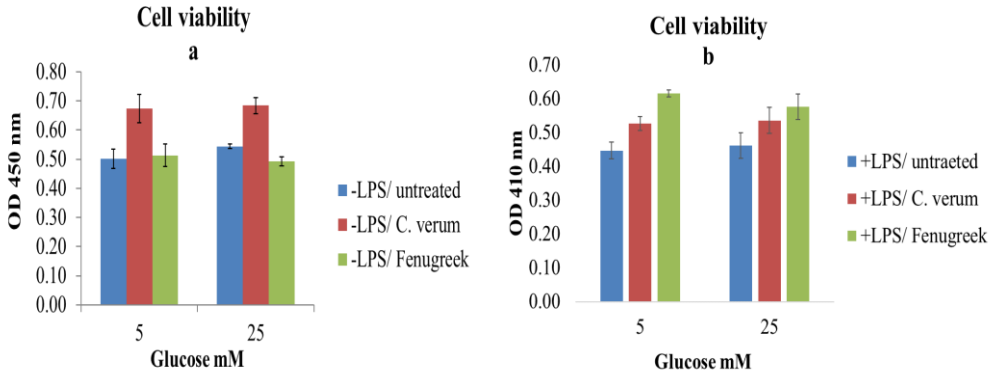

Figure 4. Cinnamon verum and fenugreek improved macrophage viability under HG with LPS, while Cinnamon verum also boosted growth in LG and HG without LPS, (a and b).

Regulation of macrophage cell lipoprotein lipase activity by Cinnamon verum and fenugreek

The present study examined the effect of *C. verum* and *fenugreek* extracts on macrophage LPL activity. The findings revealed that HG, both with and

without LPS, significantly elevated LPL expression compared to LG, with and without LPS ($P < 0.001$). Using concentrations of 250 and 2500 µg/ml, *C. verum* and *fenugreek* extracts demonstrated a significant down-regulation of LPL activity in macrophage cells stimulated by HG with and without LPS ($P < 0.001$), as represented in Figure 5 (a and b).

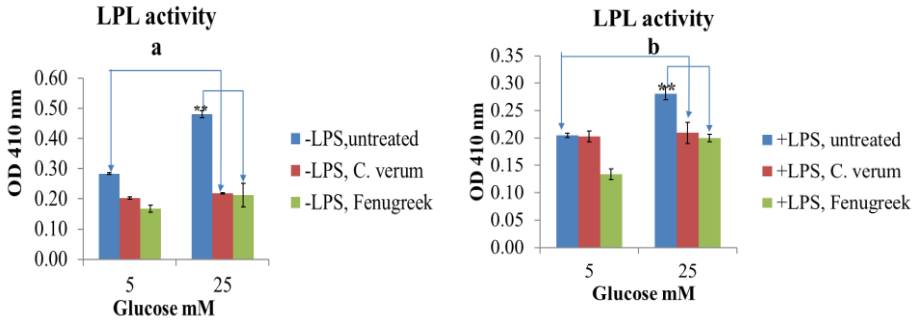

Figure 5. Increased expression of LPL compared to LG with and without LPS-stimulated cells. *C. verum* and *fenugreek* extracts show down-regulation of LPL activity in HG with and without LPS-stimulated cells (a and b).

Regulation of SOD-2 activity in macrophage cells by Cinnamon verum and fenugreek.

In this study, we examined SOD-2 secretion in macrophage cells to assess the ability of *C. verum* and *fenugreek* extracts to modulate antioxidant factors. Our findings revealed that SOD-2 levels were significantly reduced by HG, both with and without LPS stimulation ($P < 0.001$). The *C. verum* extract demonstrated a concentration-dependent upregulation of SOD-2 activity, showing significant differences in LG and HG conditions with and without LPS stimulation ($P < 0.001$) (Figure 6 (a and b). Conversely, *fenugreek* extract exhibited no effect on SOD-2 expression in macrophage cells under HG conditions with LPS stimulation (Figure 6 (b).

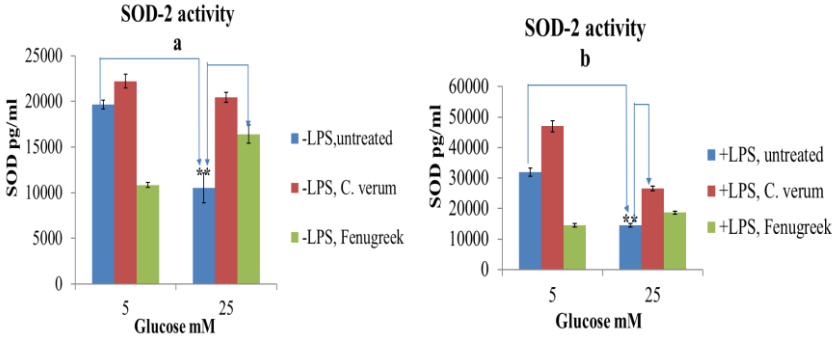

Figure 6. *C. verum* extract significantly increased SOD-2 levels in LG and HG, both with and without LPS stimulation. *Fenugreek* extract showed no effect on SOD-2 expression under LPS stimulation.

Discussion

T2DM is often accompanied by various diseases, leading to metabolic disturbances and contributing to OS and inflammation. [34] Identifying innovative regulators capable of mitigating inflammatory responses and OS represents a crucial approach to preventing diabetes-related complications. [35] In light of this, the present study examines the potential of certain herbal therapies in comparison to conventional Western medicine to assess their viability as therapeutic strategies for halting the progression of diabetes complications.

The study aimed to investigate the impact of *A. afra*, *C. verum*, *fenugreek* extracts, and *metformin* on macrophage cells subjected to HG-induced LPS stimulation. Findings indicated that LPL activity is markedly overexpressed in the presence of HG, both with and without LPS-stimulated macrophage cells. These findings are supported by the observations documented in two earlier studies. [36,37]

The extracts of *A. afra*, *C. verum*, *Fenugreek and metformin* solution were found to inhibit LPL activity in both LG and HG conditions, regardless of LPS stimulation. Similarly, previous studies have shown that *A. afra* extract appears to enhance antioxidant defence mechanisms and mitigate lipid peroxidation in diabetic rats. [38] In addition, *metformin* reduces lipid synthesis by activating mitogen-activated protein kinases. [39] However, Currently, no studies have evaluated the effects of *A. afra*, *C. verum*, *fenugreek* extracts, and *metformin* on regulating LPL activity in macrophage cells trials related to metabolic disorders associated with diabetes.

In the context of T2DM, alterations in antioxidant factors, such as SOD-2 enzyme levels, contribute to diabetes-related complications. [40] The study demonstrated that HG inhibited SOD-2 activity in macrophages, regardless of LPS stimulation, consistent with previous research showing that increased ROS production contributes to decreased SOD-2 levels in dyslipidaemia. [41] This condition contributes to the development of atherosclerosis, endothelial dysfunction, and complications of metabolic syndrome. [42] In this study, *A. afra* and *C. verum* extracts promoted cell growth under high glucose conditions more effectively than *Fenugreek* and *metformin*. These may compounds derived from *A. afra and C. verum* may directly scavenge ROS generated under

high glucose conditions, stabilize mitochondrial function, and activate cell survival pathways. [43]

The study's findings revealed that *C. verum* enhances the antioxidant enzyme SOD-2 under HG conditions, both in the presence and absence of macrophage cell stimulation. Conversely, *A. afra*, *fenugreek*, and *metformin* were shown to upregulate SOD-2 in HG conditions without stimulation. Earlier studies have demonstrated that *A. afra* restores isoproterenol levels, which are linked to decreased SOD-2 levels in rats. [38] Furthermore, previous study highlighted that *fenugreek* seeds raise hepatic SOD-2 activity during oxidative stress associated with colon cancer. [44] Furthermore, the findings suggest that the regulation of inflammation factors may occur through the generation of SOD-2, which reduces LPL-induced oxidative stress. [45] Our research confirms that inhibiting macrophage-derived LPL activity has beneficial effects on lipid accumulation and inflammatory responses in diabetes mellitus. [46]

The development of T2DM is associated with OS and chronic inflammation, which contribute to dyslipidemia and microvascular complications of diabetes. Therefore, it is recommended to evaluating the effect of antioxidants and lipid-regulating agents is advised to mitigate chronic inflammation associated with diabetes and reduce the risk of its complications. [47,48] This study confirmed that certain herbal therapies may inhibit LPL activity and possess antioxidant properties. As the results of this study, traditional therapies, such as *C. verum*, show greater promise as new treatment options for diabetes in patients with metabolic disorders, due to the suppression of LPL.

Conclusion

T2DM remains one of the most prevalent complex disorders characterized by prolonged hyperglycemia and dyslipidemia, often associated with oxidative stress and chronic inflammation. Current research continues to explore effective medications to prevent or manage diabetes-related complications. Findings from this study highlight that *C. verum* demonstrates superior antioxidant activity and more efficient regulation of LPL activity compared to *A. afra*, *fenugreek*, and *metformin*. These results suggest promising potential for novel therapeutic strategies in addressing metabolic disorders linked to diabetes. Future investigations are essential to identify and understand the bioactive molecules in these herbal therapies involved in this protocol.

Abbreviations

LPL: lipoprotein lipase

T2DM: Type 2 diabetes mellitus

Ox-LDL: Oxidative low-density lipoprotein

FFA: Free fatty acids

ROS: Reactive oxygen species

SOD-2: Superoxide dismutase-2

DMEM: Dulbecco's Modified Eagle's Medium

MEM: Minimum Essential Medium

BSA: Bovine Serum Albumin

LPS: Lipopolysaccharide

ELISA: Enzyme-Linked Immunosorbent Assay

HG: High glucose

LG: Low glucose

OS: Oxidative Stress

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Conflict of Interest

There is no conflict of interest.

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