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# Effect of lupeol on insulin resistance in adipose tissue by modulating the expression of insulin and inflammatory signaling molecules in high-fat diet and sucrose-fed diabetic rats

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ISSN 0973-2063 (online) 0973-8894 (print)
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**Abstract:**
The prevalence of obesity and diabetes has increased globally as a result of lifestyle modifications including eating a high-fat diet and not exercising. The target tissues to insulin action are the key pathophysiological event contributing to the development of type 2 diabetes mellitus. The treatments for type 2 diabetes that are now accessible are ineffectual due to their unfavourable side effects. Hence, search drugs, from plant sources. Lupeol is widely present in various medicinal plants. It has been reported to elicit multitude of bioactivities including antilipidemic and antihyperglycemic activity. However, specific effect of Lupeol on insulin signaling molecules of adipose tissue remains unclear. Hence, the study aimed to assess the beneficial role of Lupeol on the expression of insulin‑signaling molecules in adipose tissue of high fat diet and sucrose-induced type‑2 diabetic rats. The oral effective dose of lupeol at a dose of 25 mg per kg body weight per day orally for 30 days is observed. Lupeol, being a powerful antioxidant agent, normalises hyperglycemia, dyslipidaemia, and hyperinsulinemia while also suppressing oxidative stress by scavenging high levels of ROS. It also enhances insulin signalling in type 2 diabetic rats in adipose tissues. Lupeol administration decreased the levels of pro-inflammatory cytokines, which may be due to lupeol's possible antioxidant and anti-inflammatory activities, and thus it promotes insulin sensitivity via altering pro-inflammatory signalling molecules in adipose tissue such as IL-6, TNF alpha, and NFkB. As a result of the current findings, it is concluded that lupoel possesses potent anti-diabetic characteristics and could be used as a phytomedicine for the treatment of type 2 diabetes.

**Keywords:** Type 2 diabetes; lupeol; high fat diet; sucrose; adipose tissue

**Background:**
Diabetes mellitus is defined by aberrant serum insulin levels or insensitivity of target tissues to insulin action and is associated with improper carbohydrate, lipid, and protein metabolism **[1].** Diabetes affects 425 million people worldwide in 2017, with the number expected to rise to roughly 629 million by 2045 **[2].** Diabetic ketoacidosis, non-ketotic hyperosmolar coma, and diabetic coma are the acute consequences of diabetes. The chronic complication is caused by prolonged blood sugar rise, which damages blood vessels and causes dysfunction and failure of numerous organs, particularly the eyes, kidneys, nerves, and heart **[3].** The currently available medications for diabetes control have some drawbacks, necessitating the search for safer and simpler anti-diabetic drugs **[4].** The development process in anti-diabetic medication discovery has moved its focus to plant-derived therapies due to their safety, efficacy, cultural acceptability, and lower side effects **[5].** Lupeol has numerous pharmacological qualities, including anti-inflammatory and antioxidant potential **[6]**, anti-dyslipidemic **[7]**, and anti-hyperglycemic action **[8].** Sunitha et al. **[9]** discovered that lupeol had antimutagenic action both in vitro and in vivo. Lupeol has been demonstrated to decrease tumour growth by affecting critical molecular signalling molecules, cell proliferation, cell survival, and caspase-mediated cell death. Most notably, lupeol did not have any negative effects on normal cells at the concentration at which it kills malignant cells **[10].** Lupeol may be useful for the management of diabetes, according to research by Salehi et al. **[11].** Lupeol significantly inhibited protein tyrosine phosphatase 1 B (PTP1B), a negative regulator of the insulin signalling pathway and a promising potential therapeutic target, in diabetic rats that had been treated with it. It also increased the serum insulin antioxidant enzymes **[12].** According to preliminary research on lupeol's impact on antidiabetic activity, type-2 diabetic rats fed a high-fat diet and sucrose experienced much less hyperglycemia when given the drug orally at a dose of 25 mg/kg body weight. Lupeol may affect insulin and inflammatory signaling molecules, but the exact mechanisms are unknown. The current study sought to ascertain how lupeol aids influenced adipose tissue in rats with type 2 diabetes caused by a high-fat diet and sugar intake.

Table 1: Effect of lupeol on profiles (TC, TG, HDL, LDL, VLDL and FFAs) in high fat diet and sucrose-fed rats. Each bar represents mean ± SEM of 5 animals. Significance at $p< 0.05$.a-compared to control; b-compared to diabetic control; c- compared to diabetic control treated with lupeol.

| Assay | Normal control | Diabetic control | Diabetic control+ lupeol | Diabetic control+ metformin |
|---|---|---|---|---|
| $H_2O_2$ | 31±2.8 | 63±2.2[a] | 40±1.3[a,b] | 35±2[b,c] |
| LPO | 135±7.6 | 190±11.2[a] | 152±.46[a,b] | 149±6.14[a,b] |
| *OH | 288±11.50 | 392±14.26[a] | 312±9.26[a,b] | 302±12.67[a,b] |

**Materials and Methods:**
**Chemicals:**
Sigma Aldrich Company supplied the lupeol (Bommasandra-Jigani Link Road, Bengaluru - 560 100, India). All other chemicals and reagents were obtained from Sisco Research Laboratories in Mumbai, India; Amersham Biosciences in the United Kingdom; and MP Biomedicals in India. ACON Laboratories in the United States provided the blood glucose estimate kit, and Sprinreact in Spain provided the lipid estimation kit. Sigma Aldrich Company Bommasandra-Jigani Link Road, Bengaluru - 560 100, India) provided IR, IRS-2, Akt, GLUT4 and -actin specific primers for Real Time PCR analysis. ABBKINE provided insulin, TNF-alpha, NFkB, and IL-6 rat ELISA kits (Bldg C17, Optics Valley International Biomedicine Park, Wuhan, China. 430223).

**Animals:**
Healthy adult male albino rats of the Wistar strain, weighing between 180 and 200 g, were kept in clean polypropylene cages at the Central Animal House Facility available in Meenakshi Medical College and Research Institute under humidity and temperature control with a constant 12 h light and 12 h dark schedule in accordance with National Guidelines of institutional animal ethics committee (IAEC no: 006/2016).

**Induction of type-2 diabetes in animal model:**
Animals were given high-fat diets containing coconut oil (30%), conventional rat diet (66%), cholesterol (3%), cholic acid (1%) and sucrose (30%) for 60 days in order to cause type 2 diabetes. After giving the animals a high-fat diet and sucrose, the animals were held for an overnight fast before having their blood sugar levels

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 19(4): 445-453 (2023)


checked. Type 2 diabetic animals were chosen when the blood sugar level was greater than 120 mg/dL.

**Experimental design:**
Healthy adult male rats were divided into five groups each consisting of 6 animals.
Group I: Control (vehicle treated).
Group II: High fat diet-induced type-2 diabetic rats.
Group III: Diabetic rats treated with lupeol at the concentration of 25mg/kg body weight/day, orally for 30 days.
Group IV: Diabetic rats treated with standard drug metformin at the concentration of 50mg/kg, b.wt/day orally for 30days.

At the day of 28 the animals were tested for oral glucose tolerance test (OGT) and insulin tolerance test (ITT). On 30th day of treatment, animals were anesthetized by giving sodium thiopentone at the concentration of 40 mg/kg body weight, blood was drained by cardiac puncture, separated sera and stored at - 80°C and the animals were perfused with 20ml of isotonic sodium chloride solution to clear blood from the organs. Adipose tissue from control and experimental animals were dissected out and used for the assessment of gene expression, oxidative stress makers and glycogen level.

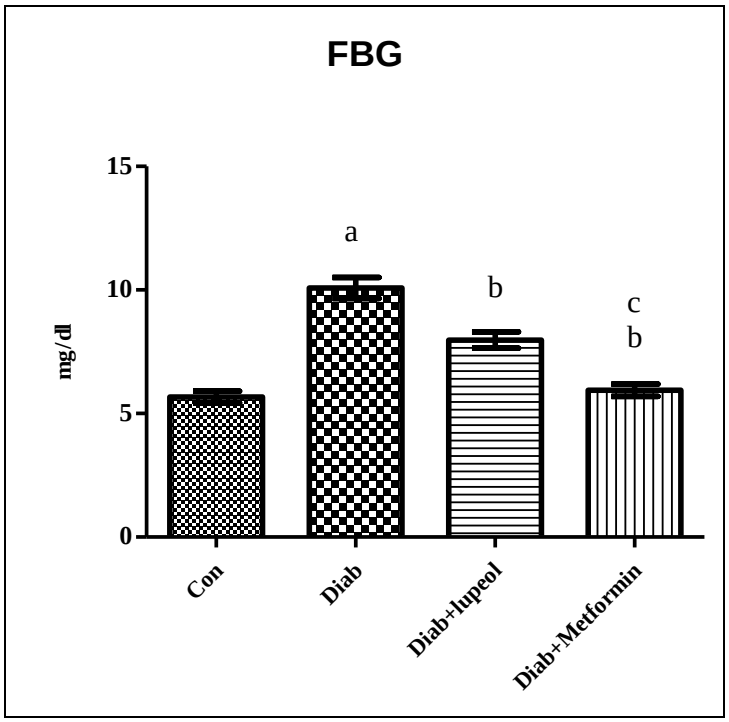


**Figure 1:** Effect of lupeol on fasting blood glucose in type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05,a-compared with control; b-compared with Diabetes; c-compared withdiabetic animal treated with lupeol.

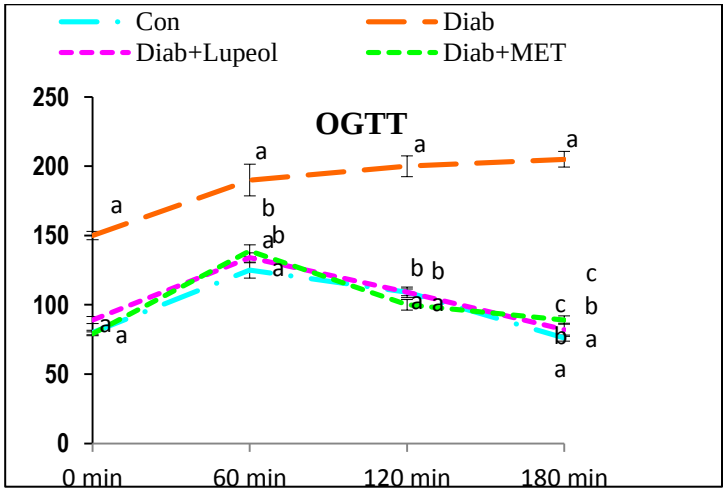


**Figure 2:** Effect of lupeol on oral glucose tolerance in type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05,a-compared with control; b-compared with Diabetes; c-compared with diabetic animal treated with lupeol.

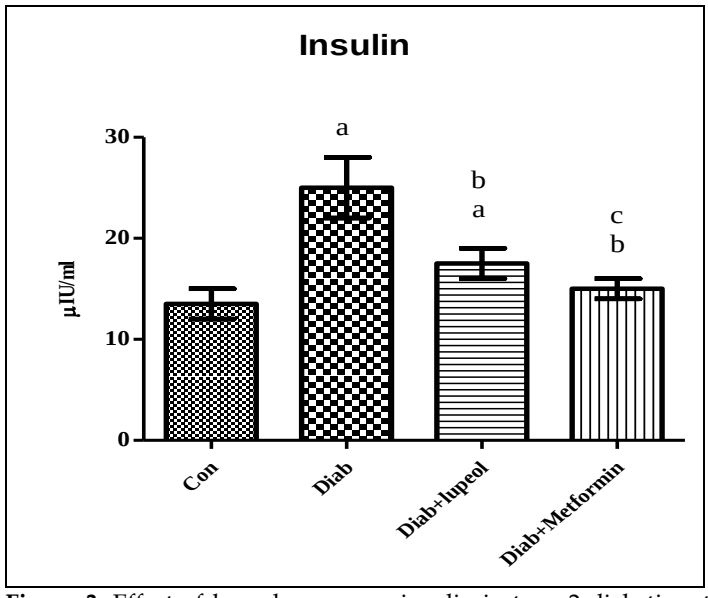


**Figure 3:** Effect of lupeol on serum insulin in type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05,a-compared with control; b-compared with Diabetes; c-compared with diabetic animal treated with lupeol.

**Estimation of fasting blood glucose (FBG):**
After overnight fasting, blood was collected from tip of rat's tail of control and treated animals and measured by On-Call Plus glucose estimation kit. The blood glucose is expressed in mg/dl.

**Assessment of oral glucose tolerance (OGT):**
To check whether lupeol improves glucose tolerance, animals were kept for overnight fasting and oral glucose tolerance was studied by giving oral glucose load (10 ml/kg; 50% w/v) at different time interval of 60, 120 and 180 min respectively using glucose test strips method Results for the glucose level is expressed as mg/dl.

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 19(4): 445-453 (2023)


**Serum insulin:**
The insulin concentration in the sample was estimated using a standard graph by using ultra-sensitive rat insulin ELISA kit (Crystal ChemInc, USA) and the findings were represented in IU/mL**.**

**Assay of adipose tissue function indicators (adipocytokines):**
Quantitative determination of adipocytokines (Adiponectin, leptin and resistin) was performed using ELISA method by the so called sandwich-assay using two specific and high affinity antibodies.

**Estimation of inflammatory cytokines and transcription factors:**
Quantitative determination of TNF-α and IL-6 (inflammatory cytokines) and NFkB were performed using ELSIA method by the so called sandwich-assay using two specific and high affinity antibodies.

**Estimation of lipid parameters:**
In the serum of control and treated animals, the total cholesterol, low-density lipoprotein, low-density lipoprotein cholesterol, triglycerides, high density lipoprotein cholesterol and free fatty acids were measured as per the commercial kits obtained from Diatek, Kolkata, India using Semi-Automated Biochemistry Analyser.

**Assessment of oxidative stress markers in adipose tissue:**
Lipid peroxidation (LPO) was measured by the method of Devasagayam and Tarachand, 1987 **[13]**. The malondialdehyde (MDA) content of the sample is expressed as nmoles of MDA formed/min/mg protein. Hydrogen peroxide generation ($H_2O_2$) was assessed by the spectrophotometric method of Pick and Keisari, 1981 **[14]** and expressed as µmoles/min/mg protein. Hydroxyl radical (OH*) production was quantified by the method of Puntarulo and Cerebrum, 1988 **[15]** and expressed as µmoles/min/mg protein.

**Assessment of antioxidant enzymes:**
Quantitative determination of antioxidant enzymes such as SOD, GPx and CAT enzyme activity were performed using ELSIA method by the so called sandwich-assay using two specific and high affinity antibodies.

**Gene expression analysis by Real Time –PCR:**
***Total RNA isolation***
In the control and treated samples, total RNA was isolated by TRIR kit obtained from Invitrogen. Total RNA was isolated as per the standard method (Fourney et al. 1988). The purity and concentration was assessed using spectrophotometer. The RNA yield was indicated in microgram.

**cDNA conversion and PCR amplification:**
For the synthesis of cDNA from adipose tissue of control and treated animals, this study utilized 2µg of total RNA. cDNA was converted as per the manufacturere's instructions of kit procured in Eurogentec, Beldium. Then the reaction mixture was made by the addition of the 2x buffer (Takara SyBr green master mix), primers for gene of interest as well as housekeeping gene. Then the mixture was thoroughly mixed by pipetting up and down and cDNA was added and reaction was kept for 40 cycles the thermal cycle consisted of 95°C for 5 minutes, 95°C for 5seconds, 60°C for 20 seconds and 72°C for 45seconds. Finally they obtained result was plotted on a graph in the PCR machine. Then the amplification plots and dissociation curve analysis obtained through which calculation of relative quantification was performed.

Table 2: Impact of lupeol on oxidative stress markers in adipose tissue of high fat and sucrose induced diabetic rats. Each value denotes mean ± SEM of 5 animals. Significance at $p< 0.05$. a- compared to control; b-compared to diabetic control; c-compared to diabetic control treated with lupeol; d-compared with diabetic control treated with standard drug metformin. $H_2O_2$: nmoles of MDA formed/min/mg protein; LPO: µmoles/min/mg protein; *OH: µmoles/min/mg protein.

| Description | Normal control | Diabetic control | Diabetic control+ lupeol | Diabetic control+ metformin |
|---|---|---|---|---|
| **TC** | 48±3.67 | 122±6.80[a] | 53±2.25[b] | 56±4.44[b] |
| **TG** | 79±2.21 | 202±7.65 [a] | 86±5.20 [b] | 74±4.5[b,c] |
| **HDL** | 25±1.14 | 12±0.93 [a] | 30±1.1[b] | 28±1.23[a,b] |
| **VLDL** | 21±1.25 | 55±3.80 [a] | 24±1.70[b] | 18±.95[b] |
| **LDL** | 60±4.45 | 132±8.76[a] | 69±4.85[b] | 59±2.75[b,c] |
| **FFAs** | 85±5.23 | 140±8.90[a] | 78±5.28[b] | 73±6.34[b] |

**Statistical analysis:**
The obtained data were analyzed statistically by one-way analysis of variance (ANOVA) and student Newman keul's comparison tests with computer-based software (Graph Pad Prism version 5) to analyze the significance of individual variations among the control and experimental groups. The significance was considered at the level of $p<0.05$.

**Results:**
**Effect of lupeol on FBG, OGT and serum insulin:**
In type-2 diabetic rats, blood sugar and insulin were found to be significantly increased ($p<0.05$) and impaired glucose tolerance was observed. However, administration of lupeol significantly restored the altered levels of the same. Lupeol treatment to the normal control rats did not affect any significant change in the parameters studied.

**Effects of lupeol alleviates lipid parameters:**
Type-2 diabetic rats significantly raised the serum TC, TG, LDL-c, VLDL and FFAs whereas serum HDL-c level was found to be decreased in diabetic rats. Despite lupeol treated diabetic rats significantly $p< (0.05)$ restored the altered levels of lipid parameters.

**Modulation of oxidative stress parameters (LPO, $H_2O_2$ and OH*) by lupeol:**
Lupeol administered diabetic rats hindered the increased levels of LPO, $H_2O_2$ and OH*$p<(0.05)$ and brought back to the control animal. Control animal treated with 20 mg/kg.b.wt dose of lupeol did not alter the levels of the oxidative stress parameters.

**Effect of lupeol on IR mRNA expression in adipose tissue:**
The IR gene expression was significantly reduced in high fat diet and high sucrose induced diabetic rats ($p<0.05$) whereas lupeol treatment effectively increased the IR expression adipose tissue to that of the control level.

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 19(4): 445-453 (2023)


**Effect of lupeol on IRS-1 mRNA expression in adipose tissue:**
The **IRS-1** gene expression was significantly reduced in high fat diet and high sucrose induced diabetic rats (*p<0.05*) whereas lupeol treatment effectively increased the IRS-1expression adipose tissue to that of the control level.

**Effect of lupeol on Akt mRNA expression in adipose tissue:**
The Akt mRNAexpression was significantly reduced in high fat diet and high sucrose induced diabetic rats (*p<0.05*) whereas lupeol treatment effectively increased the Akt mRNAexpression adipose tissue to that of the control level.

**Effect of lupeol on GLUT 4 mRNA expression in adipose tissue:**
The GLUT 4 mRNAexpression was significantly reduced in high fat diet and high sucrose induced diabetic rats (*p<0.05*) whereas lupeol treatment effectively increased the GLUT 4mRNAexpression adipose tissue to that of the control level.

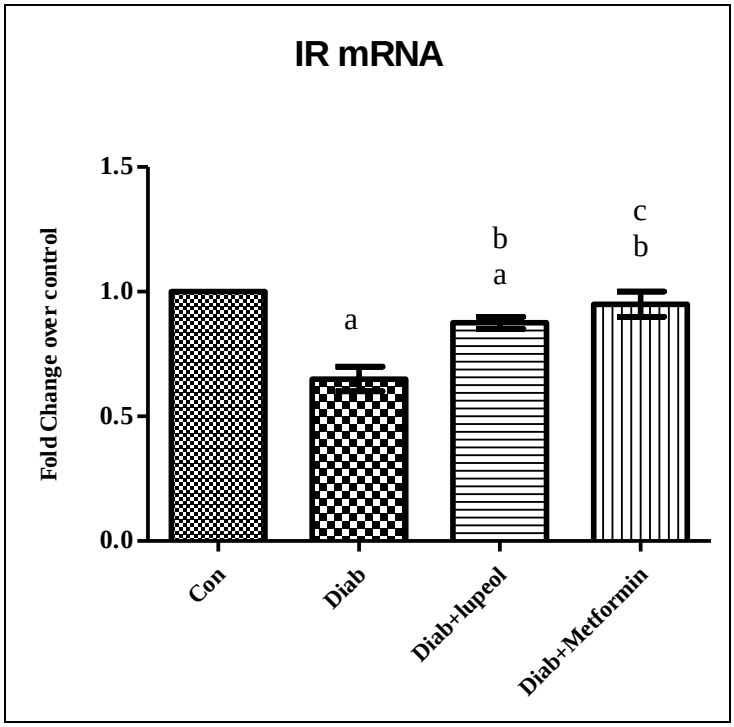


**Figure 4:** Effect of lupeol on IR mRNA expression in adipose tissue of type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05,a-compared with control; b-compared with Diabetes; c-compared with diabetic animal treated with lupeol.

**Effect of lupeol on serum adipokine levels:**
lupeol regulates the serum adipokines level (adiponectin, leptin and resistin) in type-2 diabetic rats: Adiponectin, leptin and resistin, considered as possible markers of metabolic syndrome were analysed in adipose tissue of control and experimental rats. The acquired data showed that a significant increase (P< 0.05) in the levels of leptin and resistin accompanying a notable decrease in adiponectin levels in diabetic rats; whereas treatment with lupeol recovered the altered adipokines levels in type-2 diabetic rats.

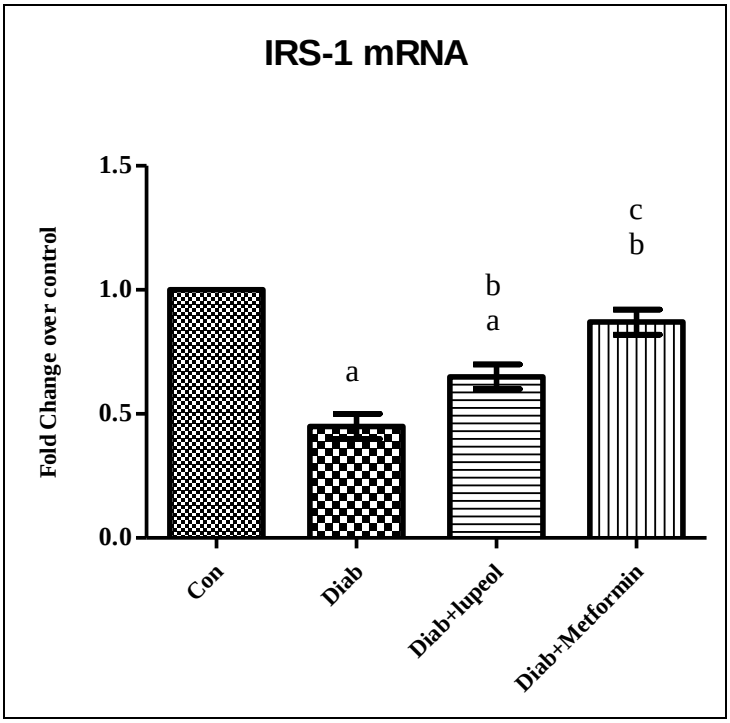


**Figure 5:** Effect of lupeol on IRS-1 mRNA expression in adipose tissue of type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05,a-compared with control; b-compared with Diabetes; c-compared with diabetic animal treated with lupeol.

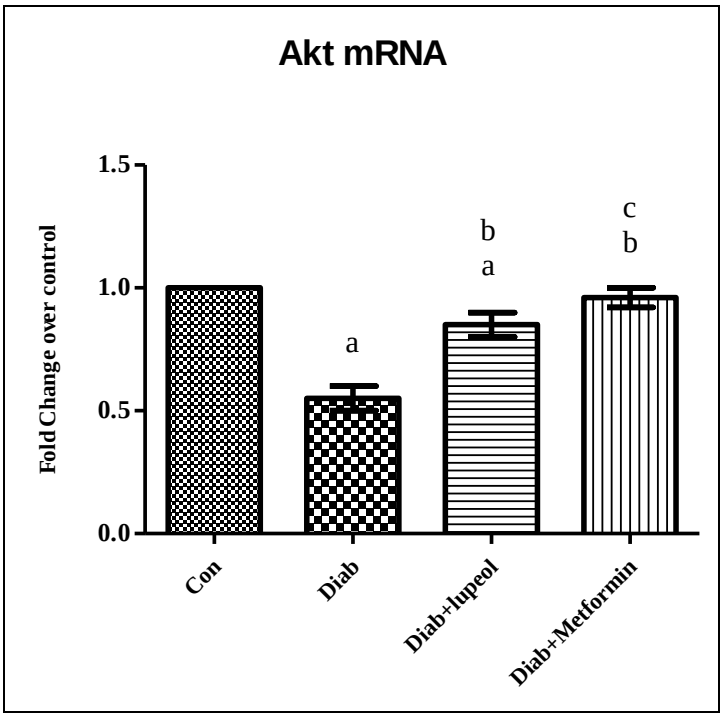


**Figure 6:** Effect of lupeol on Akt mRNA expression in adipose tissue of type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05,a-compared with control; b-compared

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 19(4): 445-453 (2023)


with Diabetes; c-compared with diabetic animal treated with lupeol.

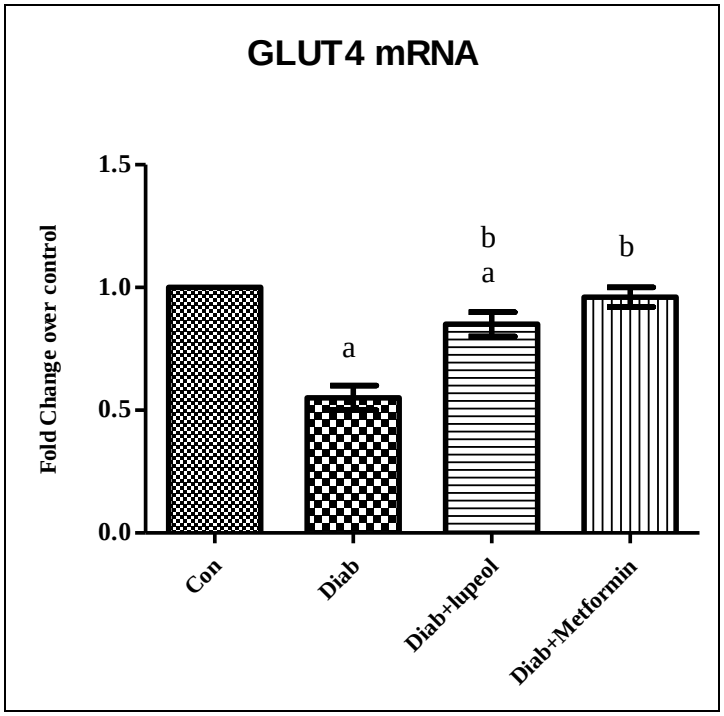


**Figure 7:** Effect of lupeol on GLUT4 mRNA expression in adipose tissue of type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05,a-compared with control; b-compared with Diabetes; c-compared with diabetic animal treated with lupeol.

**Effect of lupeol on serum pro-inflammatory cytokines (TNF-α and IL- 6):**

Lupeol declines pro-inflammatory cytokines (TNF-α and IL- 6) protein levels in adipose tissue of type-2 diabetic rats: Pro-inflammatory cytokines (TNF-α, IL- 6) are participated in various metabolic pathways relevant to insulin resistance. The study confirms a notable increase in TNF-α, IL-6 levels those molecules in type-2 diabetic rats. Treatment with Lupeol decreased the levels of protein and mRNA of TNF-α and IL- 6 considerably in adipose tissue of type-2 diabetic rats which may be due to antioxidant potential of Lupeol that suppresses oxidative stress and inflammation.

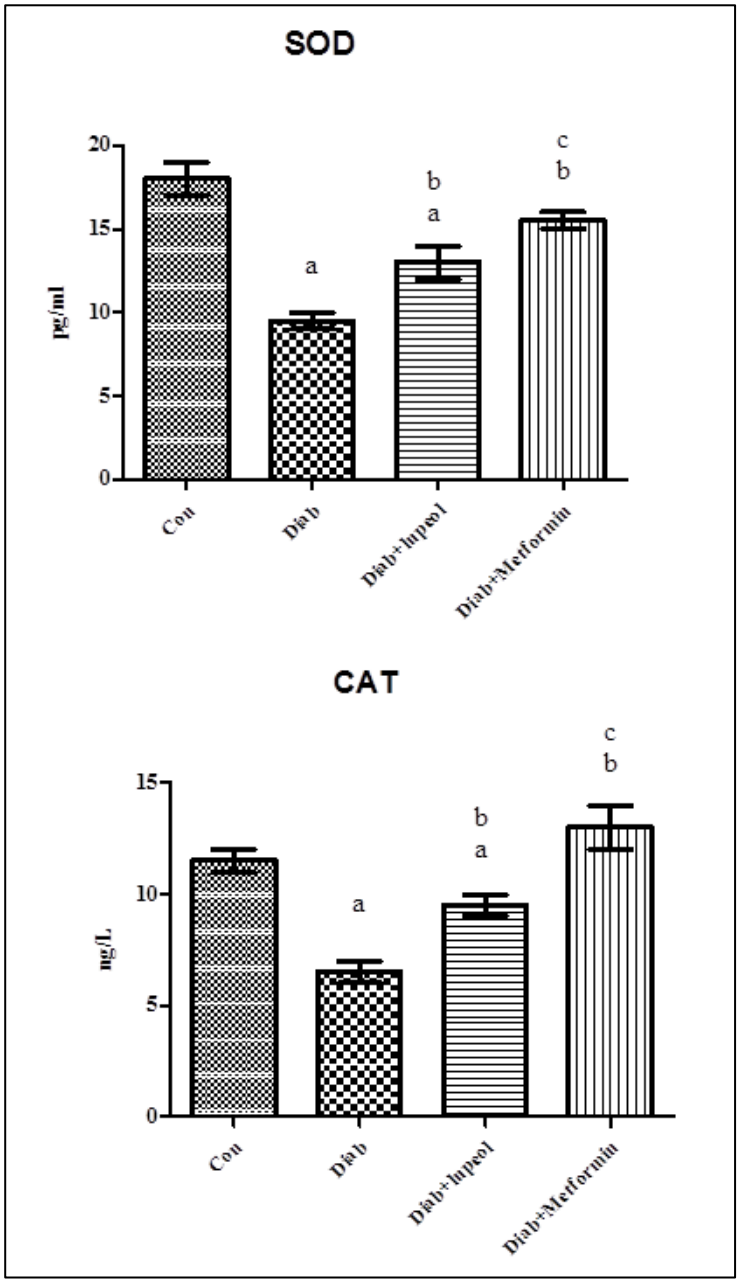


**Figure 8:** Effect of lupeol on CAT and SOD activity in adipose tissue of type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05,a-compared with control; b-compared with Diabetes; c-compared with diabetic animal treated with lupeol.

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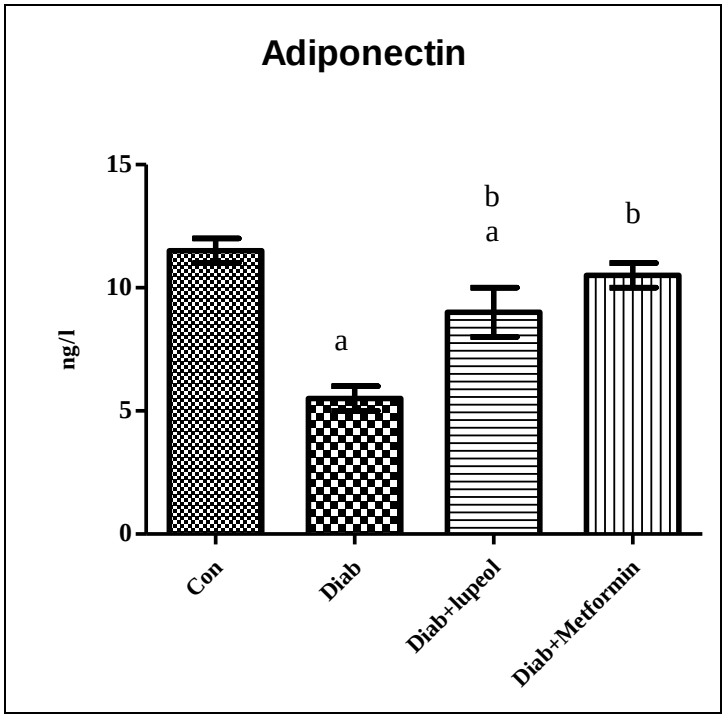


**Figure 9:** Effect of lupeol on serum adiponectin in type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05,a-compared with control; b-compared with Diabetes; c-compared with diabetic animal treated with lupeol.

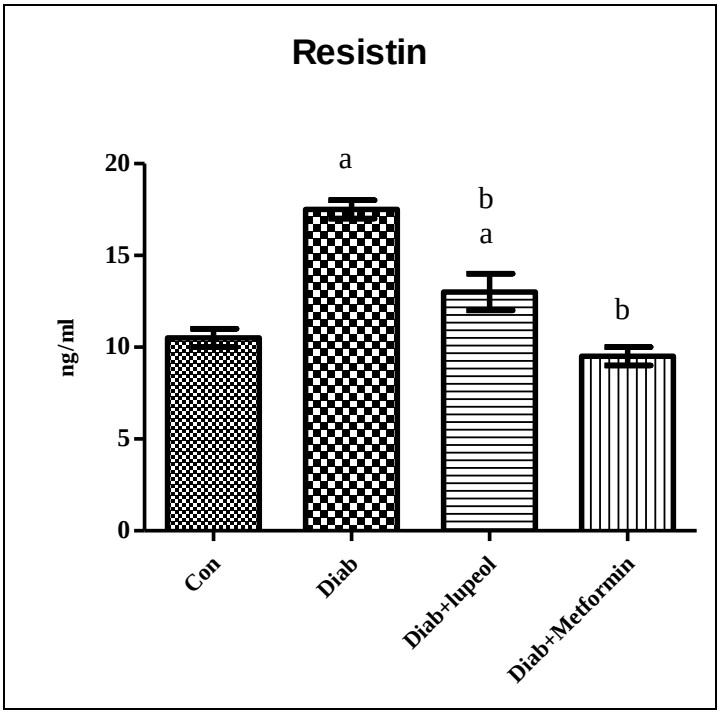


**Figure 11:** Effect of lupeol on serum leptin level in type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05,a-compared with control; b-compared with Diabetes; c-compared with diabetic animal treated with lupeol.

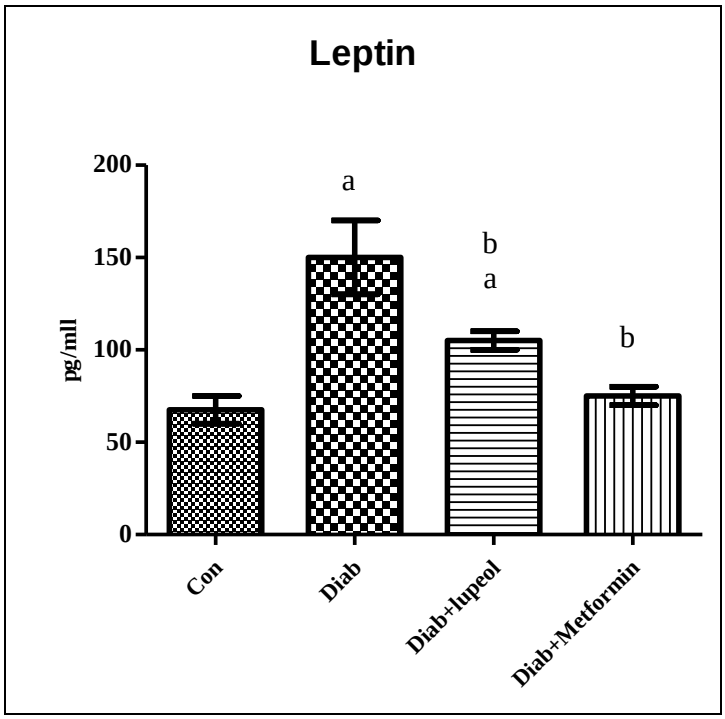


**Figure 10:** Effect of lupeol on serum leptin in type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05,a-compared with control; b-compared with Diabetes; c-compared with diabetic animal treated with lupeol.

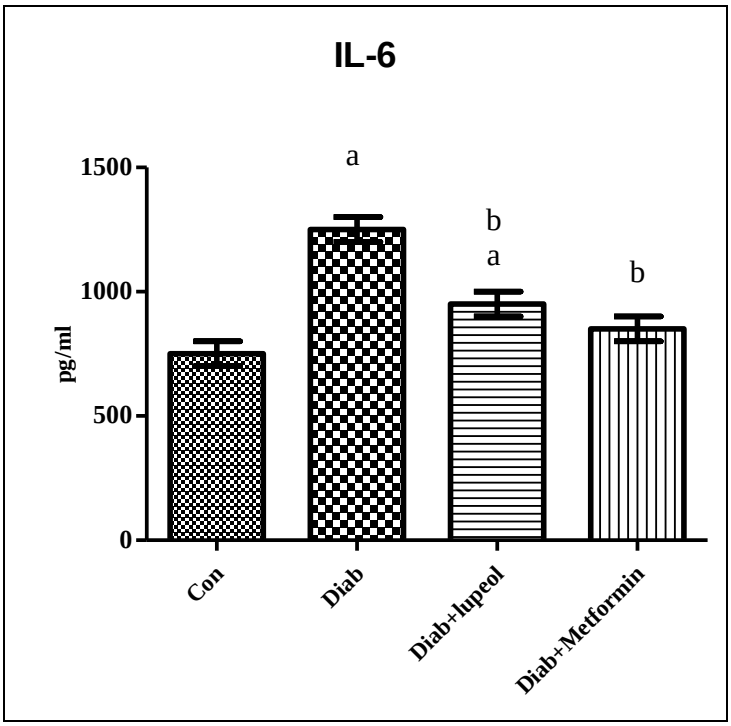


**Figure 12:** Effect of lupeol on serum IL-6 level in type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05,a-compared with control; b-compared with Diabetes; c-compared with diabetic animal treated with lupeol.

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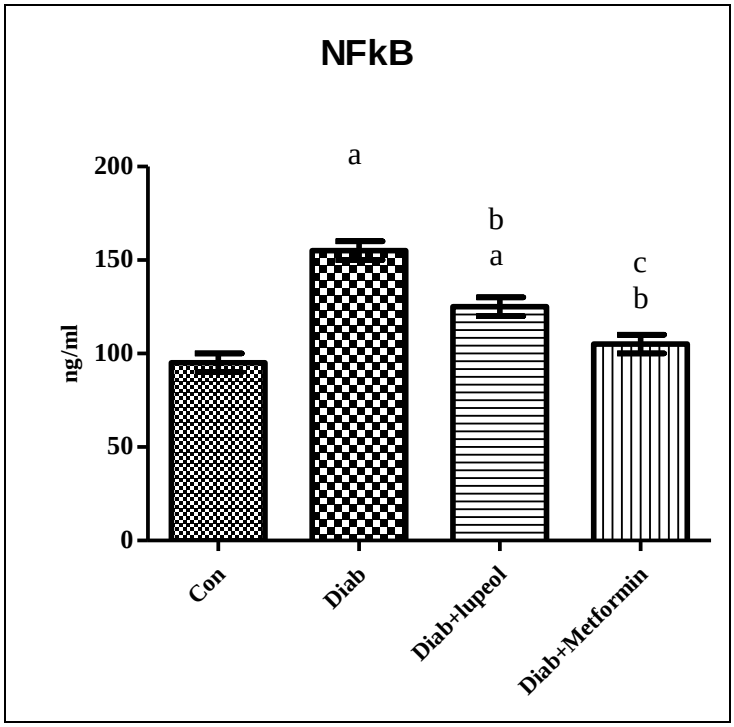


**Figure 13:** Effect of lupeol on serum NFkB level in type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05, a-compared with control; b-compared with Diabetes; c-compared with diabetic animal treated with lupeol.

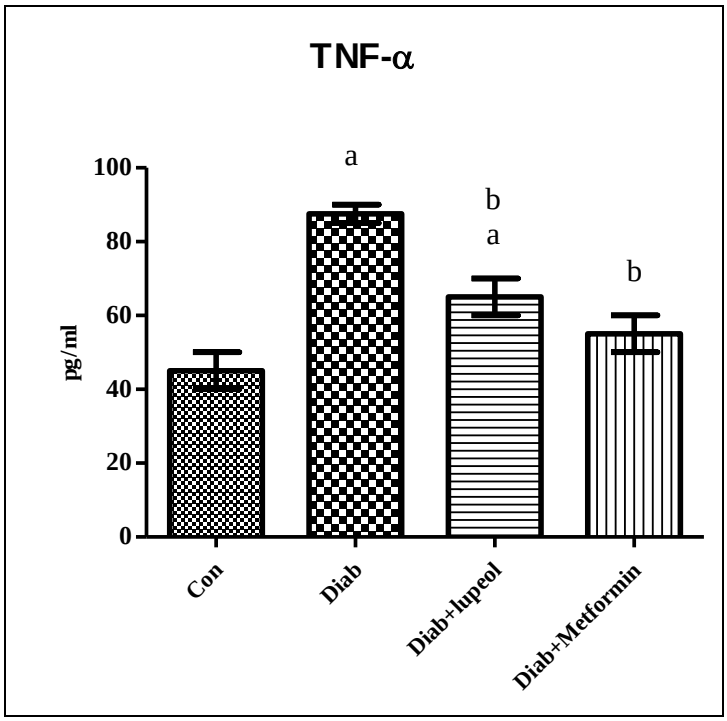


**Figure 14:** Effect of lupeol on serum TNFα levelin type-2 diabetic rats. Each bar represents mean ± SEM (n= 6). Significance at P <0.05,a-compared with control; b-compared with Diabetes; c-compared with diabetic animal treated with lupeol.

**Discussion:**

In order to control blood glucose and avoid long-term consequences in type-2 diabetes, plants serve as a significant source of dietary supplements **[16]**. Lupeol exhibits potent anti-inflammatory characteristics when investigated in vitro and in vivo, which in turn assist control diabetes **[17]**. The current study findings clearly demonstrated that Lupeol has strong anti-diabetic efficacy. The currently available antidiabetic medications for the treatment of diabetes mellitus have some limitations and are not cost-effective in developing nations. Blood sugar and insulin levels were found to be considerably higher in type 2 diabetic rats, as was glucose tolerance. On the other hand, administration of lupeol, significantly restored the altered levels of the same. Lupeol therapy of normal control rats had no effect on any of the measures evaluated. The levels of total cholesterol, FFA, triglycerides, VLDL, and LDL in diabetic rats fed HFD and sucrose increased significantly, as expected, whereas the levels of HDL cholesterol significantly decreased. These findings indicate that these rats dyslipidemia was brought on by consuming too much fat **[18]**. Despite receiving lupeol treatment, the diabetic animals abnormal lipid parameter levels were dramatically restored.

Increased oxidative stress occurs prior to the development of HFD-fed insulin resistance and obesity. It causes the formation of reactive oxygen species and increases lipid peroxidation in muscle cell membranes, resulting in insulin resistance **[19]**. As a result, when compared to control rats, HFD fed rats revealed a significant rise in the levels of H2O2,*OH, and LPO. On the other hand, lupeol therapy significantly reduced ROS levels, especially H2O2,*OH, and avoided lipid peroxidation in diabetic adipose tissues. In rat and mouse models of inflammation, lupeol has also demonstrated strong anti-inflammatory efficacy by inhibiting the release of pro-inflammatory cytokines such interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). Additionally, it has been proposed that the lupeol derivative molecule causes autophagy, which results in cell death, in the cancer cell line. **[20]**. The body must maintain glucose homoeostasis in order to use carbs, amino acids, and fatty acids in an appropriate proportion. Initiating a pro-inflammatory response by enlisting macrophages, adipocytes release pro-inflammatory adipocytokines such TNF-alpha and IL-6, which phosphorylate the IR substrate on the serine residue **[21]**. According to research by Koren & Fantus **[22],** lupeol has the potential to manage diabetes because it significantly inhibited protein tyrosine phosphatase 1 B (PTP1B), a negative regulator of the insulin signalling pathway and a promising potential therapeutic target, particularly for the treatment of type 2 diabetes. Lupeol also increased the serum insulin antioxidant enzymes. Many studies have shown that eating a high fat diet causes hyperglycemia, hyperinsulinemia, hyperlipidemia, and insulin resistance in animal models **[23-24]**. The current work aims to clarify the mechanism of action of Lupeol during insulin resistance using in vivo techniques, with the goal of determining whether Lupeol enhances gene expression of insulin signalling molecules.

The expression of IR, Akt, IRS-1, and GLUT4 mRNA was dramatically reduced in the adipose tissue of diabetic rats, as was to be predicted. In addition to insulin resistance, HFD-fed promotes of c-Jun NH-2 terminal kinase and extracellular signal-regulated kinases have been linked to decreased activity of IRS-1 proteins in diabetic rats **[25]**. This serine phosphorylation (Ser636) of IRS-1 results in impaired insulin-stimulated tyrosine phosphorylation (Tyr632) of IRS-1 **[26]**. It's interesting to note that lupeol administration increased the levels of the signalling molecules mentioned above, which increased the IR/IRS-1/PI3K/Akt/AS160 pathway in adipose tissue and boosted insulin production in these rats. Consequently, the tissue's mRNA levels increased.

In type-2 diabetic rats, lupeol controls the levels of the serum adipokines adiponectin, leptin, and resistin: In the adipose tissue of control and experimental rats, the hormones adiponectin, leptin, and resistin were examined as potential indicators of the metabolic syndrome. The collected findings demonstrated that in diabetic rats, levels of leptin and resistin significantly increased together with a significant drop in adiponectin levels; however, lupeol therapy restored the altered adipokine levels in type-2 diabetic rats. Lupeol reduces the protein levels of pro-inflammatory cytokines (TNF- and IL-6) in type 2 diabetic rat adipose tissue: TNF- and IL-6 pro-inflammatory cytokines play roles in several metabolic pathways related to insulin resistance **[27-28,29]**. The findings confirm a significant increase in TNF- and IL-6 levels in type 2 diabetic rats. Lupeol treatment significantly reduced TNF- and IL-6 protein and mRNA levels in adipose tissue of type 2 diabetic rats, which could be attributed to Lupeol's antioxidant capability, which lowers oxidative stress and inflammation.

**Conclusion:**

Lupeol, a strong antioxidant, normalises hyperglycemia, dyslipidaemia, and hyperinsulinemia while simultaneously lowering oxidative stress by scavenging excessive amounts of ROS. It also enhances insulin signalling in type 2 diabetic rat adipose tissues. And it loweres the levels of pro-inflammatory cytokines, and thus it enhances insulin sensitivity via modifying pro-inflammatory signalling molecules in adipose tissue such as IL-6, TNF alpha, and NFkB. As a result, it may improve insulin sensitivity and glucose homeostasis. As a result of the current findings, it is concluded that lupoel possesses potent anti-diabetic characteristics and could be used as a phytomedicine for type 2 diabetes.

**Declaration of Conflict Interest:**

The authors declare no conflicts of interest

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