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# Effect of Lupeol on Pro-Inflammatory Markers in Adipose Tissue of High-Fat Diet and Sucrose Induced Type-2 Diabetic Rats

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## ABSTRACT

*Background: Lupeol also called Fagarsterol is found in white cabbage, green pepper and strawberry. It is reported to have beneficial effects for various disorders. However, the mechanisms by which lupeol controls proinflammation-mediated signalling is obscure.*

*Aim: The study was aimed at assessing the effect of lupeol on the expression of proinflammatory signalling molecules antidiabetic activity of lupeol through the expression of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in adipose tissue of high fat diet-induced type-2 experimental rats.*

*Materials and methods: Male Albino Wistar rats were used for the present study and divided into 4 groups of 6 animals each. Group 1: Served as normal control rats; Group II: Serves as high fat diet-induced type-2 diabetic rats; Group III: Diabetic rats treated with Lupeol (25 mg/kg b.wt) and Group IV: Diabetic administered treated with metformin. At the end of the treatment, adipose tissues from control and treated animals were dissected out and used for the assessment of mRNA expression of proinflammatory cytokines such as IL6 and TNF-α. The data were statistically analysed using one-way-ANOVA to check the statistical significance between groups.*

*Results: The IL6 and TNF-α mRNA expression levels were measured using RT-PCR method. The results showed that the IL6 and TNF-α mRNA expression level of diabetic rats were significantly increased ($p<0.05$) whereas on the treatment with lupeol the levels were near normal which were also compared with standard drugs.*

*Conclusion: The present findings show that lupeol has a significant role in controlling the expression of proinflammatory signalling molecules in adipose tissue and hence it may be considered for the development of new antidiabetic therapeutic drugs.*

**Key words:** Novel method, Diabetes, Insulin, Lupeol, Proinflammatory cytokines, IL-6,TNF-α, Innovative technology

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## INTRODUCTION

Diabetes mellitus is a metabolic disorder characterised by high levels of blood glucose resulting from defects in insulin production. Intake of oral antihyperglycemic drugs for management of diabetes has been associated with side-effects [1]. Due to this there is a need to switch to herbal and natural alternatives. This transition not only increases the efficacy but also has minimal side-effects and low-cost. Lupeol has shown to have a wide range of biological activity against many human diseases [2]. It is useful in arthritis, cardiovascular disorders, renal disorder and hepatic toxicity.

Type 1 diabetes results from inadequate synthesis of insulin by -cells of the pancreas, while type II diabetes is characterized primarily by insulin resistance (a condition in which peripheral cells do not respond normally to insulin) or *β*-cell dysfunction. When examined under *invitro* and *invivo* conditions, Lupeol has strong anti-inflammatory properties which in turn help curb diabetes [2-5]. Lupeol has also shown to have potent anti-inflammatory activity in rat and mouse models of inflammation by reducing the release of pro-inflammatory cytokines such as InterLeukin-6 (IL-6) and tumour necrosis factor-alpha(TNF-α). It has been also suggested that the derivative molecule of lupeol induces cell death in the cancer cell line by inducing autophagy [6,7].

The anti-inflammatory effect of lupeol was also observed to be equal to dexamethasone, a well-known anti-inflammatory agent. The latex from *Hemanthus Sucuuba* was extracted and Lupeol was found to be an active constituent of this anti-inflammatory plant. The chemical formula of lupeol is C30 H50O and its melting point is 215-216° Celsius. Properties computed from the structure of lupeol show that it has a molecular weight of 426 units.

The infrared spectrum of lupeol shows the presence of hydroxyl functional groups and an olefinic moiety. The molecular formula depicts the presence of 6 degrees of unsaturation, out of which one can only be satisfied by olefinic function [8,9]. Our team has extensive knowledge and research experience that has translate into high quality publications [10-29].

The aim of this study was to assess the effect of lupeol on the expression of proinflammatory signalling molecules antidiabetic activity of lupeol through the expression of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in adipose tissue of high fat diet-induced type-2 experimental rats.

## MATERIAL AND METHOD

### Chemicals

All chemicals and reagents used in this study were purchased from Sigma Chemical Company St. Louis, MO, USA; Invitro

Gen, USA; Eurofins Genomics India Pvt Ltd, Bangalore, India; New England Biolabs (NEB), USA; Promega, USA. Lupeol was procured from Sigma Chemical Company St. Louis, MO, USA; Total RNA isolation reagent (TRIR) was purchased from Invitrogen, USA. The reverse-transcriptase enzyme (MMuLv) was purchased from Genet Bio, South Korea purchased from Promega, USA. Interleukin-1 β (IL-1 β), TNF-α and β-actin primers were purchased from Eurofins Genomics India Pvt Ltd, Bangalore, India and.

### Animals

Animals were maintained as per the National Guidelines and Protocols approved by the Institutional Animal Ethics Committee (IAEC no: 006/2016). Healthy adult male Wistar albino rats (150–180 days old weighing 180–200 g) were used in this study and maintained in clean polypropylene cages at the Central Animal House Facility, Meenakshi Medical College and Research Institute (Meenakshi Academy of Higher Education and Research) under specific humidity (65 ± 5%) and temperature (21 ± 2°) with constant 12 h light and 12 h dark schedule.

### Induction of Type-2 Diabetes in Animals

Rats were subjected to 60 days of a high-fat diet containing cholesterol 3%, cholic acid 1%, coconut oil 30%, standard rat feed 66%, and 30% sucrose through drinking water. On the 58th day of treatment, after overnight fasting, blood glucose was checked and the rats that had blood glucose above 120 mg/dL were chosen as type-2 diabetic rats. Sucrose feeding through drinking water with a high-fat diet was continued until the end of the study.

### Experimental Design

Adult male albino rats of Wistar 150–180 days old with 180–200 g body weight (b.wt) were randomly divided into five groups of six rats each

- Group I-Control (vehicle treated).
- Group II-Type-2 diabetic rats.
- Group III-Type-2 diabetic rats treated with lupeol (25 mg/kg b.wt/day) orally for 30 days.
- Group IV-Type-2 diabetic rats treated with metformin (50 mg/kg, b.wt/day orally for
- 30 days.

Two days before sacrifice, control and experimental animals were subjected to oral glucose tolerance (OGT) test and insulin tolerance test. At the end of the treatment, animals were anesthetized with sodium thiopentone (40 mg/kg b.wt), blood was collected through cardiac puncture, sera were separated and stored at −80°C, and 20 ml of isotonic sodium chloride solution was perfused through the left ventricle to clear blood from the organs. Adipose tissue from control and experimental animals was immediately dissected out and used for assessing the various parameters

### Gene Expression Analysis by Real Time PCR Analysis

### Isolation of total RNA

Total RNA was isolated from control and experimental samples using TRIR (total RNA isolation reagent) kit. Briefly, 100 mg fresh tissue was homogenized with 1 ml TRIR and the homogenate was transferred immediately to a microfuge tube and kept at -80°C for 60 min to permit the complete dissociation of nucleoprotein complexes. Then, 0.2 ml of chloroform was added, vortexed for 1 min and placed on ice at 4°C for 5 min. The homogenates were centrifuged at 12,000 x g for 15 min at 4°C. The aqueous phase was carefully transferred to a fresh microfuge tube and an equal volume of isopropanol was added, vortexed for 15 sec and placed on ice at 4°C for 10 min. The samples were centrifuged at 12,000 x g for 10 min at 4°C. The supernatant was discarded and RNA pellet was washed with 1 ml of 75% ethanol by vortexing and subsequent centrifugation for 5min at 7,500 x g (4°C). The supernatant was removed and RNA pellets were mixed with 50 µl of autoclaved Milli-Q water and dissolved by heating in a water bath for 10 min at 60°C.

Quantification of RNA

Diluted RNA samples were quantified spectrophotometrically by measuring the absorbance (A) at 260/280 nm. 40 µg of RNA in 1 ml gives one absorbance at 260 nm. Therefore, the concentration of RNA in the given sample can be determined by multiplying its A260 by 40 and dilution factor. The purity of RNA preparation can be calculated using the ratio between its absorbance at 260 and 280 nm. A ratio of absorbance at 260/280 nm> 1.8 is generally considered as good quality RNA. The purity of RNA obtained was 1.8.

Reverse transcriptase–polymerase chain reaction (RT–PCR)

RT-PCR is an approach for converting and amplifying a single stranded RNA template to yield abundant double stranded DNA products. 1. First strand reaction: Complementary DNA (cDNA) is made from the mRNA template using Oligo dT, dNTPs & reverse transcriptase. 2. Second strand reaction: After the reverse transcriptase reaction is complete, standard PCR (called the "second strand reaction") is initiated. Principle RT-PCR is a method used to amplify cDNA copies of RNA. It is the enzymatic conversion of mRNA into a single cDNA template. A specific oligodeoxynucleotide primer hybridizes to the mRNA and is then extended by an RNA dependent DNA polymerase to create a cDNA copy. First strand DNA synthesis The RT kit was purchased from Eurogentec (Seraing, Belgium). Reagents 1. 10X RT buffer: One vial containing 1.4 ml of 10X RT buffer. 2. EuroScript reverse transcriptase: One tube containing 75 µl of Moloney Murine leukaemia virus reverse transcriptase (3750 U at 50 U/µl).

Quantitative Real Time PCR Principle

The purpose of a PCR (Polymerase Chain Reaction) is to make a huge number of copies of a gene. There are three major steps in a PCR, which are as follows: Denaturation at 94°C for 3 min: During the denaturation at 94°C for 2-5 min, the double strand melts open to single stranded DNA, all enzymatic reactions stop. Annealing at 54°C-65°C for 30 sec: Ionic bonds are constantly formed and broken between primer and the single stranded template to ensure the extension process. Extension at 72°C for 30 sec: Primers that are in positions with no exact match get loose again (because of the higher temperature) and don't give an extension of the fragment. The bases (complementary to the template) are coupled to the primer on the 3' side (the polymerase adds dNTP from 5' to 3', reading the template from 3' to 5' side; bases are added complementary to the template). Because both strands are copied during PCR, there is an exponential increase of the number of copies of the gene.

**Reagents**

- 2X Reaction buffer: The PCR master mix kit was purchased from Takara Bio Inc., Japan. Contains TaKaRa Ex Taq HS (a hot start PCR enzyme) dNTP Mixture, Mg2+, Tli RNase H (a heat-resistant RNase H that minimizes PCR inhibition by residual mRNA), and SYBR Green I.
- Forward primer (10µM).
- Reverse primer (10µM).
- cDNA- Template.
- Autoclaved milli Q water.
- Primers: The following gene specific oligonucleotide primers were used.

Details of primers used in the present study

**Rat IL-1 β**

- FW-5'-GAAATGAGAAAAGAGTTGTGC-3'
- RW-5'- GGAAGTTGGGGTAGGAAGGAC-3'

**Rat TNF-α**

- FW -5'-ACGCTCTTCTGTCTACTG-3'
- RA-5'GGATGAACACGCCAGTCG-3'

**Rat β-actin**

- FW– 5'- TACAGCTTCACCACCACAGC - 3'
- RW–5'- TCTCCAGGGAGGAAGAGGAT - 3'

**PROCEDURE**

Procedure Real Time PCR was carried out on CFX 96 Real Time system (Bio-Rad). The reaction mix (10 µl) was prepared by adding 5 µl of 2X reaction buffer, 0.1 µl of sense and antisense primer, 1 µl of cDNA and 3.8 µl of sterile water. The thermal cycler protocol was as follows: Initial denaturation at 95˚C for 3 min, followed by 40 cycles of PCR, denaturation at 95˚C for 10 sec, annealing at 60˚C for 20 sec and extension at 72˚C for 20 sec. All reactions were performed in triplicate along with no template control (NTC). Melt curve analysis was performed using the thermal cycling programmed at 50-95˚C for each sample to determine the presence of multiple amplicons, non-specific products and contaminants. The results were analysed using CFX 96 Real Time system software (Bio-Rad). As an invariant control, the present study used rat β-actin.

**RESULTS**

**Effect of lupeol on IL-6 mRNA Expression on Adipose Tissue**

Figure 1 shows the level of IL-6 on control and experimental rats. A significant ($p<0.05$) in IL-6 mRNA levels in adipose tissue was observed in type-2 diabetic animals,whereas lupeol treatment decreased the IL-6 mRNA levels in type-2 diabetic animals.Lupeol treatment to control rats did not show any significant changes in IL-6 levels.

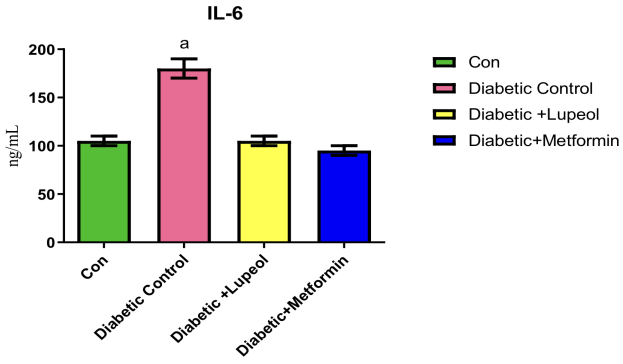


**Figure 1: Shows the relation between different groups of rats and the level of the Proinflammatory marker IL-6. X axis represents different rat groups while Y axis represents the level of IL-6. In comparison to the controlled group (100mg/dl), diabetic group has increased levels of Interleukin 6**

**(175mg/dl). However when diabetic induced control group is exposed to Lupeol and Metformin IL-6 level decreases significantly.**

### Effect of lupeol on TNF-α mRNA Expression on Adipose Tissue

Figure 2 shows the level of TNF-α on control and experimental rats .A significant ($p<0.05$) in TNF-α mRNA levels in adipose tissue was observed in type-2 diabetic animals, whereas lupeol treatment decreased the TNF-α mRNA levels in type-2 diabetic animals. Lupeol treatment to control rats did not show any significant changes in TNF-α level.

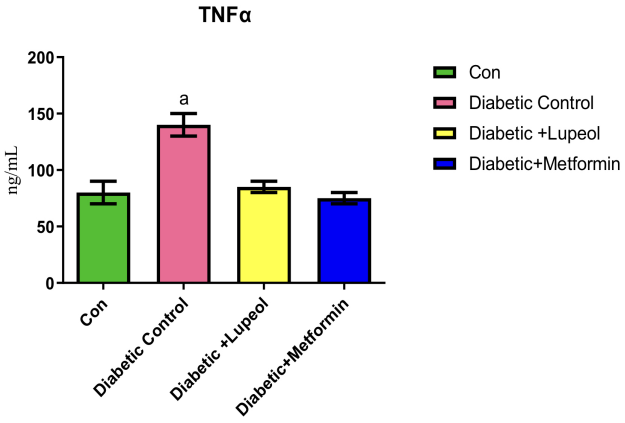


**Figure2: Shows the relation between different groups of rats and the level of the Proinflammatory marker TNF-α. X axis represents different rat groups while the Y axis represents the level of TNF-α. In comparison to the controlled group (80mg/dl), diabetic group has increased levels of TNF-α (150 mg/dl).However when diabetic induced control group is exposed to Lupeol and Metformin TNF-α level decreases significantly.**

## DISCUSSION

Glucose homoeostasis is vital for the balanced use of energy sources such as carbohydrates, amino acid and fatty acid by the body. Adipocytes recruit macrophages and initiate pro-inflammatory response, causing sustained release of inflammatory adipocytokines such as TNF-alpha and IL-6 which cause serine phosphorylation of IR substrate [3]. The result of the present study clearly indicated that Lupeol has significant antidiabetic activity. The model chosen for studying these activities have already been validated. The currently available antidiabetic drugs for the management of diabetes mellitus have certain drawbacks and are cost-effective for developing countries [3,30,31].

Impaired wound healing represents one of the major diabetes complications in clinical practice. In general Hyperglycemia causes changes in the functioning of endothelial cells and consequently, vascular dysfunction in the wounds. Clinical trials indicated that the cutaneous wound healing process occurs in three phases. Chronic inflammation is also one of the main factors contributing to delayed wound healing [8,32]. Estimation of blood glucose levels is one of the foremost successful demonstrative strategies in observing diabetes. Hence, glycaemic evaluation was chosen as the best parameter for disease progression in this study.

TNF-α appears to be a double part in diminishing granulation tissue arrangement and collagen fibre course of action. Within the display, think about lupeol treatment favourably controlling these arbiters by diminishing proinflammatory cytokines such as IL-6 ,an anti-inflammatory cytokine [32]. Lupeol anti-inflammatory effects on macrophages are its ability to increase the endocytic capacity of these cells [33].

This study reported that due to high fat diet and induction of Diabetes there is increase in inflammatory marker TNF-α in vivo with alterations in its mRNA expressions in diabetic rats as compare to normal rats. Alternatively, lupeol administration to the high fat diet induced diabetic rats altered the TNF-α mRNA expression to near normal when compared to control. These findings indicate that lupeol has been found to reduce TNF-α level by altering the inflammation. This is similar to previous study where Lupeol treatment showed decrease in generation of pro-inflammatory cytokines such as IL-beta in lipopolysaccharide treated macrophages [34]. Lupeol has been reported to inhibit the IL-6 which may be attributable to better glycaemic regulation.

## LIMITATION

The sample group size was small and only few clinical conditions were considered. The trial for this drug is time consuming and is not very cost efficient.

## FUTURE SCOPE

Lupeol should be administered in humans to understand the effect of it efficiently and its efficiency should be comparable to other drugs in the medical industry. The effect of Lupeol should be tried on other clinical conditions as well.

## CONCLUSION

It is concluded from the present study findings that lupeol plays a significant role in attenuating type-2 diabetes complications and normalizing the altered levels of biochemical changes. It causes suppression of pro-inflammatory markers. Hence Lupeol may be used as one of the potential antidiabetic herbal drugs. Further in vivo studies and clinical trials may be conducted to develop lupeol into a potential drug for treatment of diabetes.

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### Author Contribution

- Mithil Vora contributed in designing the study, execution of the project, statistical analysis, manuscript drafting.
- Dr. V Vishnupriya contributed in study design, guiding the research work, manuscript correction.
- Dr. J Selvaraj, Dr. M Kavitha, Dr. Gayathri: Study design, statistical analysis, manuscript proofreading and correction.

### CONFLICT OF INTEREST

The authors hereby declare that there is no conflict of interest in this study.

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