# بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / هناء محمد علي

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

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| **ملاحظات:**<br>.....<br>.....<br>.....<br>.....<br>..... |

**Faculty of Pharmacy**
**Clinical Pharmacy Department**

# Effect of Black Seed Oil on Markers of Endothelial Dysfunction in Patients with Type 2 Diabetes Mellitus

A Thesis submitted for the fulfillment of the Doctor of Philosophy in Pharmaceutical Sciences (Clinical Pharmacy)

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# List of abbreviations

| | |
|---|---|
| **ACCP** | **American College of Clinical Pharmacy** |
| **ADA** | **American diabetes association** |
| **ADMA** | **Asymmetrical dimethylarginine** |
| **AGE** | **Advanced glycation end product** |
| **AGIs** | **Alpha-glucosidase inhibitors** |
| **AGP** | **α1-acid glycoprotein** |
| **ALT** | **Alanine aminotransferase** |
| **ASCVD** | **Atherosclerotic cardiovascular disease** |
| **AST** | **Aspartate aminotransferase** |
| **BMI** | **Body mass index** |
| **BSA** | **Bovine serum albumin** |
| **BUN** | **Blood urea nitrogen** |
| **CAMs** | **Cell adhesion molecules** |
| **cGMP** | **Cyclic guanosine monophosphat** |
| **CHD** | **Coronary heart disease** |
| **CI** | **Confidence interval** |
| **COVID-19** | **Coronavirus disease of 2019** |
| **COX** | **Cyclooxygenase** |
| **CRP** | **C- reactive protein** |
| **CVD** | **Cardiovascular disease** |
| **DAN** | **Diabetic autonomic neuropathy** |
| **DDCT** | **Diabetes control and complications trial** |
| **DKA** | **Diabetic ketoacidosis** |
| **DKD** | **Diabetic kidney disease** |
| **DM** | **Diabetes mellitus** |
| **DME** | **Diabetic macular edema** |
| **DPN** | **Diabetic peripheral neuropathy** |
| **DPP-IV** | **Dipeptidyl peptidase – IV** |
| **D-39 Q** | **Diabetes -39 questionnaire** |
| **DR** | **Diabetic retinopathy** |
| **ED** | **Endothelial dysfunction** |
| **eGFR** | **Estimated glomerular filtration rate** |
| **ELISA** | **Enzyme linked immunosorbent assay** |
| **eNOS** | **endothelial nitric oxide synthase** |
| **ESRD** | **End-stage renal disease** |
| **ET-1** | **Endothelin-1** |
| **FBG** | **Fasting blood glucose** |

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| **FDA** | **Food and Drug Administration** |
| **FMD** | **Flow-mediated vasodilatation** |
| **FPG** | **Fasting plasma glucose** |
| **GDM** | **Gestational diabetes mellitus** |
| **GI** | **Gastrointestinal** |
| **GIP** | **Glucose-dependent insulinotropic polypeptide** |
| **GLP** | **Glucagon-like peptide** |
| **GLP-1 RA** | **Glucagon-like peptide-1 receptor agonists** |
| **HbA1c** | **Glycated hemoglobin** |
| **HDL-C** | **High density lipoprotein cholesterol** |
| **HGP** | **Hepatic glucose production** |
| **HHS** | **Hyperglycemic hyperosmolar state** |
| **2-hPG** | **2-hour plasma glucose** |
| **HSA** | **Human serum albumin** |
| **hs-CRP** | **High sensitivity c-reactive protein** |
| **ICAM-1** | **Intercellular adhesion molecule-1** |
| **IDF** | **International diabetes federation** |
| **IgSF** | **Immunoglobulin superfamily** |
| **IL-6** | **Interleukin-6** |
| **IL-β** | **Interleukin-beta** |
| **ILs** | **Interleukins** |
| **IP** | **Intraperitoneal** |
| **IQR** | **Interquartile range** |
| **LD50** | **Median lethal dose** |
| **LDL-C** | **Low density lipoprotein cholesterol** |
| **MAPK** | **Mitogen activated protein kinase** |
| **MENA** | **Middle East region and North African region** |
| **MERS** | **Middle East respiratory syndrome** |
| **MI** | **Myocardial infarction** |
| **MODY** | **Maturity-onset diabetes of the young** |
| **NF-κB** | **Nuclear factor kappa-B** |
| **NIDDM** | **Noninsulin-dependent diabetes mellitus** |
| **NO** | **Nitric oxide** |
| **NS** | ***Nigella Sativa*** |
| **OGTT** | **Oral glucose tolerance test** |
| **OR** | **Odds ratio** |
| **PAI-1** | **Plasminogen activator inhibitor-1** |
| **PI3K** | **Phosphatidylinositol-3-kinase** |
| **PKC** | **Protein kinase-C** |
| **PPAR** | **Peroxisome proliferator-activated receptor** |
| **QOL** | **Quality of life** |

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| **RCTs** | **Randomized controlled trials** |
| **ROS** | **Reactive oxygen species** |
| **SARS** | **Severe acute respiratory syndrome** |
| **SCr** | **Serum creatinine** |
| **SD** | **Standard deviation** |
| **SGLT-1** | **Sodium glucose co-transporter 1** |
| **SGLT-2** | **Sodium glucose co-transporter 2** |
| **sICAM-1** | **Soluble intercellular adhesion molecule-1** |
| **STZ** | **Streptozotocin** |
| **SU** | **Sulfonylureas** |
| **sVCAM** | **soluble vascular cell adhesion molecule** |
| **TC** | **Total cholesterol** |
| **T1DM** | **Type 1 diabetes mellitus** |
| **T2DM** | **Type 2 diabetes mellitus** |
| **TG** | **Triglycerides** |
| **THQ** | **Thymohydroquinone** |
| **TNF-α** | **Tumor necrosis factor-alpha** |
| **TQ** | **Thymoquinone** |
| **TZDs** | **Thiazolidinediones** |
| **VCAM-1** | **Vascular cell adhesion molecule-1** |
| **Vs** | **Volume at steady state** |
| **VWF** | **Von Willebrand factor** |
| **WHO** | **World Health Organization** |

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# Abstract

# Abstract


## Background and objectives:

Endothelial dysfunction is a major contributing factor for the development of diabetic vascular complications. Atherosclerotic diseases and cardiovascular mortality can be early predicted by monitoring of biochemical markers such as intercellular adhesion molecule -1 (ICAM-1) which proved to have a good correlation with cardiovascular risk factors. Additionally, C-reactive protein (CRP) is a strong and independent predictor for adverse cardiovascular events. Black seed oil is known with its antioxidant, anti-inflammatory and hypoglycemic properties that make it an attractive candidate for improving endothelial dysfunction and quality of life of type 2 diabetic patients.

## Aim of work:

The current study was designed to evaluate the effect of black seed oil as an add on therapy in the management of type 2 diabetes, endothelial dysfunction as well as patients' quality of life compared to standard treatment alone.

## Patients and methods:

The study was a prospective, randomized, placebo-controlled, double blinded study that was carried out on 50 type 2 diabetic patients. Eligible patients were randomly assigned to receive either 1800 mg/day of black seed oil or identical placebo capsules for 12 weeks. Full clinical history and fasting blood samples were obtained to determine fasting blood glucose (FBG), glycated hemoglobin (HbA1c), full lipid profile, kidney and liver functions, high sensitivity c-reactive protein (hs-CRP) levels as well as ICAM-1 at baseline and at the end of the study. Moreover, quality of life was evaluated using diabetes-39 questionnaire.

## Results:

Black seed oil supplementation at a dose of 1800 mg every day for a period of 3 months decreased the levels of HbA1c, TC (total cholesterol), TG (triglycerides), hs-CRP and ICAM-1 significantly compared to standard treatment alone. Regarding the other biochemical parameters, including FBG, HDL (high density lipoprotein), LDL (low density lipoprotein), AST (aspartate aminotransferase), ALT (alanine aminotransferase), BUN (blood urea nitrogen) and sCr (serum creatinine), black seed oil was comparable to standard treatment. All quality of life domains were not significantly changed by the end of the study period, except for diabetes control domain.

## Conclusion:

The findings from the current study support the role of black seed oil in the management of type 2 diabetes and its related complications. Administration of 1800 mg/day of black seed oil over 12 weeks showed a superior efficacy over standard

treatment alone in the management of glycemic and metabolic parameters of type 2 diabetes mellitus and amelioration of endothelial dysfunction.

## Key words:

Type 2 diabetes mellitus, Black seed oil, Endothelial dysfunction, Soluble adhesion molecules.

# Introduction