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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

FDA	Food and Drug Administration
FMD	Flow-mediated vasodilatation
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
GI	Gastrointestinal
GIP	Glucose-dependent insulintropic 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	<i>Nigella Sativa</i>
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

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