International Journal of Health Sciences and Research
Vol.13; Issue: 1; January 2023
Website: www.ijhsr.org
Review Article *ISSN: 2249-9571*

An Efficacy of Anti-hyperglycemic Agents (*Nigella sativa*) in Blood, Body Weight and Glucose levels of Diabetes Mellitus Rats: A Comprehensive Review

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DOI: https://doi.org/10.52403/ijhsr.20230109

ABSTRACT

There is a large global trend toward the use of medicinal herbs for the treatment of diabetes, and many people employ complementary and alternative medicine. The objective of the study was to provide comprehensive information on the effects of *Nigella sativa* on lipid profile, glucose level, and body weight in diabetic-induced rats. This is a comprehensive review carried out through PubMed, Science Direct, Google scholar and Springer and other Scientific Electronic Library Online databases, using the keywords; "N. *sativa"*, "black seed", "diabetes", "glucose", "lipid", "Weight", and "insulin" associated with the Boolean operator "AND". At first, 241 articles from 2000 to 2022 were discovered. Following the application of the specified inclusion and exclusion criteria, 21 papers were still available, and 15 underwent complete reading, after which all were included in the study. According to their findings, N. *sativa* has a variety of possible mechanisms for controlling hyperglycemia and abnormal lipid profiles, including its antioxidant properties and influences on insulin secretion, glucose absorption and body weight. However, further clinical studies are required to determine the N. *sativa* therapeutic benefits, as well as the kind and dose that work best for managing diabetes and its consequences.

Keywords: Diabetes Mellitus, glucose, Lipid, hyperglycemia, Metabolism, Cumin seeds

INTRODUCTION

Diabetes mellitus (DM), a disorder affecting people worldwide, is characterized by impaired insulin secretion. By 2030, the number of people with diabetes is predicted to reach 366 million, according to a report from the International Diabetes Federation (IDF) (1). In diabetic Mellitus (DM), metabolic dysfunction can increase the risk of developing cardiovascular diseases, dyslipidemia infections, morbidity, and death (2). Treatments for diabetes range from food and lifestyle modifications to biochemical and herbal medications, either alone or in combination (3).

There is a large global trend toward the use of medicinal herbs for the treatment of diabetes, and many people employ complementary and alternative medicine (4). The World Health Organization (WHO)

encourages researchers to explore the effectiveness and negative effects of medicinal herbs with potential therapeutic characteristics due to the adverse effects of some chemical medications and the high prevalence of people using them as medicine (5). Recent research found that various medicinal plants, including *Trigonella foenum*, *Urtica dioica* and *Nigella sativa* (NS), have positive benefits on regulating glucose levels and lipid profiles in diabetic models (6). One of the medicinal plants with anti-hyperlipidemia and anti-hyperglycemia properties *is nigella sativa* (7).

It is a plant belonging to the Ranunculaceae family that is very common throughout the Middle East, Its bitter-tasting, black-colored seed (8). Thymoquinone (TQ), flavonoids, nigellone, p-cymene unsaturated fatty acids and carvone are some of the chemical constituents of *nigella sativa*. It is utilized in traditional medicine in a variety of ways such as powder, extract and oil (8,9). There is evidence that N. *sativa* has several medicinal properties, such as antibacterial, anti-inflammatory, and antioxidant activities Several research has revealed that black seed has anti-diabetic properties (10).

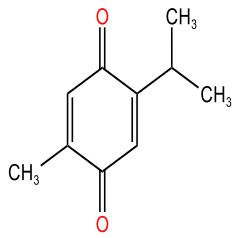
It seems that, there is no current comprehensive study that summarizes the effects of NS on lipids profiles, glycemic status and body Weight in diabetes mellitus, despite a number of narrative review studies on the medicinal characteristics of NS. Therefore, the goal of this study was to evaluate how N. *sativa* impacted the profiles, glycemic status and body Weight of DM rats.

Chemical constituents of *Nigella sativa*

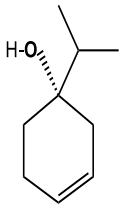
The high levels of fat, protein, and dietary fiber in cumin seeds make them a nutrient-dense food. Cumin seeds also contain significant amounts of nutritional elements, including iron, and vitamins B and E (11). Terpenoids, cymene and cuminaldehyde are the principal volatile components of cumin (12). The flavor of cumin is distinctive and potent. It contains essential oils, which give it a warm aroma. It has a warm aroma since it has essential oils in it. Cuminaldehyde and cuminic alcohol are the two primary fragrance chemical components (13). Roasted cumin also contains considerable amounts of the substituted 2-methoxy-3-sec-butylpyrazine, pyrazines, 2-ethoxy-3-isopropylpyrazine and 2-methoxy-3-methylpyrazine. Safranal, p-cymene, β-pinene, and γ-terpinene are additional ingredients (14). Nigella sativa seeds have a protein content of 26.7%, a fat content of 28.5%, a carbohydrate content of 24.9%, a crude fiber content of 8.4%, and a total ash content (4.8%). Additionally, *nigella sativa* seeds have significant amounts of several vitamins and minerals like Zn, Cu, Fe, and P (15).

Thymoquinone (30-8%), 4-terpineol (2-7%), carvacrol (6-12%), p-cymene (7-15%), t-anethole (1-4%), sesquiterpene longifolene (1-8%), and thymol are the most significant active components of N. Sativa (16–18). Most of N. sativa's pharmacological activities can be attributed to its quinine components, with TQ being the most prevalent. Unsaturated fatty acids such as linoleic acid (50-60%), oleic acid (20%), eicosadienoic acid (3%) and dihomolinoleic acid (10%) make up the majority of the fatty oil in N. sativa seeds, whereas saturated fatty acids (palmitic and stearic acids) make up as much as 30% (15). The main sterol in N. *sativa* oils is stigmasterol, which makes up 6.57% to 20.9% of all sterols accounts for 44% to 54% of all sterols (19).

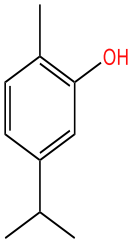
Active components in N. *Sativa*



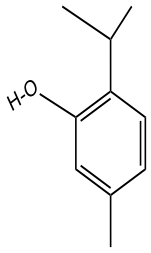
Thymoquinone



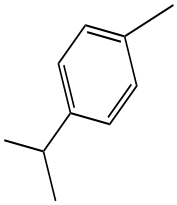
Terpinen-4-ol



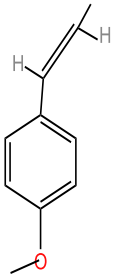
Carvacrol



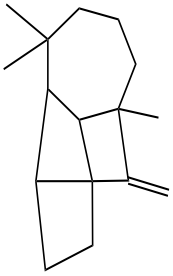
Thymol



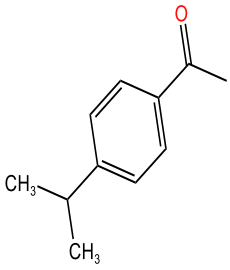
P-cymene



Anethole



Sesquiterpene longifolene



Cuminaldehyde

Pathophysiology of diabetes

Since diabetes mellitus has a complex pathophysiology and a variety of presentations, any classification of this disorder is arbitrary but yet informative. There are four primary forms of diabetes: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and diabetes associated with certain specific conditions, pathologies and disorders. In this review only type 1 and type 2 diabetes were considered.

Type 1 diabetes mellitus (T1DM)

T1DM, also known as insulin-dependent diabetes mellitus (IDDM) accounts for 5–10% of all diabetes cases. It is an autoimmune illness characterized by the T-cell-mediated death of pancreatic beta-cells, which causes an insulin deficiency and, eventually, hyperglycemia (20). Despite the fact that the etiology of this autoimmunity is still not fully understood, it has been discovered that both hereditary and environmental variables play a role. The pace of progression of this pancreatic β-cell-specific autoimmune illness as well as the condition itself is usually quick, as in newborns and young children, or it could be slow, like in adults (21). The final course of this illness is frequently defined by the diversity in the rate of immune-mediated death of the pancreatic β-cells (22).

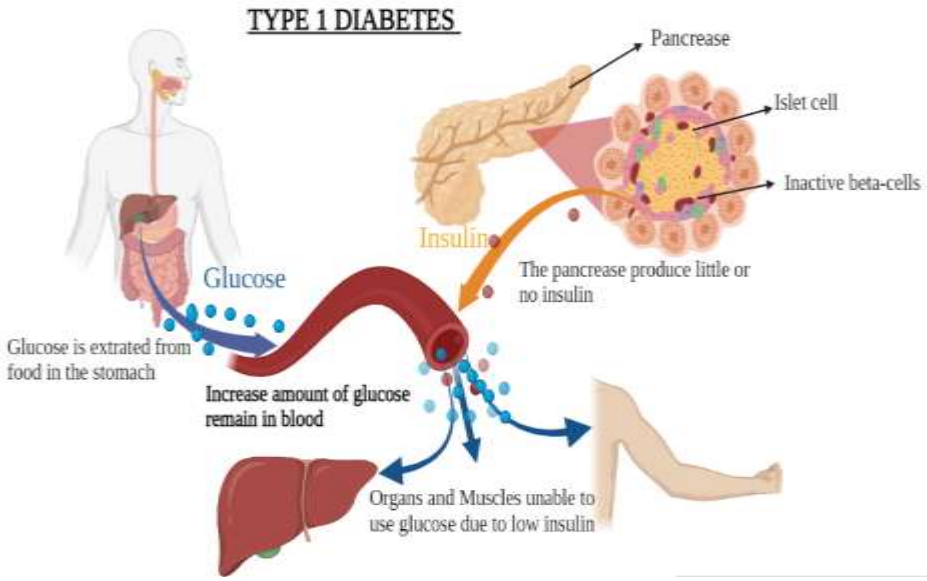


Figure 1. Pathophysiological process in Type 1 diabetes
Source: Adapted from "Type 1 diabetes", by biorender.com (2022).
https://app.biorender.com/biorender-type1diabetes

In rare instances, abrupt failures and β-cells degeneration in children and teenagers result in diabetic ketoacidosis (DKA), commonly referred to as the disease's initial symptom. Others get hypoglycemic syndrome (HDS) due to a very sluggish disease development and a little rise in fasting blood glucose levels (23). In some other situations, which include adults, β-cells may retain some degree of activity to emit only that quantity of insulin, which is only adequate to avoid ketoacidosis for many years (24). However, when their insulin deficit progresses, individual develop severe hyperglycemia and consequent ketoacidosis, which makes them insulin-dependent (25,26).

Autoantibodies in particular are one of the immunological markers associated with the autoimmune illness T1DM. The immune-mediated β-cell damage that characterizes this illness is linked to these autoantibodies. Glutamic acid decarboxylase autoantibodies (GADs) such as GAD65, islet cell autoantibodies (ICAs) to cytoplasmic proteins such as islet cell antigen 512 (ICA512), tyrosine phosphatase autoantibodies (IA-2 and IA-2), insulin autoantibodies (IAAs), and autoantibodies to islet-specific zinc transporter isoform 8 (ZnT8) are among the autoantibodies. For the clinical diagnosis of this condition, at least one of these autoantibodies can be employed, but often more of these immunological markers have been seen in between 85-90% of individuals with newly diagnosed T1DM (27). The most significant of these autoantibodies, GAD65, is discovered in between 80-90% of all T1DM patients at the time of diagnosis. IA-2α is found in between 54-75% of all T1DM patients at clinical presentation (28).

The proportion of the IAAs, which are significant immunological markers present in newborns and early children who are at risk for developing diabetes, declines with increasing. The existence of IAAs in these people who have never had insulin treatment is a crucial sign that they are developing T1DM. At the time of diagnosis,

IAAs are found in around 70% of all babies and young children (29,30). In individuals on insulin treatment, the IAAs also have a significant inhibitory effect on insulin activity. This immunological response has been seen with varied degrees of intensity in at least 40% of people on insulin therapy, while not always being clinically significant, and hence displays different clinical symptoms (31,32). The majority of these autoantibodies are polyclonal immunoglobulin G (IgG) antibodies, and they vary in how well they bind to insulin. IAAs can either have high insulin affinities with low insulin-binding capacities or low affinities with high capacities (33).

Type 2 diabetes mellitus T2DM

Insulin resistance and β-cell dysfunction are the two primary insulin-related abnormalities that define this form of diabetes (34,35). Insulin resistance is brought on by disruptions in a variety of cellular pathways, which lower the insulin sensitivity of cells in peripheral tissues, including muscle, the liver, and adipose tissue. Poor insulin sensitivity makes β-cells work excessively hard in the early stages of the illness to compensate for their inability to maintain normoglycemia by secreting more insulin.

Thus, hyperinsulinemia, or elevated insulin levels in the blood, avoids hyperglycemia. However, over time, the rise in insulin production from β-cells cannot entirely compensate for the fall in insulin sensitivity. Furthermore, β-cell function begins to decline, and β-cell malfunction ultimately leads to an insulin shortage. As a result, normoglycemia is unable to persist, and hyperglycemia develops. Even when insulin levels are decreased, in the majority of cases, the release of insulin is sufficient to prevent the onset of DKA (36).

But in severely stressful conditions, such as those brought on by infections or other pathophysiological conditions, DKA can occur. Some drugs that might result in DKA include sodium-glucose co-transporter-2 inhibitors, corticosteroids, and atypical antipsychotics (37–40). In the absence of any severe physiological stress circumstances, patients with T2DM typically do not require any insulin therapy when their illnesses first appear or even later in life (36).

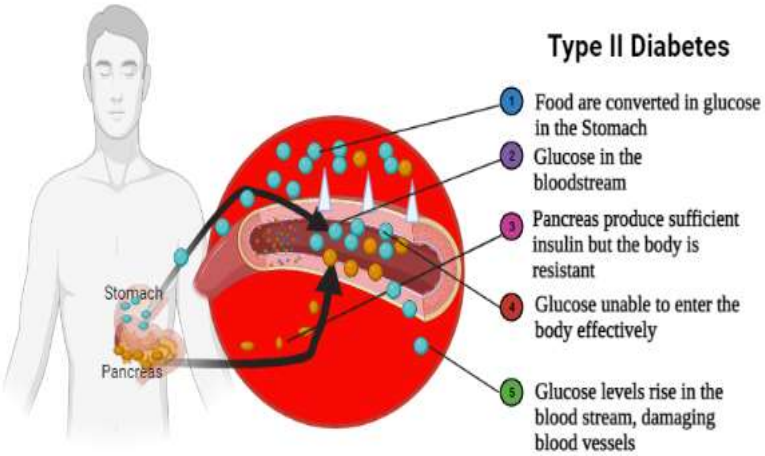


Figure 2. Pathophysiological process in Type 2 diabetes.
Source: Adapted from "Type 2 diabetes", by biorender.com (2022).
https://app.biorender.com/biorender-type2diabetes

T2DM develops very slowly and asymptomatically, and even mild hyperglycemia can take years to manifest. As a result, the condition is frequently misdiagnosed until it has advanced to the point where it is accompanied by symptoms that are typically indicative of severe hyperglycemia, such as weight loss, slowing of growth, blurred vision, polyuria, and polydipsia (34). In conclusion, the etiology of this kind of diabetes is complicated and involves a number of both known and unknown elements, including a confluence of significant environmental impacts and genetic predispositions. Ageing, obesity, family history of diabetes, physical inactivity, and adoption of contemporary lifestyles have all been linked to T2DM, which are more frequently than other risk factors: previous GDM in women, as well as pathophysiological disorders such hypertension and dyslipidemia.

MATERIALS & METHODS

We searched databases of PubMed, Science Direct, Google scholar and Springer and other Scientific Electronic Library Online databases, using the keywords; "N. *sativa"*, "black seed", "diabetes", "glucose", "lipid", "Weight", and "insulin" associated with the Boolean operator "AND".

Data were separately extracted by two reviewers, and duplicate data was removed by evaluating the titles and abstracts of each publication. To check for conformity with the inclusion criteria, the remaining articles were examined. After the papers underwent a critical review 15 articles were chosen (**Fig. 1**).

RESULT

Relevant publications of 240 were found in the literature searches. Of those, 219 papers were disregarded because they had nothing to do with DM, Nigella sativa (NS), or a bioactive component of it. The search was restricted to original publications written in English that had an abstract accessible, research solely on rats that had been given diabetes mellitus inducible, and treatments that combined an oral antidiabetic medication with NS. From the remaining 21 articles, 4 duplicate article and 2 systematic review article was removed before the full papers were retrieved for thorough reading. A total of 15 papers were selected for further assessment and underwent data extraction to be included in this review. Figure 1 depicts a flowchart of the selection procedure for exclusion.

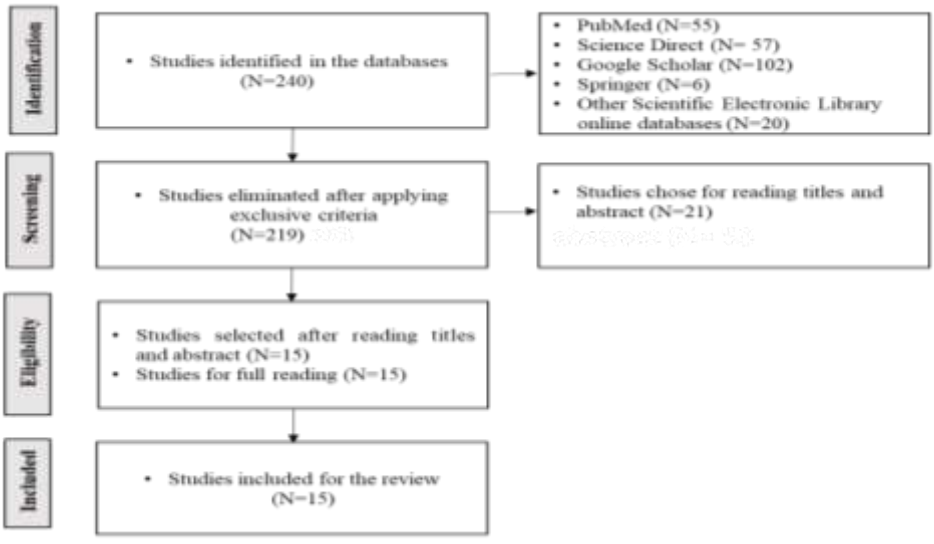


Figure 3. PRISMA Flow diagram. Source: Survey data, 2022

Table 1. Summary of the pharmacological activities of *Nigella sativa* in induced diabetic rats

Duration	Dosage	Key findings	References
30 days	2ml/kg and 5%a queous extract 0.2 ml/kg oil 3 mg/ml	Decrease Serum glucose after 10 days Increase Insulin concentration after 20 days Increase SOD level with extract and thymoquinone	(41)
	NSO 2 mL/kg	Decrease FBG Increase insulin levels	(2)
32 days	5, 10, and 20 mg/kg	Decrease in FBS Increase in Insulin secretion Increase in Pancreatic islets, cells and their diameter	(42)
3 months	1, 2 and 3 g/day	2 g/day: Decrease FBS, HbA1C Decrease 2hPG Decrease Insulin resistance Increase Beta-cell function.	(43)
20 days	50 mg/kg/ day	Decrease Plasma glucose, TC, TG Increase Insulin concentration, malate dehydrogenase in leukocytes	(44)
25days	810 mg/kg/day 2.5 ml/kg/day	Decrease in Glucose level Increase TAC	(45)
30 days	300 mg/kg/day	Increase Catalase, SOD and insulin levels Decrease in Lipid peroxidation, GPX and glutathione Decrease in Body weight	(45)
30 days	0.2 ml/kg/day	Partial regeneration/proliferation of pancreatic beta-cells Decrease in GSH, glucose level and serum nitric oxide Decrease in Lipid peroxidation and GSH Increase Insulin level, SOD and catalase levels	(46)
3 weeks	20 ml/kg	Increase Insulin level Decrease in Adrenocorticotropic hormone (ACTH)	(47)
2 months	20 ml/kg	Increase GSH and ceruloplasmin concentrations Decrease MDA and glucose levels	(48)
30 min	0.01, 0.1, 1 and 5 mg/ml	Increase insulin release	(49)
30 days	500 mg/kg	Decrease in Glucose concentration Increase in Insulin and C-peptide Increase TAC	(50)
15 days	20 ml/kg/day	Increase Insulin level Decrease Glucose level	(51)
56 days	4.0% fixed oil 0.3% essential oil	Hypoglycemic effects Increase HDL-C level Increase Total antioxidant capacity and glutathione Decrease MDA, TC, TG and LDL-c levels	(52)
5 Weeks	300 mg\kg	Increase in a high-density lipoprotein-cholesterol (HDL-C) level Decrease in levels of glucose, insulin, insulin resistance, (ALT), and (AST)	(53)

DISCUSSION

In a research by Saleh Mansi et al., oral administration of NS with 20 ml/kg aqueous extract for 15 days increased insulin levels in diabetic rats. It also had an impact on glucose metabolism by preventing the hypothalamus pituitary adrenal axis from functioning. By enhancing energy metabolism in mitochondria, TQ and other antioxidant components of NS can enhance insulin production and lessen liver damage in diabetic rats (54). Additionally, NS may enhance the insulin receptors' intracellular pathways. It can contribute to increased insulin levels and hypothalamus pituitary adrenal axis inhibition (47).

According to a research by Kaleem et al., oral treatment of 300 mg/kg ethanol extract of NS for 30 days reduced the levels of lipid peroxidation and antioxidant enzymes in diabetic rats. (20). After 25 days, the intraperitoneal administration of 2.5 ml/kg/day of NS oil and 810 mg/kg/day of crude methanol extract lowered glucose levels and elevated total antioxidant capacity (TAC) concentrations in diabetic rats (45). Most studies have linked NS potential anti-hyperlipidemia and anti-hyperglycemia capabilities to its antioxidant components. The two primary antioxidant components of NS are TQ and

dithymoquinone. Black seed can strengthen the body's antioxidant defense at all dosages, including ingesting and injecting. According to some research, NS can increase antioxidant enzymes and lower lipid peroxidation (29,31–33,41,43–45,48,49).

After 20 days of the intervention, Kanter et al. showed that 50 mg/kg thymoquinone given orally to diabetic rats enhanced leukocyte mitochondrial activity, energy metabolism, and insulin levels (46,50). Additionally, Salama et al. came to the conclusion that oral administration of 500 mg/kg NS oil to diabetic rats lowered blood glucose levels and raised insulin, pyruvate dehydrogenase, C-peptide, and TAC concentrations (50). According to a study by Alimohamadi et al., injections of a modest dose (5 mg/kg) of a hydroalcoholic extract of NS had an impact on pancreatic β-cell regeneration. As a result, in diabetic rats, insulin production rose and FBS levels fell (42). Also, according to Sultan et al., diabetic rats' glucose and malondialdehyde (MDA) levels were decreased, their lipid profiles were improved, and their body's antioxidant capacity was increased when they added 4% fixed oil and 0.3% essential oil of NS to their meal. After 56 days, they discovered that essential oils reduced oxidative damages in rats more effectively than fixed oils (52).

In diabetic models, NS can reduce gluconeogenesis, which results in hyperglycemia (41,42).TQ lower hepatic glucose synthesis and expression of the gluconeogenic enzymes; glucose-6-phosphate and fructose 1,6-bisphosphatase (45). Reduced oxidative stress aids in pancreatic β-cell regeneration (46), maintaining the health of pancreatic beta-cells , rising islet counts and islet sizes (42), increasing insulin secretion and preventing the formation of advanced glycation end products (55).

Lipid metabolism may be impacted both directly and indirectly by a reduction in free radical species. Antioxidant elements can shield tissues from lipid peroxidation and enhance the activity of enzymes involved in lipid metabolism. Additionally, glycemic improvement, particularly in people with diabetes, might modify lipid dysfunction (56). According to Le et al., a 4-week intragastric gavage of petroleum ether extract of NS resulted in a 25% decrease in food consumption. Additionally, it increased the rats' insulin sensitivity and lipid profile. They came to the conclusion that the NS petroleum ether extract had a mild anorexia effect that lowers food intake and body weight. Additionally, it can activate the protein kinase B (PKB) and mitogen-activated protein kinase (MAPK) pathways, which are implicated in the insulin-sensitizing effect (57). Also, Kaleem et al. observed that after 30 days, diabetic rats induced by streptozocin had less body weight when given 300 mg/day of an ethanolic extract of NS (58). According to a research by Najmi et al., 500 mg/day of NS oil reduced body weight and body mass index (BMI) in participants with metabolic syndrome after six weeks (59).

Moreover, NS has been shown by Bamosa et al. to reduce insulin resistance in T2DM patients. Reduced insulin resistance may result in quicker weight loss (10). DM patients' glycemic level and lipid profile may be improved with weight loss. Therefore, further research is required to fully understand how NS in DM treatment affects weight loss.

FUTURE PERSPECTIVE

Limited clinical trials without a control group have assessed the anti-hyperglycemia and anti-hyperlipidemia benefits of NS

despite, it effects on metabolic parameters in diabetic models. Future research should consider double-blind, placebo-controlled, random clinical trials to assess the effects of NS on glucose homeostasis and lipid levels in DM.

CONCLUSION

With several possible mechanism, N. sativa can enhance lipid profiles and glucose homeostasis in diabetic animals. Modification of metabolic parameters in DM can stop cardiovascular and atherosclerotic problems from developing in the body. NS can therefore be utilized in treatment of DM as supplementary therapy. However, determining the most efficient kind and amount of NS for the treatment of diabetes is challenging due to variations in models, chemical compositions of various sources of NS, dosage, and duration of intervention. More research are recommended to determine the best NS type and dose for diabetic people.

Declaration by Authors

Ethical Approval: Not Applicable
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Samuel A. Ofori, Enoch Owusu Yeboah, Papa Kofi Amissah-Reynolds et.al. An efficacy of anti-hyperglycemic agents (Nigella sativa) in blood, body weight and glucose levels of diabetes mellitus rats: a comprehensive review. *Int J Health Sci Res.* 2023; 13(1):59-70.
DOI: *https://doi.org/10.52403/ijhsr.20230109*

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