International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 709-717 www.ijprajournal.com ISSN: 2456-4494

# A Review on Comparative Evaluation of Nigella Sativa against Antidiabetic and Antioxidant Properties

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Date of Submission: 05-05-2024 Date of Acceptance: 15-05-2024

**ABSTRACT:**
Nigella sativa, commonly known as black seed, has gained significant interest for its potential health benefits. This review examines existing research on the comparative antidiabetic and antioxidant properties of Nigella sativa. We evaluate studies investigating the effects of Nigella sativa extracts and oil on blood sugar control and antioxidant enzyme activity in diabetic models. The review analyzes the efficacy of different Nigella sativa preparations and explores the potential mechanisms underlying their therapeutic effects. By comparing findings from various studies, this review aims to provide a comprehensive understanding of the current evidence on Nigella sativa's role in diabetes management and its antioxidant properties.

## I. INTRODUCTION

**PANCREAS The anatomy of pancreas**

The pancreas is an elongated organ, light tan or pinkish in color, it extended retroperitoneally across the posterior abdominal wall from the second part of the duodenum to the spleen. The right side of the organ (called the head) is encircled by the duodenum, the tapered left side extends slightly upward (called the body of the pancreas) which forms the main bulk of the organ, ends in the tail that lies in contact with the spleen[6]

**Pancreas histological structure**

The pancreas consists of exocrine and endocrine cells making upto 98% of the human pancreas. The pancreas acinar cells are grouped into lobules forming the ductal system which eventually joins into the main pancreatic duct. The main pancreatic duct itself usually joins the common bile duct to enter the duodenum as a short single duct at the ampulla of cater[3]The endocrine pancreas consists of hormone-producing cells arranged in nests or islet called the islet of Langerhans, the hormones produced are secreted directly in the circulation and there is no access to pancreatic ductular system.

**Exocrine function**

The pancreatic acinar cells are responsible for production of the digestive enzymes; these include amylase, lipase, colipase, phospholipase and the protease. These enzymes are stored within the acinar cells in secretary granules and are released by exocytosis. Most of these enzymes are secreted in the pancreas from which activated in the duodenum[9]

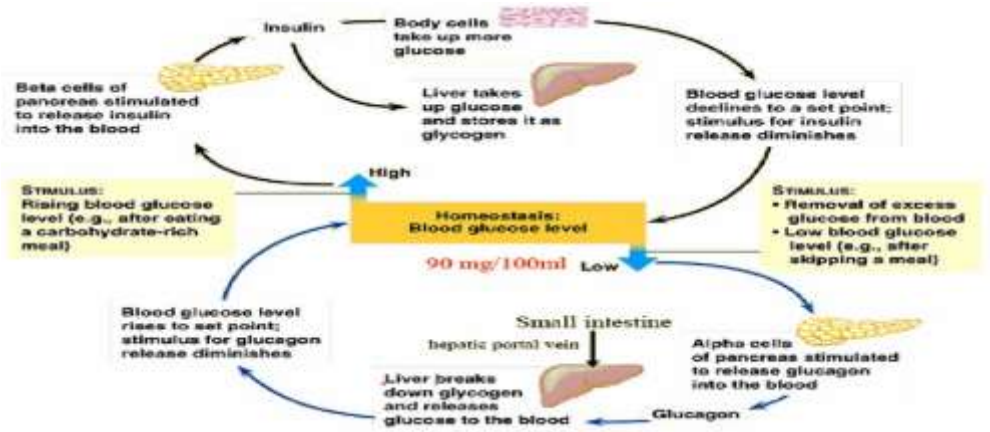


**Figure 1: The Role Of Pancreas In The Body**

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**PANCREAS FUNCTION**

**a)Exocrine function**

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**b)Endocrine function**

The islet of Langerhans consists of five main types of cells correspond to different secretory component. The B-cells which are most common and responsible for insulin production, the α- cells produce glucagon, the D-cells produce somatostatin, and pp-cells produce pancreatic polypeptides and the enterochromaffin cells produces serotonin. A number of other hormones have been identified within the endocrine pancreas including gastrin releasing peptide, neuropeptide Y and galanin. These are believed to be neurotransmitters in the neurogastrointestinal axis. [9]

**Insulin**

**Structure**

Pancreatic cells from exocrine and endocrine pancreas are also interrelated given that they lack basal membranes. Peri-insular acini possess larger number of zymogen granules than acini removed from islets. The presence of insulin nearby also impacts the morphology of peri-insular acini.These observations have put forward the concept of insulin-acinar axis, which suggests the regulation of acinar cells functioning by islet peptides. Peri-insular acini are exposed to high concentrations of islets hormones due to protrusion of efferent vessels stemmed from islets into surrounding exocrine pancreas. Insulin is produced in the beta cells of the Islets of Langerhans in the pancreas. It is a peptide hormone and the name comes from the Latin word insula, meaning island.

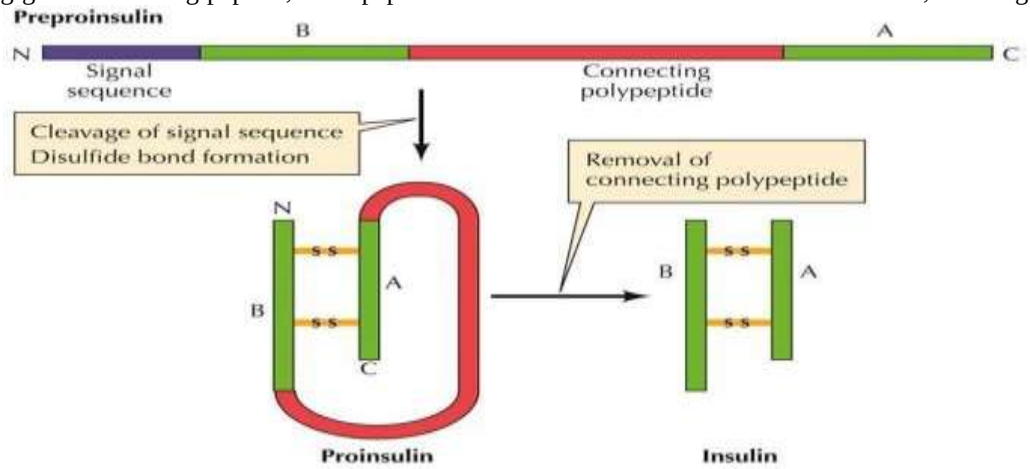


**Figure 2: Insulin Biosynthesis**

**Secretion**

Beta cells produce insulin in two phases; the first is a rapid, triggered phase and the second phase is slow release. The rapid triggered phase occurs in reaction to different types of factors such as glucose, glucagon-like peptide-1 (GLP-1), glucose independent insulinotropic peptide (GIP), adrenaline via □2 receptors, and arginine, leucine, acetylcholine and chole-cyctokinin (CCK) (Cawston et al. 2010: Layden et al. 2010). Glucose, as the main triggering factor in releasing insulin, enters pancreatic beta cells through the glucose transporter GLUT2, and once inside the cells it is converted to glucose-6 phosphate (G6P) via a phosphorylation process by glucokinase (hexokinase IV). The process is rate-limiting and is responsible for glucose-related insulin secretion. The converted form of glucose, glucose-6-phosphate, enters glycolysis, in which it forms pyruvate, which then enters the pathway for ATP generation in mitochondria[1]

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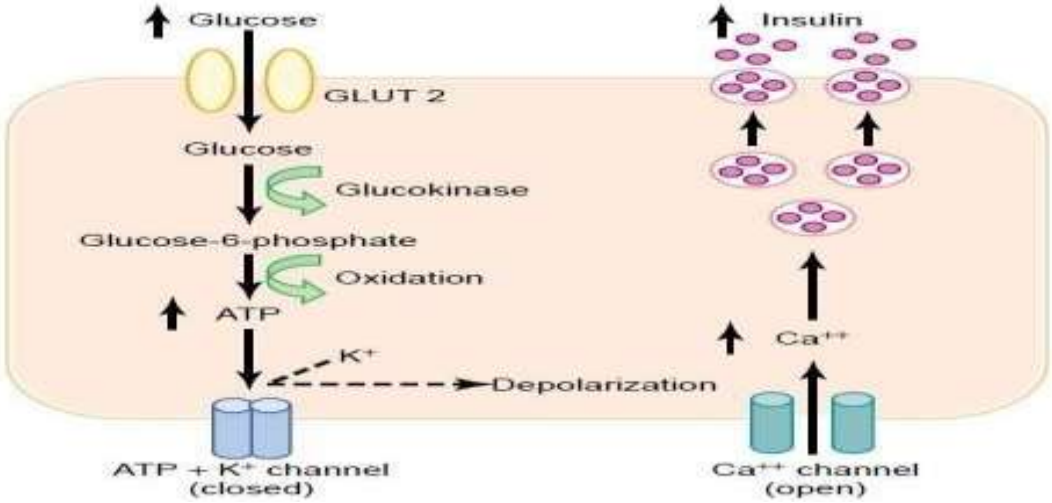


**Figure : Insulin Release And Action**

**INSULIN MECHANISM OF ACTION**

Insulin induces its effect by binding to the insulin receptors (IR) expressed on the cell plasma membrane. The receptors belong to the tyrosine kinase receptor group and in terms of functionality are similar to the insulin-like growth factor-1 (IGF-1) receptors (Lyssenko et al.2009).This transmembrane receptor is activated by insulin, IGF-I AND IGF-II (Bouatia-Naji et al.2009) and is composed of two subunits, alpha and beta, encoded by a single gene, INSR, on chromosome 19 (Miedema et al. 2005). Once the tyrosine kinase activity of the receptor is activated a series of biochemical pathways are triggered, mediated primarily by activation of insulin receptor signalling proteins (IRSs). Regulation of glucose uptake by peripheral tissues involves control of GLUT4 expression (see below), and phosphatidyl-inositol 3-phosphate kinase (PI3K) plays a central role in mediating insulin signals that inhibit gluconeogenesis, stimulate glycogen synthesis and storage and stimulate protein synthesis and lipogenesis[7]

**Other pancreatic hormones function**

Three other pancreatic hormones are produced in the islet of langerhans include: glucagon, consisting of 29 amino acids produced by the α cell. Somatostatin consisting of 14 amino acids and produced by the D cell. Pancreatic polypeptides, 36 amino acids with an amide C-terminal, produced in the PP cell. Glucagon antagonizes most of insulin, s actions, while stimulating insulin secretion. Somatostatin inhibits the three other islet hormones and a range of hormones from different origins. Pancreatic polypeptide inhibits pancreatic secretion altogether[4]

**Glucagon**

Glucagon is the hormone secreted by pancreatic -cells. Glucagon also plays a central role in the regulation of glucose homeostasis. Glucagon stimulates glycogenolysis in the liver to increase blood glucose levels. Under postabsorptive conditions, approximately half of total hepatic glucose output is dependent on the maintenance of normal basal glucagon levels and inhibition of basal glucagon secretion with somatostatin causes a reduction in hepatic glucose production and plasma glucose concentration. After a glucose containing meal, glucagon secretion is inhibited by hyperinsulinemia and the resultant hypoglucagonemia contributes to the suppression of hepatic glucose production and maintenance of normal postprandial glucose tolerance.

**[9]Diabetes mellitus (DM)**

Diabetes mellitus is a metabolic condition characterized by hyperglycemia and an inability of endogenous insulin to secrete or function properly. Diabetes is a serious health issue, and its prevalence is rising at alarming rates. According to recent estimates, diabetes mellitus is the most frequent major metabolic illness in the world, affecting around 200 million individuals. Diabetes is a leading cause of mortality.

Type 2 diabetes is caused by the interplay of genetic, behavioral, and environmental risk factors. Although the genetic basis of type 2 diabetes has yet to be established, there is significant evidence that modifiable risk factors

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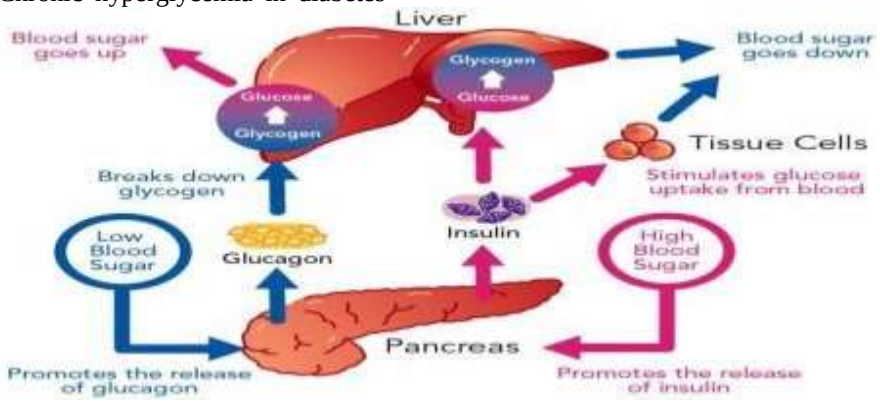
such as obesity and physical inactivity are the primary nongenetic determinants of the illness. Altered dietary pattern also participates in the increased incidence of diabetes. Diabetes is characterized by hyperglycemia with slowly progressive end organ damage in the eyes, kidneys, blood vessels, heart, peripheral nerves and brain. In poorly treated diabetic animals or humans, increased cell death occurs in several tissues and organs, contributing to secondary diabetes consequences. Chronic hyperglycemia in diabetes mellitus is a primary initiator of diabetic microvascular sequelae such retinopathy, neuropathy, and nephropathy Regulation of Glucose HomeostasisBlood sugar regulation is the process by which the levels of blood sugar, primarily glucose, are maintained by the body. Glucose regulation in the body is a process of keeping the body inhomeostasis. Blood sugar levels are regulated by negative feedback in order to keep the body in homeostasis.




**EPIDEMIOLOGY DIABETES**

The press release on 14 November - World Diabetes Day 2011 pointed out that, the new figures indicate the number of people living with DM is expected to rise from 366 million in 2011 to 552 million by 2030, if no urgent action is taken. This equates to approximately three new cases every ten seconds or almost ten million per year. In addition, report said, in some of the poorest regions in the world such as Africa, where infectious diseases have traditionally been the focus of health care systems, diabetes cases are expected to increase by 90% by 2030. At least 78% of people in Africa are undiagnosed and do not know they are living with diabetes. In addition, few clinical reports released by International Diabetes Federation are as follows 80% of people with diabetes live in low- and middle-income countries. [3]

- 78,000 children develop type 1 diabetes every year.
- The greatest number of people with diabetes are between 40-59 years of age

**Causes of diabetes**

Diabetes as a common and complex disease has been characterized by the following causes:

**a)** **Obesity:** obesity is also considered a key risk factor for T2DM. The association between increasing body mass index (BMI) and greater weight gain and risk of diabetes is most pronounced among Asians, suggesting that lower cut off BMI values are needed to identify Asians at a higher risk of diabetes.

**b)** **Abdominal adiposity:** there is also a probable indication that there is a preferential abdominal adiposity in Indians irrespective of the degree of general adiposity.

**c)** **Genes:** since 2007, genome-wide association studies has catalogued around 20 genes (like TCF7L2, HHEX, CDKAL1, SLC30A8 etc.) showing a strong association (with modest odds ratio ranges between 1.2 to 1.5) with T2DM.

**d)** **Ethnicity:** the interethnic differences (like differences in prevalence of T2DM among Europeans, Americans, Chinese, and Asian Indians) in insulin resistance may have an environmental or genetic explanation. The main acquired factors that seemingly increase insulin resistance in all ethnic groups include obesity, sedentary lifestyle, diet rich in animal products, and aging. [4]

**TREATMENT FOR DIABETES**

Diabetes is now ranked as the sixth leading cause of death by disease in the U.S (National diabetes fact sheet, Atlanta2004). Its

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treatment as well as the management of diabetesrelated complications remains a top priority for governments worldwide, since the economic burden in 2007 alone exceeded $174 billion. [10]

**Pharmacological treatment**

The aim of management is to control symptoms, prevent acute metabolic complications of ketoacidosis and hypoglycemia. Encourage self-reliance and self-care, prevent or treat complication early and prevent the increased morbidity and mortality associated with poorly managed diabetes. In type 1 DM, glycemic control is achieved by subcutaneous insulin administration two or more times a day.

**Insulin therapy**

Diabetes, being one of the primary causes of increased cardiovascular morbidity and mortality in Western countries, constitutes a large burden to health care systems in terms of both direct and indirect costs. Therefore, efficient glucose control (attainment of normal HbA1C, prandial and postprandial glucose levels) is essential to the prevention of the life-threatening complications of this disease. Insulin is a hormone that treats diabetes by controlling the amount of sugar (glucose) in the blood. When used as a medication, it is derived from either pork (porcine), beef (no longer available in the U.S.), or is genetically made to be identical to human insulin. typically taken so that two-thirds of the total daily dose is given in the morning and one-third of the total daily dose is given in the evening[12]

**ORAL HYPOGLYCEMIC AGENTS**

**1)Sulfonylureas**

The Sulfonylureas (SUs) stimulate the second phase of insulin secretion by pancreatic beta cells, that is to say, the release of preformed insulin.


**Major target organs and mechanism of actions of orally administeredantihyperglycemic agents in type II diabetes mellitus**

**Other secretagogue drugs: Repaglinide and Nateglinide Repaglinide**

Repaglinide (Novonorm®) is a derivative of carbamoyl methyl benzoic acid (meglitinide family). It has a mechanism of action very similar to that of the SUs, but differs in the specific binding site to the SU receptor. (Repaske et al., 2016).

**Nateglinide**

Nateglinide (Starlix®) is a derivative of D-phenylalanine that directly stimulates the beta cell. Its action is based on the fact that although the response to glucose is lost in the first phase of insulin secretion, the response to certain amino acids like phenylalanine is conserved.

**Biguanides**

The biguanides, unlike the SUs, do not stimulate insulin secretion by the pancreatic beta cells. Therefore, strictly speaking they cannot be considered hypoglycemic agents because they only reduce glycemia in diabetic patients.

**Thiazolidinediones**

The mechanism of action involves binding to specific nuclear receptors called PPAR(peroxisome proliferator-activated gamma receptor), whose stimulation regulates the transcription of specific genes that will lead to an increase in the number and affinity of insulin receptors, especially the glucose transporters GLUT-4.

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**Alpha-glycosidase inhibitors**

The inhibitors of the alpha-glycosidases (acarbose –Glucobay®, Glumida®– and miglitol –Diastabol®, Plumarol®-) competitively and reversibly inhibit intestinal alpha-glycosidases, thus delaying and partly impeding carbohydrate absorption. Consequently, their main effect is to reduce postprandial hyperglycemia[12].

**Induction of DM by cytotoxic agents**

Alloxan and streptozotocin are widely used to induce experimental diabetes in animal. The mechanism of their action in B cells of the pancreas has been intensively investigated and now is quite well understood. [8]

**HERBAL THERAPIES FOR DIABETES**

Herbal medicine and plant derivatives have a long history of use as therapeutics for a variety of diseases and health conditions in many cultures around the world.

**MECHANISM OF ACTION OF HERBAL ANTIDIABETICS**

The antidiabetic activity of herbs depends upon variety of mechanisms. The mechanism of action of herbal anti-diabetic could be grouped as:

1. Adrenomimeticism, pancreatic β-cell potassium channel blocking, cAMP (2nd messenger) stimulation.
2. Inhibition in renal glucose reabsorption.
3. Stimulation of insulin secretion from β-cells of islets or/and inhibition of insulin degradative processes.
4. Reduction in insulin resistance.
5. Providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the -cells.
6. Regenerating and/or repairing pancreatic β-cells.
7. Increasing the size and number of cells in the islets of Langerhans.
8. Stimulation of insulin secretion.
9. Stimulation of glycogenesis and hepatic glycolysis.
10. Protective effect on the destruction of the β-cells.

**DRUGS**

**Glibenclamide**, also known as glyburide, is an antidiabetic medication used to treat type 2 diabetes. It is recommended that it be taken together with diet and exercise. It may be used with other antidiabetic medication. It is not recommended for use by itself in type 1 diabetes. It is taken by mouth. Common side effects include nausea and heartburn.

**Chemistry**

**Glibenclamide**1-[4-[2-(5-chloro-2-methoxy benzamido) ethyl]-phenyl sulfonyl]-3-cyclohexyl urea, is a second-generation drug that differs from those described above in that it has a more complex structure in the sulfonylamideregion of the molecule into which an additional pharmacophoregroup is added. It is synthesized from 2-methoxy-5-chlorobenzoic acid chloride, which is transformed into an amide by reacting it with 2-phenylethylamine. This undergoes subsequent sulfonylchlorination by chlorosulfonic acid, and then aminationby ammonia, which gives sulfonamide.The resulting sulfonamide is reacted with cylclohexylisocyanate to give the desired glibenclamide[9]

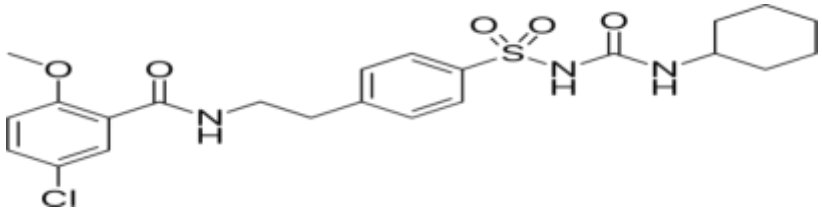

**Figure 7: Chemical structure of** G**libenclamide**

**Molecular Formula:**C23H28ClN3O5S **Molecular Weight:**494.004 g/mole

**IUPAC Name:**5-chloro-N-[2-[4-(cyclohexyl carbamoyl sulfonyl)phenyl]ethyl]-2-methoxy- benzamide.

**Density:**1.180 g/ml g/cm3

**Melting Point:**173-175°C **Storage Temp**: 2-8°C

**Odor:** Characteristic odor

**Color:**white

**Synonyms:**Diabeta, Glucovance, Glynase

**MECHANISM OF ACTION**

The medication, a sulfonylurea, works by binding to and inhibiting the ATP-sensitive potassium channels ($K_{ATP}$) inhibitory regulatory subunit sulfonylurea receptor 1 (SUR1) in pancreatic beta cells. This inhibition causes cell membrane depolarization, opening voltage-

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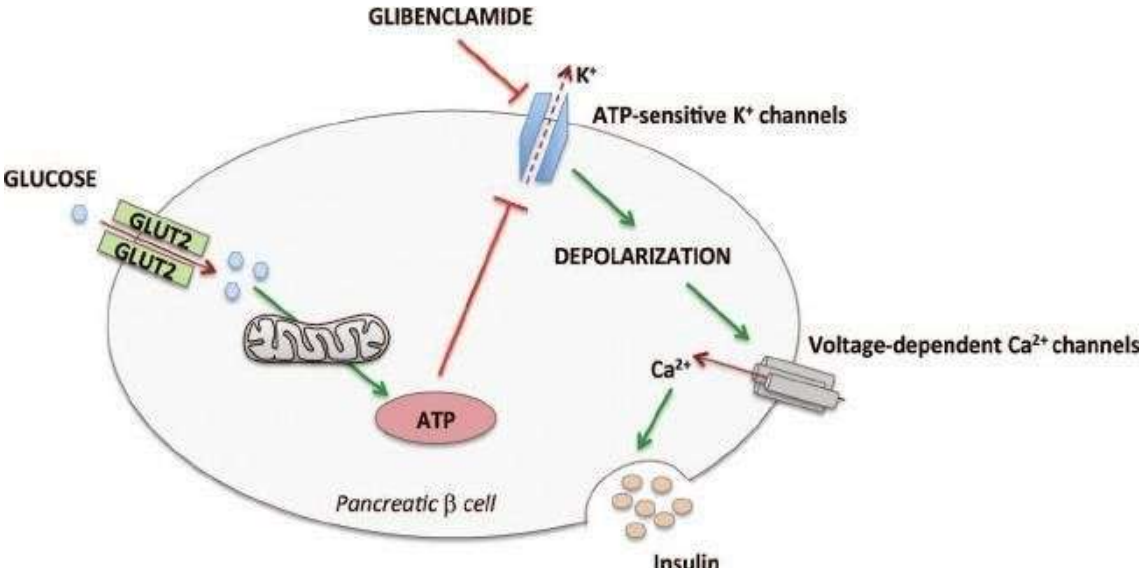
dependent calcium Channels. This results in an increase in intracellular calcium in the pancreatic beta cell and subsequent stimulation of insulin release. [7]




**PLANT PROFILE**

**NIGELLA SATIVA**

Nigella sativa L. (N. sativa) is a small shrub (20-90 cm in tall) under the botanical family, Ranunculaceae. It is native to Southern Europe, North Africa and Southeast Asia; cultivated in many countries in the world like Middle Eastern, Mediterranean region, South Europe, India, Pakistan, Syria, Turkey, Saudi Arabia.

**Morphology Of Nigella Sativa**

According to Ahmad A et al review Nigella sativa an annual flowering plant which grows to 20- 90 cm tall, with finely divided leaves, the leaf segments narrowly linear to threadlike. The flowers are delicate, and usually coloured white, yellow, pink, pale blue or pale purple, with 5-10 petals.

**Origin and global distribution**

The origin of NS is not well documented. Most probably, NS is indigenous to the Mediterranean region. As the seeds of this plant were first discovered in Tutankhamun's tomb in Egypt in the 18th dynasty.

**Classification:**

**Kingdom:** Plantae.

**Sub Kingdom:**Tracheobionata that is, vascular plant.

**Division:**Magnoliophyta

**Class:**Magnoliopsida

**Order:**Ranunculales

**Family:**Ranunculaceae

**Genus:**Nigella

**Species:**sativa

**Scientific name:**Nigellasativa L.

**Common names:**Black Cumin, Black Seed, Nigella, Kalonji

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**Microscopy**

Transverse section of seed shows single layered epidermis consisting of elliptical, thick-walled cells, covered externally by a papillose cuticle and filled with dark brown contents. Epidermis is followed by 2-4 layers of thick walled tangentially elongated parenchymatous cells, followed by a reddish-brown pigmented layer composed of thick walled, rectangular elongated cells. Inner to the pigment layer, is present a layer composed of thick walled rectangular elongated or nearly columnar, elongated cells.

## PHARMACOLOGY

**Antidiabetic activity**

The effect of N. sativa and TQ on histopathological changes of the sciatic nerve was evaluated. The treatment with N. sativa and TQ showed a sharp decrease in elevated serum glucose and an increase in lowered serum insulin concentration in streptozotocin (STZ) induced diabetic rats. The treatment with N. sativa and TQ increased the area of insulin immunoreactive beta cells significantly. Only fewer morphological changes were seen in diabetic animals treated with N. sativa and TQ. The ultra-structural features of axon also showed a remarkable improvement suggesting the utility of N. sativa and TQ as a potential treatment on peripheral neuropathy in STZ induced diabetic rat[6]

**Antioxidant capacity**

A number of in vitro and in vivo antioxidant studies have been conducted with N. sativa extracts, seed oil and TQ. The finding is suggesting having potential radical scavenging and inhibitory effects of oxidative stress. TQ effectively changed the parameters including adenosine deaminase (ADA), catalase (CAT), myloperoxidase (MPO), lipid peroxidase (LPO), reduced glutathione (GSH), glutathione-S-transferase (GSH-ST), glutathione peroxidase (GPx), superoxide dismutase (SOD) and nitric oxide (NO). It also reduced the malonilealdehyde (MDA), conjugated diene (CGD) levels and pro-inflammatory mediators interleukin-1beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and prostaglandin (PGE2) rather than interleukin-10 (IL-10)

## II. CONCLUSION

This study investigated the antidiabetic and antioxidant properties of the plant methanolic extract of Nigella sativa. The different active components are found in Nigella sativa, which may be responsible for the actual antidiabetic. The present investigation indicates that methanolic extract of Nigella sativa exert significant protection against alloxan-induced diabetes.

There are increase in the levels of Ch, TG, LDL and decrease of HDL level in diabetic group compared to control group by using alloxan induced diabetes. Decrease of Cholesterol, TG, LDL levels and increase of HDL level in standard compared to the diabetic control by using NSS showing the hypolipidemic effect of this plant. In Glibenclamide treated rats, there are reduction in the levels of Ch, TG, LDL and increase level in HDL in NSS 1200 mg/kg compared to the diabetic control. The hypolipidemic effect may be due to inhibition of fatty acid synthesis. [14]

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