INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Study of Nigella Sativa on Diabetes Mellitus

Kaje Geeta Nandkishor*, Thore Dinesh Dipak, Rupali Jadhav, Ingle R. B.

Rashtriya college of pharmacy Hatnoor kannad Dist Sambhajinagar Maharashtra India.

ARTICLE INFO

Published: 15 Jan. 2025
Keywords:
Nigelle sativa (kalonji), Diabetes mellitus, Thymoquinone
DOI:
10.5281/zenodo.14650784

ABSTRACT

Various studies have been conducted on the effect of medicinal plants in the treatment of different diseases, including diabetes. Nigella Sativa (N. sativa) is a plant with edible and medicinal properties that are of interest to scientists in traditional and complementary medicine, and much research has been conducted on this plant. Comprehensive reports are used to investigate the effect of N. sativa in vitro, animal models, and clinical trials in the treatment of diabetic diseases. An online database search was conducted to investigate the potential anti-diabetic effect of N. sativa. The results of various studies indicate that this plant can act as hypoglycemic, and due to antioxidant properties, it can have positive results in reducing blood sugar and glycosylated hemoglobin levels and controlling insulin secretion and glucose homeostasis. The effect of N. sativa in animal models has shown that N. sativa oil can eliminate oxygen-free radical species similar to hydroxyl free radicals and superoxide radical anions. Therefore, in this review study, we intend to address all the therapeutic aspects and effects of the black seed plant in the cellular and animal environment and clinical trial studies for the optimal use of this medicinal plant. In conclusion, the antidiabetic activities of N. sativa are indeed well established. However, in some cases, the molecular modulation underlying these activities remains unknown. N. sativa has been demonstrated to improve blood glucose and insulin levels, mitigate diabetes complications, and stimulate glucose absorption. Its antioxidant function, flavonoid and triterpenoid components, and potency to modulate insulin secretion in pancreatic cells introduced it as a safe medicinal herb for dietary adjuvant with antidiabetic medications. However, it has been declared to a decline in blood lipid profiles, and risk factors for cardiovascular diseases in Type 2 Diabetes patients. Further research must concentrate on patients unresponsive to available anti-diabetic drugs and hyperlipidemia T2D. Thus, further studies into its medicinal effects are recommended.

INTRODUCTION

***Corresponding Author:** Kaje Geeta Nandkishor
Address: *Rashtriya college of pharmacy Hatnoor kannad Dist Sambhajinagar Maharashtra India.*
Email ✉: kajegeeta@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Medicinal plants have been used for curing diseases for many Centuries in different indigenous systems of medicine as well As folk medicines. Moreover, medicinal plants are also used In the preparation of herbal medicines as they are considered To be safe as compared to modern allopathic medicines. Many Researchers are focusing on medicinal plants since only a Few plant species have been thoroughly investigated for their Medicinal properties, potential, mechanism of action, safety Evaluation and toxicological studies. Among various medicinal plants, Nigella sativa (N. sativa) (Family Ranunculaceae) is emerging as a miracle herb With a rich historical and religious background since many researches revealed its wide spectrum of pharmacological Potential. N. sativa is commonly known as black seed. N. sativa Is native to Southern Europe, North Africa and Southwest Asia And it is cultivated in many countries in the world like Middle Eastern Mediterranean region, South Europe, India, Pakistan, Syria, Turkey, Saudi Arabia. The seeds of N. sativa and their oil have been widely used For centuries in the treatment of various ailments throughout The world. And it is an important drug in the Indian traditional System of medicine like Unani and Ayurveda. Among Muslims, it is considered as one of the greatest forms of healing Medicine available due to it was mentioned that black seed is The remedy for all diseases except death in one of the Prophetic Hadith. It is also recommended for use on regular basis in Tibbs-e-Nabwi (Prophetic Medicine). N. sativa has been extensively studied for its biological Activities and therapeutic potential and shown to possess Wide spectrum of activities viz. as diuretic, antihypertensive, Antidiabetic, anticancer and immunomodulatory, analgesic, Antimicrobial, anthelmintic, analgesics and anti-Inflammatory, spasmolytic, bronchodilator, gastro protective, Hepatoprotective, renal protective and antioxidant properties. The seeds of N. sativa are widely used in the treatment of Various diseases like bronchitis, asthma, diarrhoea, rheumatism And skin disorders. It is also used as liver tonic, digestive, anti-Diarrheal, appetite stimulant, emmenagogue, to increase milk Production in nursing mothers to fight parasitic infections, And to support immune system. Most of the therapeutic Properties of this plant are due to the presence of thymoquinone (TQ) which is a major active chemical component of the Essential oil. Black seeds are also used in food like flavouring Additive in the breads and pickles because it has very low level of toxicity.

Pharmacognostical characteristics:

N. sativa is 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. The fruit is a large and inflated capsule Composed of 3-7 united follicles, each containing numerous Seeds.

Classification:

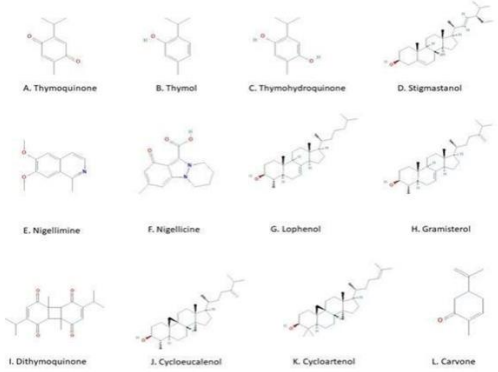
Kingdom - Plantae
Division - Magnoliophyta
Class - Magnoliopsida
Order - Ranunculales
Family - Ranunculaceae
Genus - Nigella Species: N. sativa

Figure No. 1 Nigella Sativa (whole plant, Seeds, Flower)

Characteristics of the seeds and powder:

Macroscopically, seeds are small dicotyledonous, trigonus, Angular, regulose-tubercular, 2-3.5mm 1-2 mm, black Externally and white inside, odour slightly aromatic and Taste bitter. Microscopically, 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. Endosperm consists of Thin walled, rectangular or polygonal cells mostly filled with Oil globules. The powder microscopy of seed powder shows Brownish black, parencymatous cells and oil globules.

Chemical composition of black seeds:



There is very little research work Done on the phytochemicals of N. sativa. The seeds of the plant are reported to Contain few chemical compounds like nigellone, nigellicine, nigellimine, Nigellimine-N-oxide, avenasterol-5-ene, Avenasterol-7-ene, campesterol, cholesterol, Citrostadienol, cycloeucalenol, 24-ethyl-Lophenol, obtusifoliol , sitosterol, Stigmastanol, stigmasterol, stigmasterol-7-Ene, beta-amyrin, butyrospermol, Cycloartenol, 24-ethyl-lophenol, Gramisterol, lophenol, 243-methyllophenol, Obtusifoliol, sitosterol, stigmasterol-7-ene, Beta-amyrin, butyrospermol, cycloartenol, 24-methylene-cycloarthanol, taraxerol, Tirucallol, 3-O-[β-D-xylopyranosyl (1-3)-α-L-rhamnopyranosyl (1-4)- β-D-Glucopyranosyl (1-6)β-D glucopyranosyl] Hederagenin, volatile oil (0.5-1.6%), fatty Oil (35.6- 41.6%), oleic acid,

esters, esters of Unsaturated fatty acids with C15 and higher Terpenoids, esters of dehydrosteraric and Linoleic acid, aliphatic alcohol, nigellidine, Carvone, d-limonene, cymene, α,β-Unsaturated hydroxyl ketone, steroids, Hederagenin glycoside, melanthin, Melanthigenin, bitter principle, tannins, Resin, protein, reducing sugar, glycosidal Saponin, 3-O-[β-D-glucopyranoside, Cycloart-23-methyl-7,20, 22-triene-3β, 25-Diol, nigellidine-4-O-sulfite, nigellamines A3, A4, A5, C, nigellidine A1,A2,B1 and B2 The seed oil of the plant N. sativa Contains cholesterol, campesterol, Stigmasterol, β-sitosterol, α-spinasterol, (+)-Citronellol, (+)-limonene, p-cymene, Citronellyl acetate, carvone, nigellone, Arachidic, linolenic, linoleic, myristic,oleic, Palmitic, palmitoleic and stearic acids, Fixed oil isolated from the N. sativa species Are linoleic acid (55.6%), oleic acid (23.4%) And palmitic acid (12.5%) and volatile oils Are trans-anethole (38.3%), p-cymene (14.8%) , limonene (4.3%) and carvone (4.0%), 2 –(2-methoxypropyl)-5-methyl-1, 4-benzenediol, thymol and carvacrol. Vanilliac acid are isolated from the root part Of the plant. Recently, people around the globe are opting to use herbal medicines to manage chronic conditions such as diabetes, hypertension, cancer, obesity, and others as modern Medicines may be associated with harmful and undesirable side effects. Perceived failure of allopathic medicines, Relatively high cost of allopathic medicines, social cultural Practices and/or herbal knowledge, poor accessibility to Medical facilities and safety concerns about allopathic medicines are the primary reasons for the patients' preference Of herbal remedies to manage chronic conditions. The prevalence of use of herbal medicines is higher among The patients with diabetes. A cross sectional survey determined that about 7.3% of 310 Jordanian diabetic patient's used N. sativa to manage their diabetes. Nigella sativa (Black seeds) is an herb, which belongs to Ranunculaceae family. sativa has been used to treat various chronic conditions such as diabetes, hypertension, cancer, obesity, and others. The most prominent active constituent of N. sativa is thymoquinone (TQ) and it also contains other bioactive constituents including dithymoquinone (DTQ), carvone, limonine, nigellidine, nigellicine, nigellicine and others. The present review is aimed to analyzed The antidiabetic activity of N. sativa as many type 2 diabetic Patients use it as a complementary therapy along with their Modern allopathic medications or as an alternative therapy. The use of N. sativa is very common in traditional medicines including Unani, Ayurveda, Chinese medicine, and Others. Several clinical and pre-clinical studies have already demonstrated the antidiabetic activity of N. sativa And its active constituent Thymoquinone.

Clinical studies of N. sativa

Numerous clinical studies have demonstrated the antidiabetic efficacy of N. sativa (Table 1). The administration Of powdered N. sativa seeds for 40 days in 46 patients with Type 2 DM produced a significant reduction of fasting blood Glucose (FBG), total cholesterol, LDL-cholesterol and triglyceride's while increasing the levels of insulin and HDL Cholesterol. A prospective observational study found that The administration of 2.5 mL of N. sativa oil 2 times a day In patients taking Atorvastatin 10 mg once daily and Metformin 500 mg twice daily for 6 weeks, resulted in significant improvement in plasma levels of fasting blood glucose, low density lipoprotein (LDL)-cholesterol and total Cholesterol. Furthermore, a pilot study of 41 patients with Type 2 DM revealed that the consumption of N. sativa oil Along with their regular antidiabetic medications for 40 Days resulted in significant reduction of fasting blood glucose (FBG) and enhanced insulin levels compared to the control levels.

TABLE 1. Clinical antidiabetic studies of N. sativa

S. No	Study design	Number of participants	Outcome
1	Prospective observational study.	60	Significant improvement in plasma levels of FBG, LDL-c and TC
2	Pilot study	41	Significant reduction of FBG and enhanced insulin levels compared to the control levels
3	Prospective cohort study	94	Significant reduction of FBG, 2 hours PPBG and HbA1c
4	Pilot study	80	Significant reduction of HbA1c,FBG and PPBG
5	Randomized, double-blind, placebo controlled clinical trial	70	Significant reduction of HbA1c,FBG,PPBG and BMI
6	Participants blinded, placebo controlled clinical trial	114	•Significant reduction of FBG,HbA1c and glutathione and thiobarbituric acid reactive substance (TBARS) •significant elevation of TAC,SOD and glutathione •significantly higher beta cell activity •significantly lower insulin resistance
7	Double blind, randomised controlled trial	250	•Decreased FBG and lipids like LDL and triglycerides •Improved BMI, waist circumference, circumference, blood pressure and c-reactive protein levels
8	Double blind, randomised controlled trial	72	•significant reduction of FBG, HbA1c,LDL-c and triglycerides. •Decreased insulin resistance, body weight and BMI •Elevated HDL-c levels
9	Participant blinded, placebo controlled clinical trial	60	•significant reduction of HbA1c •protected diastolic function and improved systolic function
10	Single blind, randomised controlled trial	99	Significant reduction of in HbA1c levels
11	Prospective, comparative, open -label study	63	Reduction of fasting glucose along with other parameters like serum creatinine, blood urea, and elevated GFR, and hemoglobin levels.

12	Prospective, open - labelled, randomised clinical trial	66	•Reduction of fasting blood glucose,2 hr post prandial Glucose and HbA1c levels •significant decline of body weight, waist circumference, BMI, fasting insulin, insulin resistance, TC, LDL-c and triglycerides
13	Non-randomized clinical trial	114	Significant reduction of TC,LDL-c, SBP, DBP, MAP and HR
14	Placebo - controlled clinical trial	40	Significant reduction of HOMA-IR index, and serum levels of insulin, Glucose, triglycerides, TC, LDL-c, CRP, AST, ALT, ALP
15	Randomised clinical trial	117	Statistically similar improvement in body weight, MI, glycemic, lipids and inflammatory parameters

Benefits of Black Cumin on Human Health and Disease Conditions:

Health benefits of black cumin and its bioactive TQ cover almost every physiological System, ranging from the nervous system to the integumentary system, and metabolic Disorders, and various cancer.

- Antioxidant Effect
- Anti-inflammatory Effect
- Immunomodulatory Effect
- Protection against Neurological Disorders
- Protection against Neuroinflammation
- Protection against Alzheimer's disease
- Protection against Parkinson's Diseases
- Protection against Ischemic stroke and Traumatic Brain Injury
- Anti cancer Effects
- Anti-obesity effect
- Anti-dyslipisemic effect
- Cardio protective and Antihypertensive Effects
- Antidiabetic effect
- Hepatoprotective Effects
- Pulmonary Protective Effects
- Gastro protective Effects
- Effects on Fertility and Reproduction
- Protection against Skin Diseases
- Wound Healing
- Acne Vulgaris
- Vitiligo
- Bone Regenerative Effects
- Anti-Arthritis Effects
- Protection against Emerging Diseases
- Black Cumin and TQ as a Promising Antidote
- Black Cumin **as a Galactagogue**

MATERIALS AND METHODS:

Extraction: The seeds of Nigella sativa are crushed to path powder the use of mortar pestle and passing via sieve. The extraction is finished using four distinctive solvents namely Petroleum Ether, Chloroform, Methanol, Hydro-alcoholic solution (20% DM Water in Methanol).

Extraction System In Flow Diagram:

•collect dried seed of Nigella sativa
•route with motor pestle
•Passing with sieve
•Powder load in extraction device
•Run via solvent with (no. of cycles required)
•accumulate, filter and evaporate it.

Extraction System As Follows:

Equipments used are.

1. Velocity Extractor: Grounded Powder is loaded inside the 4 chambers together with purified sand. The lead taking solvent is put in pure protected solvent. After three cycles of

computerized extraction the equipment. The procedure maintains for all 4 solvents. The extracts are saved in smooth dried box.

2. Soxhlet equipment: path the seeds of Nigella sativa and upload with solvent within the chamber. After four cycles it finished. The extracts are saved in easy dried container.

3.Aspirator: Dried grounded powders are installed closed glass aspirator. Solvent in equal order is poured over the powder so that each one powder is in direct contact with solvent. The aspirator is kept overnight undisturbed with solvent. Subsequent day the extract is accumulated and saved. All the extracts are subjected to awareness the use of Rotavapor equipment till handiest focused oil or sticky solid is left. The hydro-alcoholic component is fractionated against Petroleum ether, ethyl acetate and chloroform. The natural portion is accumulated and dried until minimal drop of oily substance is amassed. They may be mixed with parent extract and stored in cool and dry region. The best left water element is dried to shape solid.

Extraction Approach For Thymoquinone From Nigella Sativa:

Traditional strategies:

Maceration: Extract one gram of black seed with 20 mL of solvent (hexane and methanol in two exclusive conical flasks) turned into macerated at room temperature for 4 h. Then, the extract solution turned into centrifuged at 4000 rpm at 4°C for 10 min and filtered.

Percolation: Extract one gram of black seed with 20 mL of solvent (hexane and methanol in two one of a kind conical flask) become heated in a 40°C water tub for four h. Then, the extract solution became centrifuged at 4000 rpm at 4°C for 10 min and filtered.

Non-conventional strategies:

UAE : One gram of black seed with 20 mL of solvent (hexane and methanol in two different conical flasks) changed into ultrasonicated for 1 h. Then, the extract solution was centrifuged at 4000 rpm at 4°C for 10 min and filtered.

Loose radical scavenging pastime: The antioxidant hobby of the N. sativa seed changed into analyzed via studying the scavenging interest of the strong free radical DPPH. DPPH answer turned into prepared with the aid of dissolving 9.75 µg of DPPH in a 250 mL volumetric flask with methanol. Zero.20 mL of pattern diluted with 0.8 mL methanol was then combined with 2 mL of DPPH solution. The absorbance of the combinations was measured at the wavelength of 517 nm. The percentage of DPPH radical scavenging became decided with respective solvents as blank. Ascorbic acid became used as a fine manage on this take a look at. The proportion of unfastened radical scavenging interest is calculated with the aid of using the subsequent system.

Statistical evaluation: A one-manner ANOVA test has been hired to determine the sizable difference among the amount quantified via UV-Vis spectroscopy based on the absorbance. Similarly, a one-way ANOVA test turned into achieved to determine the great distinction among the DPPH radical scavenging activity and different extraction methods.

Chemical Test:

1. Tests for Alkaloids

Mayer's Test:

Add Mayer's reagent (potassium mercuric iodide) to the extract. A creamy white precipitate indicates the presence of alkaloids.

Dragendorff's Test:

Add Dragendorff's reagent (potassium bismuth iodide) to the extract. An orange or reddish-brown precipitate confirms alkaloids.

2. Tests for Saponins

Foam Test:

Shake the extract vigorously with water. Persistent foam formation for about 10 minutes indicates the presence of saponins.

3. Tests for Fixed Oils and Fats

Spot Test:

Press a small quantity of the extract between filter paper. An oily translucent stain indicates the presence of fixed oils.

Sudan III Test:

Add a few drops of Sudan III dye to the extract. Formation of a red color indicates the presence of fats and oils.

4. Tests for Phenolic Compounds and Flavonoids

Ferric Chloride Test:

Add 1% ferric chloride solution to the extract. A green or blue color indicates the presence of phenolic compounds.

Alkaline Reagent Test:

Add a few drops of sodium hydroxide to the extract. A yellow coloration that disappears on adding dilute acid confirms flavonoids.

5. Tests for Tannins

Gelatin Test:

Add 1% gelatin solution with sodium chloride to the extract. A white precipitate indicates the presence of tannins.

Ferric Chloride Test:

A dark green or blue-black coloration with ferric chloride confirms tannins.

6. Tests for Thymoquinone (Key Bioactive Compound)

Thin Layer Chromatography (TLC):

Use silica gel plates and an appropriate solvent system (e.g., chloroform: methanol 9:1).Spray with vanillin-sulfuric acid reagent. A reddish-brown spot confirms thymoquinone**.**

Spectrophotometric Analysis:

Extract thymoquinone and measure its absorbance at 254 nm in a UV-visible spectrophotometer.

7. Tests for Carbohydrates

Molisch's Test:

Add a few drops of alpha-naphthol and sulfuric acid to the extract. A violet ring at the interface indicates carbohydrates.

8.**Tests for Proteins**

Biuret Test:

Add sodium hydroxide and copper sulfate to the extract. A violet color indicates proteins.

Xanthoproteic Test:

Add concentrated nitric acid to the extract. A yellow color that turns orange upon adding an alkali confirms proteins.

Table No.2 Chemical Test

Test Perform	Chemical Test	Observation	Result
Test for Alkaloids	Saturated solution of picric acid + Filtrate	Yellow color precipitate	Positive
Test for Fixed oil	Drops of filtrate on filter paper	Stain on filter paper	Positive
Test for volatile oil	1.Drops of field rate on filter paper. 2.Filtrate + Sudan 3 dye	Permanent stain on filter paper Red color obtained	Positive Positive
Test for Tannins	5% solution of fecl3 + filtrate	Green color or yellow color obtained	Positive
Test for Flavonoids	NaOH solution + filtrate	Yellow color produced	Positive
Test for Glycoside	Dilute H2So4 + filtrate + 5% solution of NaOH + add Fehling solution (A+B)	Red color produced	Positive
Test for steroids	Concentrated sulfuric acid + Filtrate	Yellow color on top	Positive
Test for Triterpenes	Concentrated sulfuric acid + Filtrate	Green color on bottom	Positive

Introduction: Diabetes Mellitus

Diabetes mellitus comprises of a Greek word 'diabetes'., to go through, and a Latin Word 'mellitus', i.e., sweet. IN 150 AD Arateus, a Greek physician of Cappadocia was The First one to use the word diabetes. WHO (World Health Organization) defines diabetes As, a chronic, metabolic Disease characterized by elevated levels of blood glucose (or Blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. It is also Known as Hyperglycemia or Adult-onset diabetes. According to World Health Organization, in 2014 it is found that 422 million adults Are affected by diabetes. It causes 1.5 million deaths in 2012 and it is seen that the Majority of population are mainly affected by type-II diabetes. It is also found that Previously type-It diabetes was diagnosed among adults but now it occurs in children Also . The oxidative stress is a known diabetes which causes due to increased free Radical production and impaired antioxidant defenses. Diabetic is a chronic Metabolic disease causing significant morbidity and premature cardiovascular mortality Worldwide. According to the World Health Organization (WHO) approximately 537 Million adults (ages 20–79 years) are living with diabetes today, and this number is Predicted to rise to 643 million by 2030 and 783 million by 2045. Diabetic Mellitus is A very common metabolic disorder which affects the human population throughout The world, characterized by hyperglycemia and arises due to defects in insulin secretion, insulin action or both. Chronic hyperglycemia which is a common effect of Uncontrolled diabetes causes long-term damage, dysfunction and failure of several Organs such as kidneys, eyes, nerves, heart and blood vessels. Diabetes is Mainly categorized into two types, type-I diabetes and type-II diabetes.

Types Of Diabetes Mellitus:

- Insulin dependent or juvenile-onset diabetes mellitus (Type 1 Diabetes mellitus)
- Non insulin dependent or maturity-onset diabetes mellitus (Type 2 Diabetes Mellitus)

Type 1: Diabetes Mellitus

Insulin dependent diabetes mellitus (IDDM), i.e., patients require periodic doses of Insulin it can occur at any age, commonly occurs in children, Characterized by the Marked inability of the pancreas to secrete insulin because of autoimmune destruction Of the beta cells. Kidney malfunctioning, nerve impairment, cardiovascular disease and Retinal degeneration occur.

Type 2 : Diabetes Mellitus

Type 2 diabetes is non-insulin dependent diabetes mellitus (NIDDM). It accounts for About 90% of the diagnosed cases of diabetes and affects 18% of the population over 65 years of age. Insulin receptors on insulin responsive cells do not respond normally to Insulin and are therefore called as "insulin resistant", thereby increasing blood glucose Level.

Some Oral anti-diabetic drugs-

Type of anti-diabetic drugs-

1· Sulfonylureas/insulin tropics: Glipizide, Glimepiride

2· Biguanides: Metformin

3· a-Glycosidase inhibitors: Acrabose, Voglibose.

4· Thiazolidinedione: Pioglitazone, Rosiglitazone.

5· DPP-4 inhibitors (Glistens): Sitagliptin, Vildagliptin.

Current status:

In 2012, approximately 1.5 million deaths were attributed to diabetes. The terms "diabetes" and "mellitus" are derived from Greek, with "diabetes" meaning "a passer-through" and "mellitus" meaning "sweet," likely due to the excessive Urination attracting flies and bees in diabetic patients. Since its first description over 3000 years ago by ancient Egyptians and Araetus of Cappadocia, significant progress has been made in understanding diabetes. Economic status and

insurance Coverage may influence the prevalence of type 2 diabetes, while recent studies Suggest race also plays a role in both type 1 and type 2 diabetes Prevalence. Diabetes mellitus is a serious chronic illness characterized by Hyperglycemia resulting from deficient insulin production by pancreatic beta cells or Inefficient insulin utilization by the body. It is the seventh leading cause of death in The USA, with 422 million adults worldwide diagnosed with diabetes in 2014, four Times higher than in 1980. Carbohydrates and fats in the diet may contribute to Diabetes, as inhibiting starch-digesting enzymes or glucose transporters can reduce Glucose absorption. Despite being one of the greatest health crises of the 21st Century, many health authorities overlook the impact of diabetes and its Complications. Estimates project a significant increase in diabetic patients by 2040, with type 2 diabetes being more prevalent, especially in developed countries due to Factors like aging populations, urbanization, sedentary lifestyles, and poor dietary Habits. While the exact cause of diabetes remains uncertain, genetics, environmental Factors, and conditions like autoimmune destruction of pancreatic beta cells are Believed to contribute to its development.

The International Diabetes Federation Reported a global diabetic population of 436 million in 2019, with 90% having type 2 Diabetes. The availability and efficacy of oral antidiabetic drugs have improved over The years, with seven types now available in Japan. Projections from the World Health Organization indicate a further increase in the diabetic population to over 300 Million by 2025. India, China, and the USA are expected to have the largest diabetic Populations by 2030. Type 1 diabetes accounts for over 90% of childhood and Adolescent cases in most western countries, with less than half diagnosed before Age 15.

Current synthetic drugs in the Treatment of T2DM

1. Biguanides : The class of Biguanides includes the metformin and two withdrawn Agents phenformin and buformin. The reason for Removing phenformin and buformin From the market was The occurrence of fatal lactic acidosis . Introduced in The market in 1950, metformin is a well-accepted first-line choice for the treatment of T2DM Due to its good efficacy, low price and low rate of adverse effects especially in long- term use . Metformin reduces fasting plasma glucose concentrations by Reducing rates of hepatic glucose production through a reduction in gluconeogenesis And glycogenolysis .Metformin also affects peripherally and improves skeletal Myocyte glucose uptake, reduces the overall plasma free fatty acid (FFA) concentration And induces mild weight loss through reduction of caloric intake .

Advantage:

• Good glucose-lowering effect
• Flexible dosing
• Oral route
• Low cost
• No hypoglycemia

Disadvantage:

• Risk of lactic acidosis in patients With impaired kidney function,
• Heart failure, hypoxemia,
• Alcoholism, cirrhosis, contrast Exposure,
• sepsis, and shock.
• Gastrointestinal side effects.
• B12 deficiency

2. Sulphonylureas:

Sulphonylureas as the fast insulin secretagogues are the oldest Available class of oral Glucose-lowering agents which were Introduced in the market in the 1940s and approved for use in 1994 for T2DM before metformin. This class of oral drugs include the second-generation Agents glipizide, gliclazide, glibornuride, gliquidone, glisoxepide, glyclopyramide and glibenclamide as well as the First generation agent's

acetohexamide, chlorpropamide, tolazamide and tolbutamide. The third-generation sulphonylurea glimepiride is as effective as second- generation sulphonylureas and appears to have several clinical advantages over Conventional sulphonylureas. In clinical studies, glimepiride provides more stable blood Glucose control, lowers risk of hypoglycemia and induces less weight gain in Comparison to other sulphonylureas .

Advantage:

• Good glucose-lowering effect
• Low cost
• Inexpensive
• Oral route

Disadvantage:

• Risk of hypoglycemia
• Significant drug-to-drug Interactions
• Weight gain
• Limited durability
• Risk of cardiovascular events.

3.Thiazolidinediones:

Troglitazone was the first thiazolidinedione approved as a Glucose-lowering therapy for Patients with T2DM in 1997 .Troglitazone was subsequently withdrawn from Use, in March 2000, because of causing severe hepatic toxicity . Two currently available PPAR-g agonists, rosiglitazone and pioglitazone, were approved in 1999. This class of Agents also known as glitazones like the biguanides metformin do not increase insulin Secretion but rather increase insulin Sensitivity in muscle and adipose tissue and in the liver by Activating PPAR-g and Affecting gene regulation in the target Cells. PPAR-g is essential for normal metabolism of lipids such as Adipocyte differentiation And proliferation as well as fatty acid Uptake and storage. Thiazolidinediones Exert their Insulin-sensitizing actions by promoting genesis of small adipocytes and Redirect fat from non-adipose tissues, such as liver fat, To (subcutaneous) adipose Depots . Although thiazolidinedione may enhance insulin sensitivity by keeping Fat where It belongs and sparing other tissues such as the liver, skeletal Muscle and Possibly b-cells from lipotoxicity, indirect effects May also be involved via alteration of Gene transcription such As adiponectin. Adiponectin, an adipocytokine, produced Exclusively by adipose tissue increases insulin sensitivity .

Advantage:

• Good glucose-lowering effect
• Reduces CVD (pioglitazone)
• Oral route
• No hypoglycemia

Disadvantage:

• Slow onset of action.
• Contraindicated in patients with Heart failure,
•hemodynamic instability, and hepatic dysfunction
• Osteoporosis
• Weight gain
• Small increase in LDLc

4.Disaccharidase inhibitors (a-glucosidase Inhibitors)

The a-glucosidase inhibitors acarbose and miglitol are two of These agents which were Released in the market in 1996 . Initial investigations of voglibose as another disaccharidase Inhibitor have not been Proceeded further. Absorption Of carbohydrates requires eventual breakdown of Disaccharides Into monosaccharides by the a-glucosidase enzyme in the brush Border Of the small intestine. Disaccharidase inhibitors, such as Acarbose and miglitol, inhibit Digestion of carbohydrates by affecting the breakdown of disaccharides to Monosaccharides In the intestinal epithelium. As a consequence, delayed and Decreased absorption of the sugars happen. The a-glucosidase Inhibitors decrease both Postprandial blood glucose and postprandial insulin levels and in that way these Improve sensitivity To insulin and release the stress on b-cells .According to some studies, acarbose does not directly alter Insulin resistance but may Lower postprandial

plasma insulin Levels, fasting blood glucose, glycosylated Haemoglobin, Plasma triglycerides and/or cholesterol concentrations .Acarbose is Only minimally absorbed from the gut and thereby Considered as a non-absorbable Inhibitor that makes this drug With no systemic adverse effects even after long-term Administration. The symptoms, which is due to undigested carbohydrates, occur in ~ 30 – 60% of patients and tend to decrease With time and seem to be dose-dependent . Acarbose is Composed of an acarviosin moiety with a maltose at the reducing Terminus. Acarviosin is a sugar composed of cyclohexitol Unit linked to a 4-amino-4,6-dideoxy-D-glucopyranose unit, Which is part of the acarbose and its derivatives .

Advantage:

• Mild glucose-lowering effect
• Relatively inexpensive
• Oral route
• No hypoglycemia

Disadvantage :

• Gastrointestinal side effects.
• Contraindicated in patients with Inflammatory bowel disease.
• Partial bowel obstruction, or Severe renal or hepatic disease.
• Frequent dosing schedule
• Avoid if renal disease

5.DPP-4 inhibitors:

DPP-4 inhibitors are promising new class of anti-diabetics That are extremely studied . In October 2006, the first DPP-4 inhibitor, sitagliptin, was introduced in the Market. Indeed, several other drugs such as vildagliptin, saxagliptin, Alogliptin, linagliptin And anagliptin have been approved in Certain countries for the treatment of T2DM. Other candidates have been demonstrated to be in an advanced stage of Clinical trials For T2DM .Inhibition of DPP-4, a serine protease, enhances endogenous GLP-1 Activity by decreasing the rate of GLP-1 degradation, which represents a promising Approach to the treatment Of T2DM . DPP-4 inhibitors increase circulating GLP-1 And GIP levels in humans, which leads to increased Glucose-dependent secretion of Insulin and decreased blood Glucose, haemoglobin A1C and glucagon levels**.**DPP-4 is a 766 residue N-terminal dipeptidyl exopeptidase That specifically Cleaves an amino acid sequence having proline or alanine at the N-terminal penultimate (P1) position but may also cleave substrate with non-preferred amino acids at This Position . DPP-4 inhibitors include diverse structural types. Many DPP-4 inhibitors have five- membered heterocyclic rings Such as pyrrolidine, cyanopyrrolidine, thiazolidine and Cyanothiazolidine as a proline mimetic in the P1 part. Vildagliptin Structure as a Cyanopyrrolidine derivatives are presented in(cyanopyrrolidine ring is highlighted in red) Despite the positive results of vildagliptin in clinical trials, One of the issues Encountered with the use of 2-cyano pyrrolidine derivatives is their stability in solution Due to the participation of cyano group in an intramolecular cyclisation Process leading To inactive products .

Advantage:

• Moderate glucose-lowering effect
• Decreases postprandial glucose
• Oral route
• No hypoglycemia
• Decreases BP

Disadvantage:

• Concern regarding acute Pancreatitis.
• Pancreatic disease
• Arthritis
• Bullous pemphigoid
• Relatively expensive
• Modest glycemic lowering.

Sicknesses: (Diabetes Mellitus):

Diabetes mellitus is a chronic disorder of carbohydrates, fat and protein metabolism. A defective or poor insulin secretary response, which interprets into impaired carbohydrates (glucose)

use, is a characteristic feature of diabetes mellitus, as is the resulting hyperglycaemia's Diabetes mellitus (DM) is generally called a "sugar" and it is the most commonplace Endocrine disease and usually takes place whilst there is deficiency or absence of insulin or rarely, Impairment of insulin activity (insulin resistance) . The worldwide Diabetes Federation (IDF) estimates the entire wide variety of diabetic subjects to be round 40.9 million in India and that is further set to rise to 69.9 million through the 12 months 2025 .

Symptoms Of DM :

Fatigue Polyphagia, Polydipsia, polyuria, vomiting, dehydration etc., are common symptoms & signs are observed in Diabetes Mellitus. Diabetes Mellitus is particularly as a result of the destruction of beta cells inside the pancreas. Its purpose's autoimmune disorders along with Addison's ailment, Hashimoto's Thyroiditis & Graves' ailment.

Effect of kalonji on DM:

As per the observe, the extract of Nigella Sativa has effective anti-diabetic ability. Thymoquinone was injected in diabetic mice. The result confirmed a reduction in blood glucose level with augmentation of insulin degree and C-peptide in fashions. Any other in-vivo take a look at was conducted within the mice to evaluate the Anti-Diabetic interest [24,25,26]. The aqueous extract of a few current studies Nigella Sativa was administered every day within the models via gavage. It became discovered that extract substantially reduced the glycemia, TG, T-cholesterol, LDSL-c and TBARS and possessed antihyperglycemic, antihyperlipidemic and antioxidant impact . Seeds had been washed and dried. After accumulating final analysis facts of glycemic control and lipid profile, a dose of two-month Nigella Sativa seeds (2g/day) changed into given to patients in group-2 to be chewed and consumed. Every concern glycemic manipulate turned into measured through recording FBS, PPBS and HbA1c at the beginning of the trial. Blood samples had been assayed for serum lipid profiles. Advice about dietary and way of life changes had been given to each Nigella sativa and popular agencies. This study turned into authorized via the moral committee of Kannur medical university. After informed consent changed into received, blood samples had been drawn after an overnight fast at baseline and after months used. HbA1c turned into assessed by way of intervention. For the dedication of HbA1c EDTA blood was an enzymatic method. Fasting plasma glucose became measured by using the hexokinase technique given in each agencies.

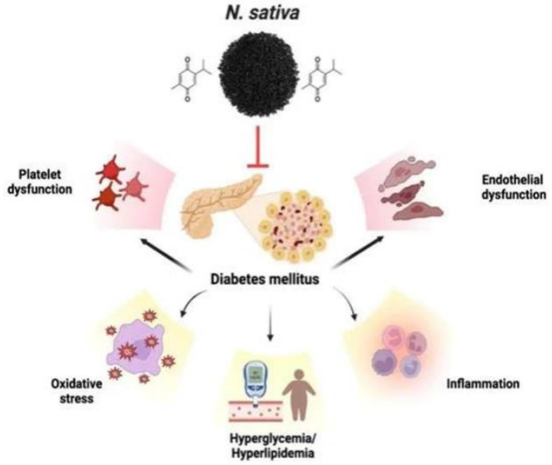


Fig.No.2 Various complications associated with diabetes

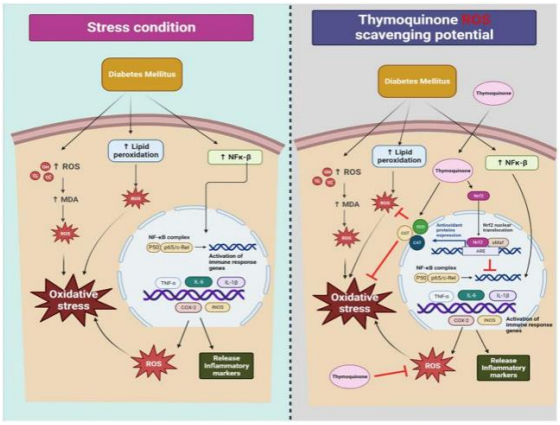


Figure No. 3 Mechanistic elements of oxidative stress and it's Mitigation though Thymoquinone

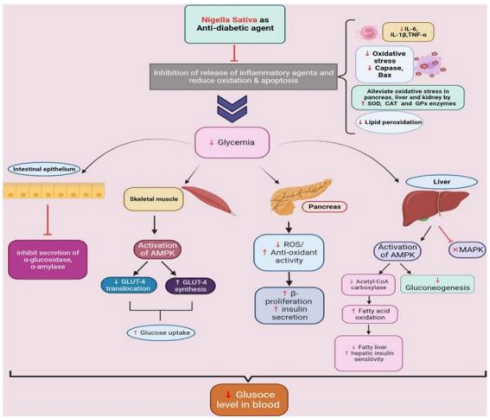


Figure No.4 Mechanism Of Nigella Sativa on Diabetes Mellitus

CONCLUSION:

The use of herbal medicine to manage chronic conditions including diabetes is increasing. Numerous clinical studies have demonstrated the antidiabetic efficacy of black seeds (N. sativa) and its major bioactive constituent thymoquinone. Various mechanisms including decreased insulin resistance, accelerated β-cell proliferation, enhanced pancreatic insulin secretion, diminished hepatic gluconeogenesis, enhanced glucose uptake, and attenuated oxidative stress have been proposed for the antidiabetic activity of N. sativa. The patients with diabetes may use N. sativa as an adjuvant therapy, which may help to reduce the dose of modern antidiabetic medicines and adverse events.

REFERENCES

1. Pinti, M. V., Fink, G. K., Hathaway, Q. A., Durr, A. J., Kunovac, A., & Hollander, J. M. (2019). Mitochondrial dysfunction in type 2 diabetes mellitus: An organ-based analysis. American Journal of Physiology-Endocrinology and Metabolism, 316(2), E268–E285. https://doi.org/10.1152/ajpendo.00314.2018
2. Lotfy, M., Adeghate, J., Kalasz, H., Singh, J., & Adeghate, E. (2017). Chronic complications of diabetes mellitus: A mini review. Current Diabetes Reviews, 13(1), 3–10. https://doi.org/10.2174/1573399812666160421121254
3. Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., … & IDF Diabetes Atlas Committee. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Research and Clinical

Practice, 157, 107843. https://doi.org/10.1016/j.diabres.2019.107843

4. Maideen, N. M. P., & Balasubramaniam, R. (2018). Pharmacologically relevant drug interactions of sulfonylurea antidiabetics with common herbs. Journal of HerbMed Pharmacology, 7(3), 200–210. https://doi.org/10.15171/jhp.2018.33
5. Pakkir Maideen, N. M., Manavalan, G., & Balasubramanian, K. (2018). Drug interactions of multimode antidiabetics involving CYP enzymes and OATP1B1 transporter. Therapeutic Advances in Endocrinology and Metabolism, 9(9), 259–268. https://doi.org/10.1177/2042018818794324
6. Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. Frontiers in Pharmacology, 4, 177. https://doi.org/10.3389/fphar.2013.00177
7. James, P. B., Wardle, J., Steel, A., & Adams, J. (2018). Traditional, complementary and alternative medicine use in Sub-Saharan Africa: A systematic review. BMJ Global Health, 3(5), e000895. https://doi.org/10.1136/bmjgh-2018-000895
8. Alqathama, A., Alluhiabi, G., Baghdadi, H., Aljahani, L., Khan, O., Jabal, S., … & Ali, M. (2020). Herbal medicine from the perspective of type II diabetic patients and physicians: What is the relationship? BMC Complementary Medicine and Therapies, 20(1), 65. https://doi.org/10.1186/s12906-020-2857-5
9. Otoom, S. A., Al-Safi, S. A., Kerem, Z. K., & Alkofahi, A. (2006). The use of medicinal herbs by diabetic Jordanian patients. Journal of Herbal Pharmacotherapy, 6(2), 31–41. https://doi.org/10.1080/J157v06n02_04
10. Maideen, N. M. P. (2020). Prophetic medicine—Nigella sativa (black cumin seeds): Potential herb for COVID-19? Journal of Pharmacopuncture, 23(2), 62–70. https://doi.org/10.3831/KPI.2020.23.2.62
11. Ahmad, A., Husain, A., Mujeeb, M., Khan, S. A., Najmi, A. K., Siddique, N. A., … & Ali, S. (2013). A review on therapeutic potential of Nigella sativa: A miracle herb. Asian Pacific Journal of Tropical Biomedicine, 3(5), 337–352. https://doi.org/10.1016/S2221-1691(13)60075-1
12. Bilal, A., Masud, T., & Uppal, A. M. (2008). BS5-5 Black seed (Nigella sativa) regulates glucose, insulin level, and lipid profile in patients with Type 2 diabetes. Diabetes Research and Clinical Practice, 79(Suppl 1), S19–S20. https://doi.org/10.1016/j.diabres.2007.11.018
13. Najmi, A., Nasiruddin, M., Khan, R. A., & Haque, S. F. (2008). Effect of Nigella sativa oil on various clinical and biochemical parameters of insulin resistance syndrome. International Journal of Diabetes in Developing Countries, 28(1), 11–14. https://doi.org/10.4103/0973-3930.40323
14. Bilal, A., Masud, T., Uppal, A. M., & Naveed, A. K. (2009). Effects of Nigella sativa oil on some blood parameters in type 2 diabetes mellitus patients. Asian Journal of Chemistry, 21(7), 5373–5381.
15. Bamosa, A. O., Kaatabi, H., Lebdaa, F. M., Elq, A. M., & Al-Sultan, A. (2010). Effect of Nigella sativa seeds on the glycemic control of patients with type 2 diabetes mellitus. Indian Journal of Physiology and Pharmacology, 54(4), 344–354
16. El-Shamy, K. A., Mosa, M. M. A., El-Nabarawy, S. K., & El-Qattan, G. M. (2011). Effect of Nigella sativa tea in type 2-diabetic patients as regards glucose homeostasis, liver,

and kidney functions. Journal of Applied Sciences Research, 7(12), 2524–2534

17. Najmi, A., Nasiruddin, M., Khan, R. A., & Haque, S. F. (2012). Therapeutic effect of Nigella sativa in patients of poor glycemic control. Asian Journal of Pharmaceutical and Clinical Research, 5(Suppl 3), 224–224 - 8
18. Hosseini, M. S., Mirkarimi, S. A., Amini, M., Mohtashami, R., Kianbakht, S., Fallah. Huseini, H., … & Mahdavi, M. (2013). Effects of Nigella sativa L. seed oil in type II diabetic patients: A randomized, double-blind, placebo-controlled clinical trial. Journal of Medicinal Plants, 12(4), 93–99.
19. Kaatabi, H., Bamosa, A. O., Badar, A., Al-Elq, A., Abou-Hozaifa, B., Lebda, F., … & Al-Qahtani, H. (2015). Nigella sativa improves glycemic control and ameliorates oxidative stress in patients with type 2 diabetes mellitus: A placebo-controlled participant-blinded clinical trial. PLoS ONE, 10(5), e0113486. https://doi.org/10.1371/journal.pone.0113486
20. Amin, F., Islam, N., Anila, N., & Gilani, A. H. (2015). Clinical efficacy of the co-administration of turmeric and black seeds (Kalongi) in metabolic syndrome – A double-blind randomized controlled trial – TAK-MetS trial. Complementary Therapies in Medicine, 23(2), 165–174. https://doi.org/10.1016/j.ctim.2015.02.003
21. Heshmati, J., Namazi, N., Memarzadeh, M. R., Taghizadeh, M., & Kolahdooz, F. (2015). Nigella sativa oil affects glucose metabolism and lipid concentrations in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. Food Research International, 70, 87–93. https://doi.org/10.1016/j.foodres.2015.02.035
22. Bamosa, A., Kaatabi, H., Badar, A., Al-Khadra, A., Al Elq, A., Abou-Hozaifa, B., … & Al-Qahtani, H. (2015). Nigella sativa: A potential natural protective agent against cardiac dysfunction in patients with type 2 diabetes mellitus. Journal of Family & Community Medicine, 22(2), 88–95. https://doi.org/10.4103/2230-8229.159774
23. Rachman, P. N. R., Akrom, & Darmawan, E. (2017). The efficacy of black cumin seed (Nigella sativa) oil and hypoglycemic drug combination to reduce HbA1c level in patients with metabolic syndrome risk. IOP Conference Series: Materials Science and Engineering, 259, 012018. https://doi.org/10.1088/1757-899X/259/1/012018
24. Ansari, Z. M., Nasiruddin, M., Khan, R. A., & Haque, S. F. (2017). Protective role of Nigella sativa in diabetic nephropathy: A randomized clinical trial. Saudi Journal of Kidney Diseases and Transplantation, 28(1), 9–14. https://doi.org/10.4103/1319-2442.198578
25. Moustafa, H. A. M., El Wakeel, L. M., Halawa, M. R., Sabri, N. A., El-Bahy, A. Z., & Singab, A. N. (2019). Effect of Nigella sativa oil versus metformin on glycemic control and biochemical parameters of newly diagnosed type 2 diabetes mellitus patients. Endocrine, 65(2), 286–294. https://doi.org/10.1007/s12020-019-02065-2
26. Badar, A., Kaatabi, H., Bamosa, A., Al-Elq, A., Abou-Hozaifa, B., Lebda, F., … & Al-Qahtani, H. (2017). Effect of Nigella sativa supplementation over a one-year period on lipid levels, blood pressure, and heart rate in type-2 diabetic patients receiving oral hypoglycemic agents: A nonrandomized clinical trial. Annals of Saudi Medicine, 37(1), 56–63. https://doi.org/10.5144/0256-4947.2017.56

27. Jangjo-Borazjani, S., Dastgheib, M., Kiyamarsi, E., Jamshidi, R., Rahmati-Ahmadabad, S., Helalizadeh, M., … & Shaterzadeh, M. (2021). Effects of resistance training and Nigella sativa on type 2 diabetes: Implications for metabolic markers, low-grade inflammation, and liver enzyme production. Archives of Physiology and Biochemistry. https://doi.org/10.1080/13813455.2021.1886 11
28. Mostafa, T. M., Hegazy, S. K., Elnaidany, S. S., Shehabeldin, W. A., & Sawan, E. S. (2021). Nigella sativa as a promising intervention for metabolic and inflammatory disorders in obese prediabetic subjects: A comparative study of Nigella sativa versus both lifestyle modification and metformin. Journal of Diabetes and Its Complications, 35(12), 107947. https://doi.org/10.1016/j.jdiacomp.2021.1079 47
29. Sapra, A., & Bhandari, P. (2023). Diabetes. In StatPearls. StatPearls Publishing. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK55 1501/
30. Carello, A. (2002). Oxidative stress and plyumisega. Meubelen, 27(28). https://doi.org/10.1016/0026-0495(00)80082-7
31. Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., et al. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. The Lancet, 380(9859), 2163–2196. https://doi.org/10.1016/S0140-6736(12)61729-2
32. International Diabetes Federation. (n.d.). IDF Diabetes Atlas. Retrieved from https://diabetesatlas.org/
33. WHO Expert Consultation. (2002). Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care, 25(Suppl 1), S5–S20.
34. Ross, G. (2006). Gestational diabetes. Australian Family Physician, 35(6), 392–396.
35. World Health Organization. (2016). Global report on diabetes. Geneva: WHO.
36. Lee, M. S., Kim, C. H., Hoang, D. M., Kim, B. Y., Sohn, C. B., Kim, M. R., & Ahn, J. S. (2009). Genistein-derivatives from Tetracera scandens stimulate glucose uptake in L6 myotubes. Biological and Pharmaceutical Bulletin, 32(3), 5048.
37. World Health Organization. (2016). Global report on diabetes. Geneva: WHO.
38. Piero, M. N. (2015). Diabetes Mellitus – A Devastating Metabolic Disorder. Asian Journal of Biomedical and Pharmaceutical Sciences, 4(40), 1–7.
39. Patlak, M. (2002). New weapons to combat an ancient disease: Treating diabetes. FASEB Journal, 16(14), 1853.
40. Ahmed, A. M. (2002). History of diabetes mellitus. Saudi Medical Journal, 23(4), 373–378.

HOW TO CITE: Kaje Geeta Nandkishor*, Thore Dinesh Dipak, Rupali Jadhav, Ingle R. B., Study of Nigella Sativa on Diabetes Mellitus, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 1, 1152-1168. https://doi.org/10.5281/zenodo.14650784