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Review Article

A CRITIQUE ONMECHANISM OF *NIGELLA SATIVA* AS AN ANTI-DIABETIC DRUG: FOCUS ON THE THERAPEUTIC DOSE BASED ON ASSORTED EXPLICATIONS

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ABSTRACT

Globally, Diabetic mellitus is a rapidly progressing metabolic disorder and is becoming a worldwide concern with several complications and deaths every year. Despite conventional anti-diabetic drugs, numerous kinds of research are going on to get the best cost-effective therapeutic agents with the least adverse effects for the management of diabetes and its complications. *Nigella sativa* is a spice with multi-effects on various disorders like anti-diabetic, anti-cancer, immune modulator, anti-microbial, anti-inflammatory, anti-spasmodic, relives pain, bronchodilator, hepato and renal protective, gastro-protective, anti-oxidant properties. Amongst all effects, the anti-diabetic properties remained a cornerstone and was explored. Anti-diabetic effect of *N. sativa* was due to the presence of Thymoquinone, a major constituent responsible for its effect. Since long ago, studies revealed that the active constituent thymoquinone had a significant reduction in fasting and post-prandial blood glucose levels (glycemic control), probably affecting the pancreatic β-cells, on insulin production and secretion; moreover, lipid profile was shown to be improved in both clinical and preclinical trials. However, there are not many studies on the exact dose to be administered for the therapeutic effect clinically. This review investigated and emphasized the molecular mechanism of *N. sativa* based on the pre-clinical, clinical and toxicological evaluations. This aimed for the estimation of effective dose of *N. sativa* therapeutically for healthier out-turn.

Keywords: *Nigella sativa*, Diabetes mellitus, Mechanism of action, Dose, Side effects

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INTRODUCTION

Diabetes mellitus is a chronic endocrine disorder characterized by persistent increase in blood glucose levels (hyperglycemia), polyuria (excess urination), insulin resistance, and pancreatic dysfunction [1]. Diabetes mellitus is associated with a plethora of complications of various organs, majorly, kidneys, eyes, and heart and nervous. There is a high risk of heart disease and stroke, around 50% of diabetic individuals die from cardiovascular diseases [2]. The mortality rate is highly noticed in developing countries with lower and middle income [3]. India is at its peak and now become a diabetic capital globally. It is estimated that the number of people affected with diabetes has reached 300 million by this year and around 700 million people will be affected by 2045 [4]. As a consequence of this analyzed epidemiological data, the International Diabetes Federation (IDF, 2021) continued studies on pathogenesis and treatment for diabetes mellitus [5, 6]. In countries like India, all are looking for affordable medications to manage diabetes with the fewest side effects. In the current review, exploration has been made on herbal/unani drugs, which have long been in the subject of research for their effects on various chronic illnesses.

Generally, as diabetes is considered as chronic lifestyle disorder which exists for a whole life time, there can be every chance of incessant high blood glucose levels that subsequently can generate free radicals and further lead to the genesis of oxidative stress in different parts of the body [7]. This will additionally may create many complications on different organs of the body like heart, brain, kidneys, eyes and blood vessels. Hence, there is a mandatory requirement for such a drug which targets these free radicals and have an action at molecular level is always preferred as they combat the root cause of a disease and have sufficient therapeutic effect.

Since ancient times, medicinal plants have been used by mankind as traditional treatments for a wide range of acute and chronic ailments. According to the World Health Organization (WHO), more than three-fourths of the population in resource-constrained nations rely on medicinal plants. This might be because of the inaccessibility and cost of allopathic medicines [3, 9].

Amongst the plethora of medicinal plants, *Nigella sativa* (NS) is considered an excellent ancient herb with miraculous therapeutic effects, which belongs to the family Ranunculaceae. It is commonly called as black cumin (or) kalonji [10, 11], and has been used in the ancient system of medicine for its potential benefits [12]. These therapeutic effects of *N. sativa* are due to the presence of the compound Thymoquinone. Thymoquinone (2-Isopropl-5-methyl benzo-1,4-quinone) is an active ingredient present in the seeds of *Nigella sativa* [13].

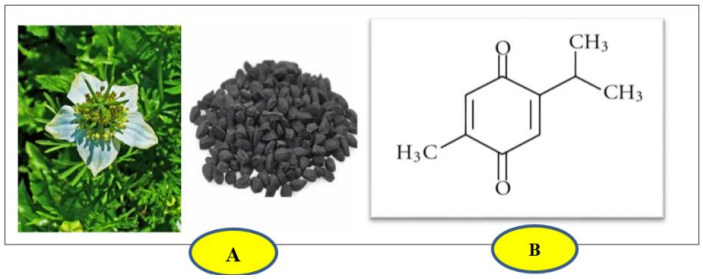

Fig. 1: A) *Nigella sativa*, flower and seeds [14], B) The chemical structure of Thymoquinone [14]

Nigella sativa is considered a Prophetic medicine in Islam and has a wide variety of therapeutic uses in various illnesses because of which it is known as 'Habbah Sawda' or 'Habbat el Baraka' (in Arabic, which means 'Seeds of blessing'), 'Panacea' (in Latin, translated as 'cure-all'), 'kalo jeera' (in Bangladesh), 'hei zhong cao' (in China), and 'kalonji' (in India). It is a popular spice widely distributed in Asian countries like India, Pakistan, Bangladesh, Afghanistan and Sri Lanka [15, 16]. Both, the seeds and oil from *Nigella sativa* can be used for medicinal purposes, and a few of them include anti-cancer, anti-diabetic, anti-hypertensive, anti-inflammatory, anti-microbial, analgesic, immunomodulatory, spasmolytic, gastro-protective, hepato-protective, renal-protective, bronchodilatory and anti-oxidant activities[17-20]. Among all the activities it showed spectacular hypoglycemic effect by various mechanisms, which is essential for the management of Diabetes mellitus in the affected population [21], and also it is imperative to know about the side effects of the drug being used for therapy. The current study explored the beneficial effects and emphasized mechanistic values of *N. sativa* on glycemic control based on the pre-clinical and clinical effects.

Methods

We retrieved the data from various known databases like Pubmed, Scopus, Google scholar and SciFinder. The search filter was kept for up to 10 years. To gather the information key words such as 'thymoquinone', 'black cumin', '*Nigella sativa* compound', pharmacological activity of *Nigella sativa*, therapeutic potential of *Nigella sativa*, 'anti-diabetic effect of *Nigella sativa'* 'effect of *Nigella sativa* on blood glucose levels', '*Nigella sativa* in diabetes', 'toxic effects of *Nigella sativa'*. The search language of publications and articles was done in English.

Inclusion criteria

Articles conveying information about anti diabetic effect of *Nigella sativa* have been included in the study.

Investigatory aspects in pre-clinical and clinical studies

Nigella sativa as an anti-diabetic drug on pre-clinical platform

Many studies have been carried out on the potential effects of *Nigella sativa* on diabetes mellitus and were found that it reduced blood glucose levels, NO (Nitrous oxide), HbA1c and altered lipid profile [22]. Studies were conducted on rats and mice using the streptozotocin-induced diabetic model and explored the mechanisms as described below [23]. Partial regeneration of pancreatic beta cells with the secretion of insulin was also observed with the *N. sativa* [24]. Previous studies revealed that the presence of thymoquinone compound in Nigella sativa is responsible for its anti-diabetic effect, also *N. sativa* acts on AMPK (AMP-activated protein kinase), thereby inhibiting gluconeogenesis in both the liver and muscles, aids in decreased absorption of glucose from the intestine [25, 26]. The duration of studies, doses and routes of administration along with the standard drug and the test drugs, were depicted in table 1.

Table 1: Effect of *Nigella sativa* on experimental diabetes in animal models

S. No.	Models for induction of diabetes mellitus in animals	Dose and duration	Effect of *N. sativa*/Thymoquinone on blood glucose	References
1	STZ induced diabetes (60 mg/kg,ip) in rats	*N. sativa* extract (200 and 400 mg/kg oral route) 6 w	Serum glucose levels decrease significantly	[27]
2	STZ induced diabetes (90 mg/kg, i. p) in rats.	Methanolic extract of *N. sativa* (25,50,100 and 200 µg/ml in situ intestinal perfusion technique) 3 mo	Enhanced glucose utilization and decrease glucose absorption from GIT. Improved insulin release from beta cells in rats (thereby effective in lowering serum glucose levels)	[28]
3	STZ induced diabetes (30 mg/kg body weight i. p) in rats	*N. sativa* 0.5 ml, 1 ml, 1.5 ml per rat was administered orally. 40 d	Significant anti-diabetic effect with three doses due to the regeneration of beta cells of pancreas.	[23]
4	Nicotinamide (110 mg/kg) and Streptozotocin (65 mg/kg, i. p) induced in rats	Thymoquinone (20, 40, 80 mg/kg,p. o.) 21 d	Decreases fasting blood sugar levels effectively. Decreases gluconeogenesis in liver. Increases utilization of glucose by increased sensitivity to the release of insulin from pancreas.	[29, 30]
5	STZ induced in rats (65 mg/kg body weight)	Thymoquinone (at a dose of 50 mg/kg body weight) by gastric lavage 4 w	Significant decrease in the levels of HbA1c, lipid peroxidase and NO (Nitric Oxide)	[22]
6	STZ induced in rats (30 mg/kg bodyweight)	*Nigella sativa* seed extract (0,24,48,72 mg/kg body weight) orally 4 w	Prevents polyphagia, weight loss and improves blood glucose levels in type diabetic rats.	[31]
7	STZ induced in rats (40 mg/kg body weight,i. p.)	Thymoquinone (10,20 mg/kg, orally) 14 w	Significant reduction in blood glucose levels, additionally lipid profile and PPARγ levels were improved.	[22]
8	STZ (150 mg/kg,i. p.), induced In mice	Metformin+Thymoquinone (200 mg/kg+50 mg/kg) orally 21 d	Showed a distinct hypoglycemic effects along with metformin.	[33]
9	Alloxan induced (150 mg/kg) in rabbits	*N. sativa* oil 2.5 ml/kg body weight orally 24 d	Found to be effective in reducing blood glucose levels	[34]
10	STZ (50 mg/kg body weight, i. p.) induced in rats	Thymoquinone (20 mg/kg/day by gavage) 5 w	Serum glucose levels decrease	[18, 35]
11	*In vitro* biochemical assay	*N. sativa* silver nano particles	Inhibits alpha amylase activity	[36]

Thymoquinone and *Nigella sativa* extract was found to produce synergistic action on blood glucose levels with standard anti diabetic drugs like metformin [37] and glibenclimide [38].

Clinical aspects of *N. sativa*

With the administration of *N. sativa* clinically, few reports revealed that this plant was effective against hyperglycemia and hyperlipidemia [39]. Patients given with *N. sativa* seeds, extracts and oil were found to have a reduction in fasting blood glucose levels (FBG), post prandial blood glucose (PPBG) levels with improvement in glycated hemoglobin (HbA1c) levels, decreased triglycerides and increased high density lipoproteins (HDL) [40, 41]. The investigation included a maximum of 113 patients to evaluate the anti-diabetic clinical trials [42]. In almost all investigations, *N. sativa* was evaluated with the co-administration of any conventional drug, thus might be help analyze the synergistic effect, with no adverse effects [43].

Probable mechanism of action of *N. sativa*

Nigella sativa acts as an anti-hyperglycemic agent by the various expected mechanisms from the mentioned data, thus binds to the insulin receptors in the pancreas, increases glucose uptake by the cells, activates voltage-sensitive calcium channels and binds to Peroxisome Proliferator Activated Receptor gamma (PPAR-γ) in the nucleus. In contrast to this drug, conventional hypoglycemic drugs either bind to receptors (or) only act on glucose metabolism to exert their mechanism whereas NS has multiple hypoglycemic mechanisms to reduce blood sugar levels.

NS inhibits gluconeogenesis in the liver by releasing insulin from secretagogues, it activates insulin receptors, which enhances the production of cAMP and also cause calcium-dependent depolarization of cell concomitantly blocking ATP-sensitive k+ channels. NS affects glucose metabolism through GLUT-2 transporter, which will result in decrease number of glycated

hemoglobin (HbA1c) (fig. 2). NS also consequence in genetic transcription by binding to PPAR-γ in the nucleus, this mechanism equally plays a crucial role in inhibiting gluconeogenesis.

Table 2: Clinical aspects of *Nigella sativa*

S. No.	Study design	Drug dose and duration	Sample size (n)	Effects	References
1	Randomized placebo-control	30 ml *Nigellasativa* oil for 80 d	41	Fall in fasting blood glucose (FBG) levels and an increase in insulin levels.	[44, 45]
2	Perspective study	500 mg NS seeds for 17 mo	80	Significant decrease in fasting and postprandial blood glucose and improved HbA1c levels.	[40, 46]
3	Randomized clinical trial	2.5 ml of NS seed oil for 3 mo	70	Improved HbA1c, decreased FBG and Post-prandial blood glucose (PPBG)	[41]
4	Randomized single blind control trial	1.5-and 3-ml NS seed oil per day for 20 d	99	Significant decrease in HbA1c levels	[47]
5	Randomized double blind control trial	3g/day NS oil soft capsules for 12 w	72	FBG, HbA1c, Triglycerides (TGs) and Basal metabolic index (BMI) changes.	[48]
6	Randomized control trial	500 mg/kg NS seeds per day for 12 mo	113	Improved blood glucose levels and enhanced anti-oxidant system.	[42]
7	Randomized, double blind and placebo-controlled trial	1 g of NS oil per day for 8 w	44	Improved HDL levels decreased FBG, liver enzymes and inflammatory mediators. in Non-Alcoholic Fatty Liver Disease (NAFLD) patients	[49-51]
8	Perspective, open-label randomized clinical trial	450 mg NS oil capsule 3 times a day for 12 w	44	Significant decrease in serum levels of FBG.	[52]
9	Randomized clinical trial	50 mg of TQ with 1000 mg of metformin for 90 d	60	Great reduction in FBG and PPBG was observed and improved HbA1c.	[31]
10.	Randomized trial	2 g of NS seeds crushed per day for 8 w	40	Marked effects on serum glucose levels and insulin were seen.	[53, 54]

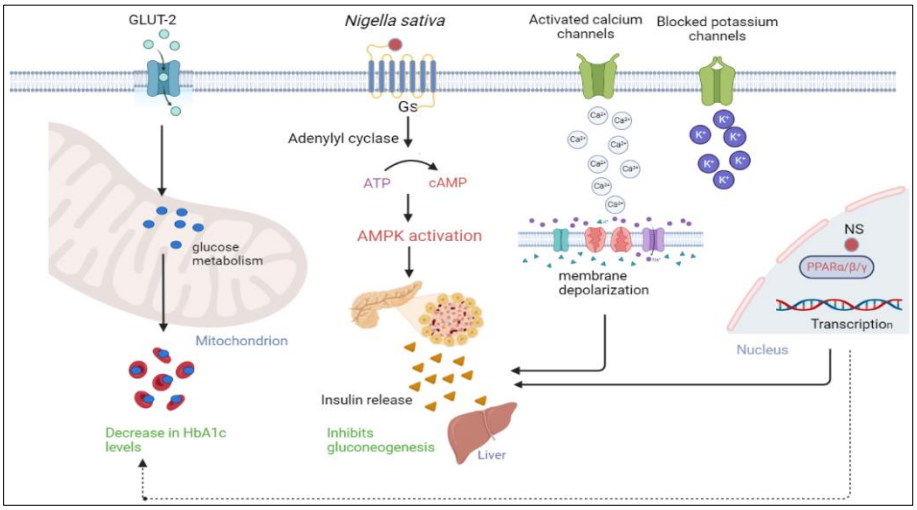

Fig. 2: Exploration of probable mechanistic insights of *N. sativa* at molecular basis. The mechanism was modified accordingly and created by using biorender software) [16, 18]

Adverse effects/Toxicological investigations of *N. sativa*

Based on the adverse effects of *N. sativa,* toxicological investigations were done by Abukhader *et al.* on possible adverse effects of thymoquinone in Wistar rats [55, 56]. Various adverse effects with different routes of administration, acute pancreatitis were observed in rats with i.p. injection and some short-term toxic effects were seen with oral administration in rats [57, 58]. Deaths were observed at 500 mg/kg dose [59]. Few studies have reported adverse effects like abnormal vision, dizziness and drowsiness [60], decreased BP and tachycardia [61], nausea, vomiting, stomachache, flatulence [62] and hypersensitivity reactions [63]. The exact clinical and preclinical doses which produce these effects were unknown [64]. A few effects of Thymoquinone were depicted on various organs in table 3.

Table 3: Side effects of *N. sativa* on experimental animals

S. No.	Organs	NS side effects	References
1.	Central Nervous System	Dizziness, drowsiness, fatigue, abnormal vision	[59]
2.	Cardiovascular System	Tachycardia and hypotension	[60, 65]
3.	Gastrointestinal System	Nausea, vomiting, flatulence, epigastric pain, abdominal cramps, diarrhea or constipation	[61, 17]
4.	Renal system	Reversible nephritis, Crystalluria	[66]
5.	Joints and muscles	Chondrotoxicity	[67]
6.	others	Hypersensitivity reactions	[63]

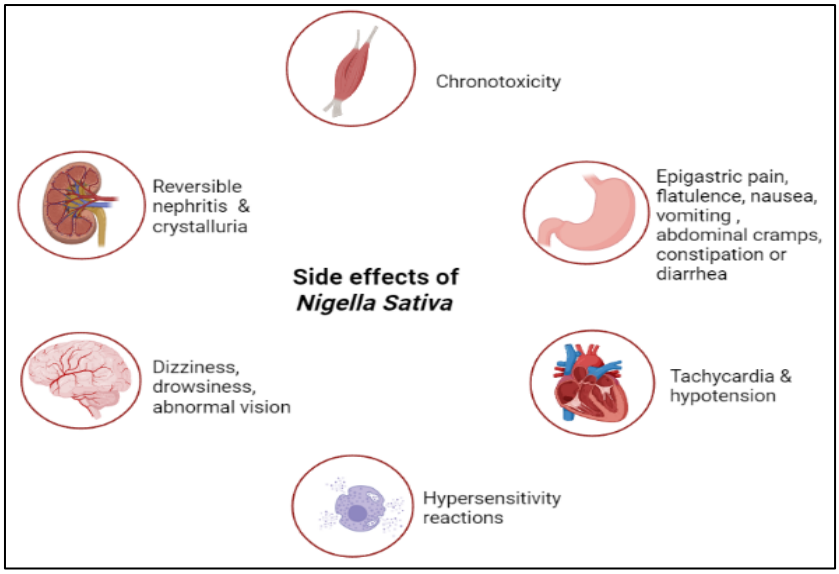

Fig. 3: Exploration of side effects of *Nigella sativa,* modified and changed accordingly using biorender software) [68]

CONCLUSION

It can be concluded that *Nigella sativa* exhibited an anti-hyperglycemic effect due to the presence of its chemical constituent, Thymoquinone. The mechanism was derived keeping given the above studies, however until present, in the clinical trials reported, the exact dose was in chaos, which might be considered as one of the causes for side effects. Thus, a mandate investigation on a large population becomes crucial for fixing the dose so that the side/adverse effects can be closely monitored and resolved simultaneously. Detecting a therapeutic dose, there inclines to favorable outcomes along with patient compliance. In the present review, though the mechanism was acquired, still significant, satisfactory and more detailed pharmacodynamics is possible with further studies. Additionally, as consumption of the conventional drug with the herbal medicines as a combination has been recommended in the present era, there is an option for a possible synergistic effect to be identified if exists. Hence, in future, experimental investigations on determination of the therapeutic dose of *N. sativa* are essential to elucidate the exact mechanism at the molecular level, which in turn may be helpful to conquer the side effects.

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AUTHORS CONTRIBUTIONS

SB has written the manuscript, guided and edited by SR, has also contributed in preparation of diagrammatic illustration in the manuscript. RKV and SB collected the information required for writing Manuscript.

CONFLICTS OF INTERESTS

The authors declared no conflicts of interest.

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