International Journal of Applied Research 2019; 5(3): 247-255

ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2019; 5(3): 247-255
www.allresearchjournal.com
Received: 14-01-2019
Accepted: 18-02-2019

Murtaza Rashid
Dept. of Chemistry, Govt. Shyama Prasad Mukherjee sci. and Comm. College (old Benazir), Bhopal, Madhya Pradesh, India

Sudhanshu Dhar Dwivedi
Dept. of Chemistry, Govt. Shyama Prasad Mukherjee sci. and Comm. College (old Benazir), Bhopal, Madhya Pradesh, India

Correspondence
Murtaza Rashid
Dept. of Chemistry, Govt. Shyama Prasad Mukherjee sci. and Comm. College (old Benazir), Bhopal, Madhya Pradesh, India

Nigella sativa as highly potent hypoglycemic agent

Murtaza Rashid and Sudhanshu Dhar Dwivedi

Abstract
The aim of present study is to review on hypoglycemic property of *Nigella sativa* L. hyperglycemic condition occurs either due to non-functioning of pancreatic beta cells or inability of body cells to utilize insulin. Currently diabetes is one of the fast growing diseases which covers nearly 2.8 % of world population and is predicted to increase up to 4.4 % by 2030. *Nigella sativa* (NS) also known as Black cumin and Kalonji, is an annual herb of Ranunculaceae family which grows up to 20-60cm in height. NS is also referred as miracle herb of century because it holds so many health curing properties. NS seeds has long history for their usage to treat various diseases in Middle East and Indian subcontinent. In traditional folk practice black seeds were used as spice and medicine. The black seeds were traditionally used to treat the ailments like asthma, arthritis, backache, diabetes, diarrhea, dry cough, rhinitis, hair greying, hair loss, dry cough, hypertension, fatigue, memory improvement, muscle aches, anxiety, sexual impotency, Insomnia, toothache, gum disease, amenorrhea and dysmenorrhea, anthelminthic and skin eruptions. However, extensive research on NS seeds were found to contain various bioactive compounds which have therapeutic properties against many diseases. Among all bioactive compounds Thymoquinone (TQ), a volatile mono oxygenated terpene has been found to possess hypoglycemic activity.
NS seed extract and TQ hypoglycemic activity has been studied in many animal models including human clinical trials. All studies revealed that mechanism of hypoglycemic activity mainly occurs to lowering plasma glucose levels and increasing insulin levels. Moreover, some studies also reported loss of appetite, weight loss, and reduction in glyceride levels and partial regeneration of pancreatic beta cells. Randomized Clinical trials of NS in diabetic patients has resulted reduction in levels of fasting blood glucose, postprandial glucose, LDL cholesterol, triglycerides and body weight.

Keywords: *Nigella sativa* hypoglycemia, thymoquinone, beta cells, bioactive compounds, black cumin

Introduction
The hyperglycemia condition is caused due to an increased glucose concentration of body because beta cells in Pancreas are either unable to secrete insulin or body is unable to utilize insulin. Type-1 diabetic condition is autoimmune disorder occurs primarily during the onset of juvenile stage. Immune system attacks its own pancreas with specific antibodies causes malfunctioning of pancreas to secrete insulin. Type 2 diabetes is insulin independent condition where body cells show resistance towards insulin to metabolize glucose. According to the American Centre for diseases and prevention statistics 2017 reported that nearly about 30.3 million people are suffering from diabetes which is equal to 9.4% of the US population. World health organization (WHO) 2018 reported 422 million people are suffering from diabetes worldwide. India alone has nearly 40 million people diagnosed with diabetes and number of people is reported to get doubled by 2030 [1].
Medicinal plants had gained remarkable fame past few years in both developed and developing countries because of their divine origin and fewer side effects [2-.6]. According to the world health organization, 80 per cent of people in developing countries are dependent on medicinal plants [7]. *Nigella sativa* L. is one of such medicinal herb whose highly potent bioactive compounds have different pharmacological properties [8-12]. It an annual herb of Ranunculaceae family also known as black cumin, black caraway black seeds grows up to the height of 30-60 cm. In India, it is commonly known as Kalonji and is used as a spice in pickles for preservative purposes [13]. *Nigella sativa* has several beneficiary effects such as Immunomodulatory [14, 15, 16, 17], Anticancer [18], Antihyperglycemic, [19, 20] Antimicrobial [22], Hepatoprotective [22], Cardioprotective [23, 24], Anti-schistosomiasis [25], Antioxytocic [26]

Neuro-protective [27, 28], Nephroprotective [29, 30], Anxiolytic [31, 32] and Antinociceptive [33]. The present review is based on the antihyperglycemic activity of *Nigella sativa*.

Chemical composition

The *Nigella sativa* is rich and diverse in chemical composition. Historically first chemical analysis of the *Nigella sativa* black seed was done in 1880 which showed the presence of 36-38 % amino acid and 4.1% residue [24]. Proximate analysis of *Nigella sativa* seeds detected protein 21 %, lipids 35.5%, vapour 5.5%, ash 3.7% and carbohydrates 34.3% [35-39]. Lipid layer comprises both saturated and unsaturated fatty acids. Linolenic acid has been found as major fatty acid. Other fatty acids found include myristic acid, palmitic acid, oleic acid and eicodadienoic acid [40-43]. *Nigella sativa* seed has been found to contain fixed and essential oil with percentage of oil yield has been found in between 25-35% [44]. Percentage oil yield is effect by geographical and stress conditions [45, 46]. The major chemical constituents reported seed oils is thymoquinone, dithymoquinone, thymohydroquinone, t-anethole thymol, p-cymene, carvacol, terpineol, longifolene, α-pinene, α-hederin, Sabinene, α-Thujene, Myrcene, α-Phellandrene, Limonene, γ-Terpinene, Fenchone, Dihydrocarvone, Carvone, sesquiterpenoid α-Longipinene [47-52]. Other components reported are sterols like campesterol, Stigmasterol, βSitosterol, vitamins tocopherol, thiamin, riboflavin, pyridoxine, niacin, Folic acid and inorganic elements P, Ca, Fe, Cu and Zn [53-58]. Seeds oils also contain alkaloids of isoquinoline type Nigellimine, Nigellimine- N-oxide, indazole ring type nigellicine, nigellidine [59] and dollabene type Nigellimines (A1-A5) and Nigellimines (B1- B2) [60]. It also contain sterols and saponins like stigmastanol, melanthin, melanthigenin, 24-methylene-cycloartanol, stigmasterol-7-ene, lophenol, cholesterol, -amyrin, butyro- spermol obtusifoliol, citrostadienol, β, cycloartenol, taraxerol and 3-*O*- [β-d-xylopyranosyl-(1–3)-α-l-rhamnopyranosyl-(1–2)-α-l-arabinopyranosyl]-28-*O*-[α-l rhamnopyranosyl - (1–4)-β-d-glucopyranosyl-(1–6)-β-d-glucopyranosyl] [61-63].

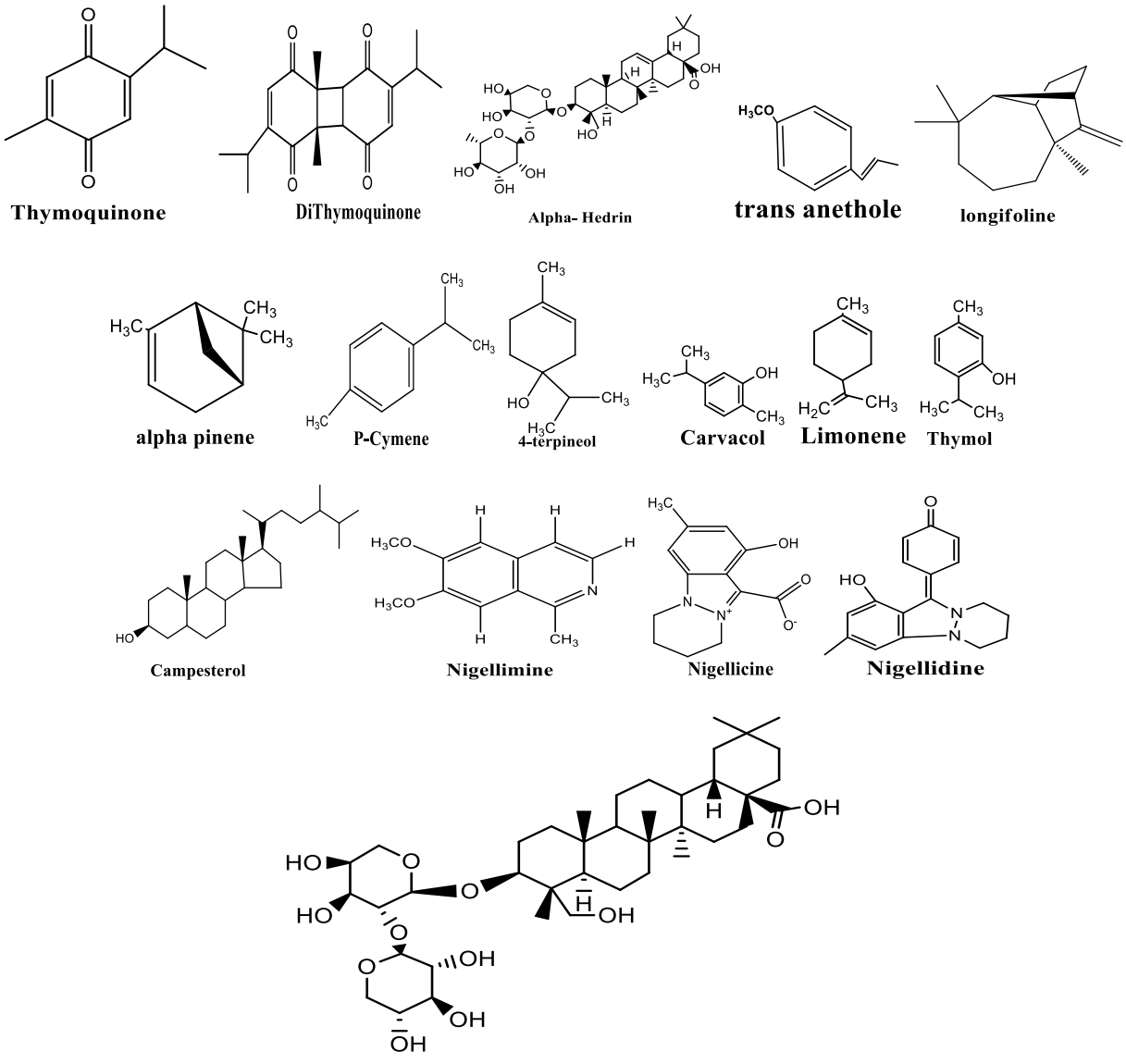

Fig 1: Chemical structures of major chemical constituents of Nigella sativa seed oil.

Table 1: Percentage of Fatty acid composition and sterols present in Nigella sativa seeds.

Fatty acids	Percentage (%)
Palmitic	12.5-13.1
Linoleic	55.6-58.5
Arachidic	0.2-0.5
Stearic	2.3-3.4
Myristic	0.5-1.0
Oliec	23.4-24.9
Eicosadienoic	2.5-3.1
Lauric	0.2-0.6
Linolenic	0.4-0.6

Sterols	Percentage (%)
Cholesterol	0.9-1.0
Campesterol	12.8-13.1
Stigmasterol	17.8-18
β-Sitosterol	49.4-51.3
Avensterol	8-12.4

Toxicological studies

The toxicological studies are necessary to determine the adverse effects and level of exposure of any herbal medicine. The toxicity studies are useful for measuring risks associated with medicinal herbs. Prior to drug formulation from medicinal plant extracts it is important to determine toxicity of these extracts in pre-clinical and clinical stages. Toxicity tests helps in identifying toxicants which can be removed to form safer and effective drugs. Extensive research has been done in order to find the acute toxicity of the *Nigella sativa* (NS) and its components. NS extract of 50 mg/kg intraperitoneal (i.p.) administration in rats were found to be nontoxic because it did not have major impact on metabolic activities of organs [65]. In another research it was found that mice tolerated the oral administration of NS seed powder 2g/kg/day for 5 days [66]. Oral administration NS seed powder of 2g/kg/day in humans for 28 days were found to tolerable [67]. The LD_{50} value of thymoquinone was found to be 2.4 g/kg however, higher doses showed significant increase in plasma metabolites levels and breathing complications along with reduction of plasma glucose levels [68]. In another study oral administration doses of NS oil up to 10 ml/kg in rats did not show any toxicity and mortality during observation period of 48 hours [69]. Similar results were obtained for observation period of 12 weeks [70]. Oral administration of 21 g/kg dose of NS methanolic and chloroform extracts showed insignificant results of toxicity in rats [71]. Lethal doses LD_1, LD_{10}, LD_{50}, LD_{90} and LD_{99} of NS essential and fixed oil were determined in Swiss albino mice. NS essential oil lethal doses in ml/kg were found as LD_1 0.057, LD_{10} 0.157, LD_{50} 0.542, LD_{90} 1.866 and LD_{99} 5.111 whereas lethal doses of fixed oil were LD_1 2.517, LD_{10} 5.060, LD_{50} 11.915, LD_{90} 28.058 and LD_{99} 56.403 [72]. In a recent study oral administration dose 100 mg /kg of Thymoquinone (TQ) and Thymoquinone enclosed in nanostructured lipid carrier (TQNLC) in both sexes of mice of did not show any significant histopathological changes and mortality. 10 mg /kg was found to safe dose without any toxic effects [73]. The acute toxicity LD_{50} values of thymoquinone for intraperitoneal and oral administration found to 104.7 mg/kg and 870.9 mg/kg respectively in mice whereas LD_{50} in rats were found 57.5 mg/kg i.p and 794.3 mg/kg orally administrated [74]. Thymoquinone rich fraction nano emulsion (TQRFNE) was studied for acute toxicity in Sprague Dawley rats. The TQRFNE 20 ml (containing 44.5 mg TQ/kg) were found to non-lethal and nontoxic during observation period of 14 days [75]. thymol-water emulsion on oral administration in albino rats showed Median lethal dose (LD_{50}) at 2462.23 mg/kgbw and safe dose (NOAEL) was found to be 61.55 mg/kgbw [76].

Hypoglycemic activity in normal animal models

Intraperitoneal injections of 50 mg/ kg/day *Nigella sativa* volatile oil extract in fasting normal and alloxan-induced diabetic rabbits showed 15%-23% decrease in plasma glucose levels in normal rabbit and 12% -21% in diabetic rabbits for period 4 and 6 hours respectively. However, insulin levels remained constant in all animal groups [77]. In another study it was found that NS extract of about 35 mg/kg did not affect Body weight and serum insulin levels in both diabetic and normal animals [78]. Oral glucose tolerance test was conducted in rat groups treated with 2g/kg/day of NS extract and 300mg/kg/day metformin for six weeks showed improved glucose tolerance and reduced body weight without any toxic effect. However, *in vitro* studies of rat jejunum treated with NS aqueous extract of about 0.1 pictogram per ml - 100 Nano gram per ml revealed inhibition of sodium-dependent glucose transport in it [79]. In another study by group of researchers reported the NS Petroleum ether extract treatment in normal rats showed reduction in body weight, insulin and triglycerides levels along with increased levels of HDL-cholesterol. However, plasma glucose levels remained constant. Weight loss occurred due to 25% reduction in food in food intake capacity [80]. Hypoglycemic activity NS extract five doses and thymoquinone 6 doses were studied in normal rats for duration period of 14 days. The rats were observed in five duration periods ranging from 1st, 4th, 5th, 7th and 14th day. All doses of NS and thymoquinone showed significant decrease of blood glucose levels in all durations except 1st day [81]. another research work reported decreased levels of serum cholesterol by 15.5%, triglycerides by 22 % and plasma glucose by 16.5%, in rats treated with 1ml/kg i.p of NS fixed oil for the period of 12 weeks [82]. Defatted NS seed extract showed significantly promoted the release of insulin from the pancreatic islets isolated from a rat in presence of 8.3 mmol/L glucose medium [83].

Antihyperglycemic activity in Streptozotocin (STZ) induced diabetic animals

Farrah *et al.* reported *N. sativa* oil decrease in blood glucose level and increase in serum insulin level when treated with for 4 weeks in Streptozotocin plus Nicotinamide-induced diabetic hamsters [84]. Another research by same group of researchers reported decline in the levels of blood glucose, glycated haemoglobin and rate of gluconeogenesis process in STZ induced diabetic hamsters when treated with thymoquinone 50mg/kg/day for 30 days [85]. Kanter *et al.* studied fifty male Wistar rats which were divided into two groups. The streptozotocin (STZ) was injected intraperitoneally to induced diabetes in 24 hours. After the induction of diabetes one group was treated 0.20 ml/kg/day for 30 days. The *N. sativa* extract caused a decrease in serum glucose, a rise in the serum insulin concentrations and partial regeneration /proliferation of pancreatic β-cells in STZ-induced diabetic rats [86]. Kaleem *et al.* find similar results with 300mg/kg /day *Nigella sativa* Ethanolic extract in STZ induced diabetic rats for 30 days [87]. Abdelmeguid *et*

al. also similar results with 0.2 ml/kg of *Nigella sativa* aqueous extract and 3mg /ml of thymoquinone in STZ induced diabetic rats. The intraperitoneal injections were given 6days/week for 30days [88]. Rchid *et al.* studied the effect of *N. sativa and C. zeylanicum* oils in STZ induced diabetic rats. Diabetic rats were treated with these oils showed a significant decrease in blood glucose, triglycerides, cholesterol, LDL–cholesterol and ALT, however, levels of HDL cholesterol, total protein, uric acid and creatinine were reported to increase as compared to untreated diabetic rats. *C. zeylanicum* oil treated independently in diabetic rats showed a noteworthy decrease in ALT level [89]. Alimohammadi *et al. studied* five groups twenty-five Wister-albino rats in which Streptozotocin (60mg/kg) was used to induce diabetes. The hydroalcoholic extract of *N. sativa* ranging from 5-20 mg/ kg/day was intraperitoneally injected into three groups respectively for 32 days. The data collected on 1st, 16th and 32nd day showed that *N. sativa* with a safe dose of 5mg/kg/day has maximum hypoglycemic effect whereas, higher doses of 10 and 20 mg/kg/day didn't show any therapeutic effect [90]. Asaduzzaman *et al.* recently studied that *N. sativa* ethanolic extract (300 mg/kg) injected in STZ induced diabetic rats and hyper Cholesterol rats for 28 days had shown significant hypoglycemic and hypolipidemic activity [91]. Similar work has been reported by Abbas [92]. Kanter *et al.* studied that *N. sativa* volatile oil acts hypoglycemic agent in Streptozotocin-diabetic rats. Streptozotocin (50mg/kg) induced in diabetic rats produces oxidative stress because of increased lipid peroxidation and serum nitric oxide (NO) concentrations and decreased antioxidant enzyme activity. *Nigella sativa* volatile oil (0.2 mg/kg/day) treatment for 4 weeks has shown amelioration of oxidative stress and protection of pancreatic β cells [93]. In another study by Kanter *et al.* reported the protective effect of *N. sativa* and thymoquinone on histopathological changes of sciatic nerves in Streptozotocin-induced diabetic rats. The diabetic rats were given doses 400 mg/kg and 50mg/kg of *N. sativa* and thymoquinone respectively. Both treatments showed the increased area of insulin immunoreactive β-cells with no histopathological changes in sciatic nerves. However, myelin breakdown decreased and axon showed a lot of improvements [94]. Al-Wafai recently reported that *N. sativa* and its main active ingredient thymoquinone ameliorates oxidative stress and reduces cyclooxygenase-2 production in pancreatic tissues of Streptozotocin-induced diabetic rats [95]. Abbasali *et al*. reported that *N. sativa* at a dose of 200 mg/kg/days for 45 days resulted in a decrease of serum glucose, weight and ameliorated oxidative stress in hippocampus of STZ induced diabetic rats [96].

Nigella sativa hypoglycemic activity against cadmium induced diabetes

Cadmium (Cd) is a non-essential element which shows high permeability towards plants and animals. The adults exposed to Cd poising in a smaller amount (30-50µg) were diagnosed with increased levels of bone fracture, cancer, kidney dysfunction and hypertension [97]. Cadmium chloride 2mg/kg/day treated in rats for 7 days showed increased levels of glucose with suppression of insulin release. *In-vitro* studies of mouse pancreatic islets displayed that Cd concentration of 10^{-6}M suppressed glucose-stimulated insulin secretion [98]. However, *in-vivo* studies revealed that intraperitoneal administration of Cadmium acetate in mouse showed a high concentration of pancreatic Metallothioneins. These are cysteine-rich metal binding proteins and has a protective effect against cadmium toxicity [99, 100]. Kanter *et al.* study the protective effect of *Nigella sativa* against oxidative stress caused by cadmium toxicity in rats. The rats were divided into three groups: group A (control), group B (Cd-treated) and group C (Cd+ Ns treated). Group A was treated with sodium chloride 2ml/kg/day and group B and C were treated cadmium chloride 0.49 mg/ kg/day. In addition to this group C also IP injections of *Nigella sativa* 0.2 ml/kg/day prior to cadmium chloride induction. Cd-treated groups were seen to have increased levels malondialdehyde in plasma and erythrocytes with oxidative stress due to an increase of antioxidant levels. The group C rats treated with *N. sativa* for 30 days considerably decreased levels of malondialdehyde in plasma and erythrocytes and ameliorated oxidative stress [101]. Demir *et al.* with similar kind of research procedures studied the protective nature of *Nigella sativa* against Cd-induced toxicity in rats. Cd-treated rats showed a decrease in blood cell count, increased heart rates. 34% β cells of pancreatic islets were found to be necrotic, degenerated and degranulated which result in hyperglycemia and hypoinsulinemia in cd induced rats. Intraperitoneal injection of *Nigella sativa* extract 2ml/kg/day in Cd-treated rats improved anaemic condition, heart rate and reduced the degeneration of β cells of pancreas thereby resulting in an increase of insulin levels [102].

Nigella sativa against HAART induced diabetes

HAART an acronym of highly active antiretroviral therapy is a combination of three drugs incorporated with protease inhibitor used to reduce highly viral plasma levels in HIV patients to minimal levels [103]. Chandra *et al.* studied the role of *Nigella sativa* against insulin tolerance in Sprague–Dawley rats by HAART therapy. The rats were fed with three antiretroviral drugs nelfinavir 200 mg/kg, zidovudine 50 mg/kg and efavirenz 20 mg/kg for 7 months. HAART treatment caused a Substantial increment in the levels of insulin and C-peptide. The size of pancreatic islets was also reported to have reduced. Treatment of Black seed oil from *Nigella sativa* 400µl/kg reduced this hyperinsulinemia and C-peptide levels in rats. *In vitro* studies by the above group of researchers reported that nelfinavir independent treatment produced oxidative stress and suppressed insulin secretion in the insulinoma cell line (INS-1). Black seed oil or thymoquinone treatment restored insulin production in cells [104]. In another study by the same group of researchers reported that treatment of HIV-1 protease inhibitors (PI) incorporated with HAART drugs i.e. nelfinavir, saquinavir and atazanavir were responsible for insulin resistance syndrome (IRS). The insulin secretion stimulated by glucose was reduced from the pancreatic β cell of rats. The thymoquinone and *Nigella sativa* treatments increased the insulin secretion and decreasing glucose levels [105].

Clinical trials of *Nigella sativa* in diabetic patients

The survey on traditional use of *Nigella sativa* in diabetic and hypertensive patients of Oriental Morocco was reported by Ziyyat *et al.* in 1997. They have reported 626 patients with 61% diabetic and 23% hypertensive which were treated with 42 medicinal plants [106]. Laadim *et al.* recently reported ethnopharmacological use of *Nigella sativa* infusion in diabetic patients of Sidi Slimane town (Morocco) for a period of 2 months to one year [107]. Otoom *et al.*

reported a cross-sectional study of 310 diabetic patients from Jordan which were treated with medicinal herbs. The diabetic patients treated with *Nigella sativa* 7.3% [108]. *Al*-Rowais conducted a survey on traditional use of medicinal herbs by diabetic patients of Riyadh Saudi Arabia. 300 diabetic patients were surveyed in which 19.6 % were using *Nigella sativa* as remedies for diabetes mellitus [109]. Bamosa *et al.* in 1997 investigated the effect of *Nigella sativa* on blood glucose in healthy humans. The study was carried out in 16 healthy humans which were orally given 2g of *Nigella sativa* seeds for 14 days. In the first week, a significant decrease in blood glucose level was reported (74.4 mg/dl) as compared to base value (85 mg/dl) however, in second-week glucose level were reported to get increased (82.2 mg/dl). Qidwai *et al.* with similar work were unsuccessful to spot significant decrease in blood glucose levels by *Nigella sativa* seed powder because the sample studied was smaller in size [110]. Bamosa *et al.* in another research work studied the effect of *Nigella sativa* three doses on glycemic control in uncontrolled type 2 diabetic patients. The study included 94 patients, 46% male and 54% females which were orally administrated with 1, 2 and 3 gm/day doses of *Nigella sativa* seeds for 3 month period. The blood glucose levels were decreased significantly by the dose of 2gm/day as compared to other doses [111]. Bamosa group in recently conducted a patient blinded clinical trial in 114 uncontrolled diabetes mellitus type 2 patients. They were equally divided into two groups: placebo or control group and NS group. Control group were administered with charcoal as placebo and NS group were administered with 2mg/kg of *Nigella sativa* for one year. NS group has shown a significant reduction in fasting blood glucose, random blood glucose and glycosylated haemoglobin (HbA1c) [112]. Heshmati *et al.* with carried out a double-blinded randomized clinical trial of *Nigella sativa* in 72 diabetic type 2 patients. The intervention group received 3g/kg/day and similar amounts sunflower oil was received placebo group. The results of intervention group compared to baseline value showed significant decrease in levels of fasting blood sugar (−9.1%), glycosylated haemoglobin (-5.1%), total cholesterol (−9.8%), triglycerides (−4.3%), and low-density lipoprotein cholesterol (−17.6%) in the. Comparison of the two groups at the end of the study also indicated that FBS, HbA1c, TG and LDL-C changed significantly in the intervention group compared to the placebo group [113]. Hadi *et al.* find similar results in their randomized double-blind clinical trial which include 43 diabetic type 2 patients, *Nigella sativa oil* 1g/day was used adjunctive therapy for 8 weeks [114]. Hosseini *et al.* also confirmed similar results with 70 type 2 diabetic patients treated with *Nigella sativa* 5ml/day for three months [115].

Najmi *et al.* piloted clinical trial on sixty metabolic disorder patients. They were equally divided into two groups: standard group and NS group. The standard group received Atorvastatin 10 mg/day and Metformin 1g/day while *Nigella sativa* group received adjunctive therapy of *Nigella sativa* 5ml/day for six weeks. Comparison of results of both groups indicated that the NS group showed a noteworthy reduction in levels of fasting blood glucose, postprandial glucose, LDL cholesterol, triglycerides and body weight than standard group. The HDL cholesterol level was increased NS group [116]. Similar results were confirmed by Madhvi *et al.* in their study of 84 obese female. However, it confirmed a decline in triglycerides and LDL cholesterol [117]. Datau *et al.* in their clinical trial of *Nigella sativa* on obese male patient confirmed the significant decrease in body weight, waist circumference and systolic blood pressure, however insignificant reduction of serum free testosterone, diastolic pressure and HDL cholesterol. The insignificant decrease in fasting blood sugar and triglycerides is also confirmed which antagonist to the above trials [118].

References

1. World Health Organization. Global report on diabetes, http://www.who.int/diabetes/global-report/en, 2018.
2. Tomlinson Timothy R, Olayiwola Akerele. University of Pennsylvania press Chevallier, Andrew. Dorling Kindersley, 1996.
3. Hoareau Lucy, Edgar DaSilva J. Electronic Journal of biotechnology. 1999; 2(2):3-4.
4. Kapoor LD. Herbal reference library. Routledge, 2011.
5. Daniel M. Medicinal plants: chemistry and properties. CRC Press, 2016.
6. World Health Organization. World Health Organization, 1999, 2.
7. Khan Akram M. Inflammopharmacology. 1999; 7(1):15-35.
8. Ali BH, Blunden G. International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2003; 17(4):299-305.
9. Gilani Hassan A, Jabeen Q, Khan MA. Pak Journal of Biological Sciences. 7(4):441-51.
10. Paarakh Padmaa M. *Nigella sativa* Linn.–A comprehensive review, 2010.
11. Wesam Kooti *et al.* Chin J Nat Med. 2016; 14(10):732-745.
12. Gupta Mradu. Pharmacological properties and traditional therapeutic uses of important Indian spices: A review. International Journal of Food Properties. 2010; 13(5):1092-1116.
13. Majdalawieh Amin F, Muneera W. Fayyad. Immunomodulatory and anti-inflammatory action of *Nigella sativa* and thymoquinone: A comprehensive review. International Immunopharmacology. 2015; 28(1):295-304.
14. Salem Mohamed Labib. Immunomodulatory and therapeutic properties of the *Nigella sativa* L. seed. International Immunopharmacology. 2005; 5(13-14):1749-1770.
15. Gholamnezhad Zahra, Rana Keyhanmanesh, Mohammad Hossien Boskabady. Anti-inflammatory, antioxidant, and immunomodulatory aspects of *Nigella sativa* for its preventive and bronchodilatory effects on obstructive respiratory diseases: A review of basic and clinical evidence. Journal of Functional Foods. 2015; 17:910-927.
16. Andrade Luciana, Damião de Sousa. A review on anti-inflammatory activity of monoterpenes. Molecules. 2013; 18(1):1227-1254.
17. Randhawa Mohammad Akram, Mastour Safar Alghamdi. Anticancer activity of *Nigella sativa* (black seed)-a review. The American Journal of Chinese Medicine. 2011; 39(06):1075-1091.
18. Mathur Murli L *et al.* Antidiabetic properties of a spice plant *Nigella sativa*. Journal of Endocrinology and Metabolism. 2011; 1(1):1-8.

19. Al-Hader Aqel, Aqel M, Hasan Z. Hypoglycemic effects of the volatile oil of *Nigella sativa* seeds. International Journal of Pharmacognosy. 1993; 31(2):96-100.
20. Forouzanfar Fatemeh, Bibi Sedigheh Fazly Bazzaz, Hossein Hosseinzadeh. Black cumin (*Nigella sativa*) and its constituent (thymoquinone): a review on antimicrobial effects. Iranian Journal of Basic Medical Sciences. 2014; 17(12):929.
21. Mollazadeh Hamid, Hossein Hosseinzadeh. The protective effect of *Nigella sativa* against liver injury: a review. Iranian Journal of Basic Medical Sciences. 2014; 17(12):958-66.
22. Gonca E, Kurt C. Cardio Protective effect of Thymoquinone: A constituent of *Nigella sativa* L., against myocardial ischemia/reperfusion injury and ventricular arrhythmias in anaesthetized rats. Pakistan journal of pharmaceutical sciences. 2015; 28(4).
23. Shabana A, El-Menyar A, Asim M, Al-Azzeh H, Al Thani H. (Cardiovascular benefits of black cumin (*Nigella sativa*). Cardiovascular toxicology. 2013; 13(1):9-21.
24. Shenawy EL, Nahla S, Soliman MF, Reyad SI. The effect of antioxidant properties of aqueous garlic extract and *Nigella sativa* as anti-schistosomiasis agents in mice. Revista do Instituto de Medicina Tropical de São Paulo. 2008; 50(1):29-36.
25. Aqel M, Shaheen R. Effects of the volatile oil of *Nigella sativa* seeds on the uterine smooth muscle of rat and guinea pig. Journal of Ethnopharmacology. 1996; 52(1):23-26.
26. Asiaei F, Fazel A, Rajabzadeh AA, Hosseini M, Beheshti F, Seghatoleslam M. Neuroprotective effects of *Nigella sativa* extract upon the hippocampus in PTU-induced hypothyroidism juvenile rats: A stereological study. Metabolic brain disease. 2017; 32(5):1755-1765.
27. Kanter M, Coskun O, Kalayc M, Buyukbas S, Cagavi F. Neuroprotective effects of *Nigella sativa* on experimental spinal cord injury in rats. Human & experimental toxicology. 2006; 25(3):127-133.
28. Cascella M, Palma G, Barbieri A, Bimonte S, Amruthraj N, Muzio M *et al*. Role of *Nigella sativa* and its constituent thymoquinone on chemotherapy-induced nephrotoxicity: evidences from experimental animal studies. Nutrients. 2017; 9(6):625.
29. Saleem U, Ahmad B, Rehman K, Mahmood S, Alam M, Erum A. Nephro-protective effect of vitamin C and *Nigella sativa* oil on gentamicin associated nephrotoxicity in rabbits. Pak J Pharm Sci. 2012; 25(4):727-730.
30. Firdaus F, Zafeer MF, Ahmad M, Afzal M. Anxiolytic and anti-inflammatory role of thymoquinone in arsenic-induced hippocampal toxicity in Wistar rats. Heliyon. 2018; 4(6):e00650.
31. Perveen T, Haider S, Kanwal S, Haleem DJ. Repeated administration of *Nigella sativa* decreases 5-HT turnover and produces anxiolytic effects in rats. Pakistan Journal of Pharmaceutical Sciences. 2009; 22(2).
32. Abdel-Fattah AFM, Matsumoto K, Watanabe H. Antinociceptive effects of *Nigella sativa* oil and its major component, thymoquinone, in mice. European journal of pharmacology. 2000; 400(1):89-97.
33. Greenish HG. Contribution to the Chemistry of *Nigella sativa* Pharmac J Trans. 1880; 10:909-911.
34. Babayan VK, Koottungal D, Halaby GA. Proximate analysis, fatty acid and amino acid composition of *Nigella sativa* L. seeds. Journal of Food Science. 1978; 43(4):1314-1315.
35. Al-Jassir Saleh M. Chemical composition and microflora of black cumin (*Nigella sativa* L.) seeds growing in Saudi Arabia. Food Chemistry. 1992; 45(4):239-242.
36. Nergiz Cevdet, Semih Ötleș. Chemical composition of *Nigella sativa* L. seeds. Food chemistry. 1993; 48(3):259-261.
37. Takruri Hamed RH, Majdoleen Dameh AF. Study of the nutritional value of black cumin seeds (*Nigella sativa*L). Journal of the Science of Food and Agriculture. 1998; 76(3):404-410.
38. Rasoli MS, Khalili M, Mohammadi R, Soleimani A, Kohzadi R, Ilkhanipour M *et al*. The Chemical Composition of *Nigella sativa* L. and Its Extract Effects on Lipid Peroxidation Levels, Total Antioxidant Capacity and Catalase Activity of the Liver and Kidney in Rats Under Stress. Gene, Cell and Tissue, 2018.
39. Atta MB. Some characteristics of nigella (*Nigella sativa* L.) seed cultivated in Egypt and its lipid profile. Food Chem. 2003; 83:63-68.
40. Nickavar B, Mojab F, Javidnia K, Amoli MAR. Chemical composition of the fixed and volatile oils of *Nigella sativa* L. from Iran. *Zeitschrift für Naturforschung* C. 2003; 58(9-10):629-631.
41. Cheikh-Rouhou S, Besbes S, Hentati B, Blecker C, Deroanne C, Attia H. *Nigella sativa* L. Chemical composition and phytochemical characteristics of lipid fraction. Food Chem. 2007; 101:673-681.
42. Saxena SN, Rathore SS, Diwakar Y, Kakani RK, Kant K, Dubey PN *et al*. Genetic diversity in fatty acid composition and antioxidant capacity of Nigella, 2017.
43. Akram Khan M. Chemical composition and medicinal properties of *Nigella sativa* Linn. Inflammopharmacology. 1999; 7:15-35.
44. Bourgou S, Bettaieb I, Saidani M, Marzouk B. Fatty acids, essential oil, and phenolics modifications of black cumin fruit under NaCl stress conditions. J Agric. Food Chem. 2010; 58:12399-12406.
45. Al-Kayssi AW, Shihab RM, Mustafa SH. Impact of soilwater stress on nigellone oil content of black cumin seeds grown in calcareous-gypsifereous soils. Agric. Water Manage. 2011; 100:46-57.
46. Aboutabl B, El-Azzouny A, Hammerschtüiidt F. Aroma volatile of *Nigella sativa* seeds. Prog Essent Oil Res, Proc Int Symp Essent Oils. 1986; 16th:49-55.
47. Nickavar Bahman *et al*. Chemical composition of the fixed and volatile oils of *Nigella sativa* L. from Iran. Zeitschrift für Naturforschung C. 2003; 58(9-10):629-631.
48. Mattha¨ us, B, O¨ zcan MM. Fatty acids, tocopherol, and sterol contents of some Nigella species seed oil. Czech J Food Sci. 2011; 29:145-150.
49. Cheikh-Rouhou S, Besbes S, Lognay G, Blecker C, Deroanne C, Attia H. (). Sterol composition of black cumin (*Nigella sativa* L.) and Aleppo pine (*Pinus halepensis* Mill.) seed oils. Journal of Food Composition and Analysis. 2008; 21(2):162-168.

50. Ghahramanloo, Kourosh Hasanzadeh *et al*. "Comparative analysis of essential oil composition of Iranian and Indian *Nigella sativa* L. extracted using supercritical fluid extraction and solvent extraction. Drug design, development and therapy. 2017; 11:2221. *Sativa* L. genotypes. LWT-Food Science and Technology, 78:198-207.
51. Doan LP, Nguyen TT, Long PQ, Pham MQ, Thuy TTT, Minh PTH *et al*. Fatty acid, tocopherol, sterol compositions and antioxidant activity of three Garcinia seed oils. Records of Natural Products. 2018; 12(4):323.
52. Al-Yahya MA. Phytochemical studies of the plants used in traditional medicine of Saudi Arabia. Fitoterapia. 1986; 57(3):179-182.
53. Riaz M, Syed M, Chaudhary FM. Chemistry of the medicinal plants of the genus Nigella (Family-Ranunculaceae). Hamdard Med. 1996; 39:40-45.
54. Jadayil Abu S, Kh Tukan S, Takruri HR. Bioavailability of iron from four different local food plants in Jordan. Plant Foods for Human Nutrition. 1999; 54(4):285-294.
55. Haq Afrozul *et al*. Immunomodulatory effect of *Nigella sativa* proteins fractionated by ion exchange chromatography. International journal of Immunopharmacology. 1999; 21(4):283-295.
56. Burits M, Bucar F. Antioxidant activity of *Nigella sativa* essential oil. Phytotherapy research. 2000; 14(5):323-328.
57. Guergouri FZ, Sobhi W, Benboubetra M. Antioxidant activity of Algerian *Nigella sativa*total oil and its unsaponifiable fraction, 2018.
58. Malik S, Zaman K. Nigellimine: a new isoquinoline alkaloid from the seeds of *Nigella sativa*. Journal of Natural Products. 1992; 55(5):676-678.
59. Morikawa T, Xu F, Ninomiya K, Matsuda H, Yoshikawa M. Nigellamines A3, A4, A5, and C, new dolabellane-type diterpene alkaloids, with lipid metabolism-promoting activities from the Egyptian medicinal food black cumin. Chemical and pharmaceutical bulletin. 2004; 52(4):494-497.
60. Ansari AA, Hassan S, Kenne L, Wehler T. Structural studies on a saponin isolated from *Nigella sativa*. Phytochemistry. 1988; 27(12):3977-3979.
61. Hadi MY, Mohammed GJ, Hameed IH. Analysis of bioactive chemical compounds of *Nigella sativa* using gas chromatography-mass spectrometry. Journal of Pharmacognosy and Phytotherapy. 2016; 8(2):8-24.
62. Taşkin MK, Çalişkan ÖA, Anil H, Abou-Gazar H, Khan IA, Bedir E. Triterpene saponins from *Nigella sativa* L. Turkish Journal of Chemistry. 2005; 29(5):561-569.
63. Mahmoudvand H, Sharififar F, Assadipour A, Hassan Moshafi M, Alishahi F. Bioassay screening of the Essential Oil and Various Extracts of *Nigella sativa* L. Seeds Using Brine Shrimp Toxicity Assay. Herbal Medicines Journal. 2017; 2(1):26-31.
64. El-Daly ES. Protective effect of cysteine and vitamin E, Crocus sativus and *Nigella sativa* extracts on cisplatin induced toxicity in rats. J Pharm Bel. 1998; 53:87-95.
65. Ali BA, Erwa HH. Effect of *Nigella sativa* on ingestion ability of mice peritoneal macrophages. Saudi Pharm J. 1993; 1:18-22.
66. El-Kadi A, Kandil O. Effect of *Nigella sativa* the black seed on immunity. Proceeding of the 4th International Conference on Islamic Medicine, Kuwait. Bull. Islamic. Med. 1986; 4:344-348.
67. Badary OA, Al-Shabana OA, Nagi MN, Al-Bekairi AM, Elmazar MMA. Acute and subchronic toxicity of thymoquinone in mice. Drug Development Research. 1998; 44:56-61.
68. Khanna T, Zaidi FA, Dandiya PC. CNS and analgesic studies on *Nigella sativa*. Fitoterapia. 1993; 5:407-410.
69. Zaoui A, Cherrah Y, Mahassini N, Alaoui K, Amarouch H, Hassar M. Acute and chronic toxicity of *Nigella sativa* fixed oil. Phytomedicine. 2002; 9(1):69-74.
70. Vahdati-Mashhadian N, Rakhshandeh H, Omidi A. An investigation on LD50 and subacute hepatic toxicity of *Nigella sativa* seed extracts in mice. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2005; 60(7):544-547.
71. Ozbek H, Oztürk M, Oztürk A, Ceylan E, Yener Z. Determination of lethal doses of volatile and fixed oils of several plants. Eastern J Medicine. 2004; 9:4-6.
72. Ong YS, Yazan LS, Ng WK, Noordin MM, Sapuan S, Foo JB *et al*. Acute and subacute toxicity profiles of thymoquinone-loaded nanostructured lipid carrier in BALB/c mice. International journal of nano medicine. 2016; 11:5905.
73. Al-Ali A, Alkhawajah AA, Randhawa MA, Shaikh NA. Oral and intraperitoneal LD50 of thymoquinone, an active principle of *Nigella sativa*, in mice and rats. J Ayub Med Coll Abbottabad. 2008; 20(2):25-27.
74. Tubesha Z, Imam MU. Mahmud R, Ismail M. Study on the potential toxicity of a thymoquinone-rich fraction nanoemulsion in Sprague Dawley rats. Molecules. 2013; 18(7):7460-7472.
75. Gad MME, Mohammad YS, Mohammad TGM. Acute and repeated-doses (28 Days) toxicity of Thymol formulation in male albino rats. Australian Journal of Basic and Applied Sciences. 2012; 7(8):915-922.
76. Al-Hader Aqel, Aqel M, Hasan Z. Hypoglycemic effects of the volatile oil of *Nigella sativa* seeds. International journal of pharmacognosy. 1993; 31(2):96-100.
77. Al-Awadi FM, Khattar MA, Gumaa KA. On the mechanism of the hypoglycaemic effect of a plant extract. *Diabetologia*. 1985; 28(7):432-434.
78. Meddah Bouchra *et al*. *Nigella sativa* inhibits intestinal glucose absorption and improves glucose tolerance in rats. Journal of ethnopharmacology. 2009; 121(3):419-424.
79. Le PM, Benhaddou-Andaloussi A, Elimadi A, Settaf A, Cherrah Y, Haddad PS. The petroleum ether extract of *Nigella sativa* exerts lipid-lowering and insulin-sensitizing actions in the rat. Journal of ethnopharmacology. 2004; 94(2-3):251-259.
80. Hawsawi Zubaida A. Basil A. Ali, and Abdullah O. Bamosa. Effect of *Nigella sativa* (black seed) and thymoquinone on blood glucose in albino rats. Ann Saudi Med. 2001; 21(3-4):242-244.
81. Zaoui A, Cherrah Y, Alaoui K, Mahassine N, Amarouch H, Hassar M. Effects of *Nigella sativa* fixed oil on blood homeostasis in rat. Journal of Ethnopharmacology. 2002; 79(1):23-26.
82. Rchid H, Chevassus H, Nmila R, Guiral C, Petit P, Chokaïri M *et al*. *Nigella sativa* seed extracts enhance glucose-induced insulin release from rat-isolated

Langerhans islets. Fundamental & clinical pharmacology. 2004; 18(5):525-529.
83. Fararh KM, Atoji Y, Shimizu Y, Takewaki T. Isulinotropic properties of *Nigella sativa* oil in Streptozotocin plus Nicotinamide diabetic hamster. Research in veterinary science. 2002; 73(3):279-282.
84. Fararh KM, Shimizu Y, Shiina T, Nikami H, Ghanem MM, Takewaki T. Thymoquinone reduces hepatic glucose production in diabetic hamsters. Research in veterinary science. 2005; 79(3):219-223.
85. Kanter M, Meral I, Yener Z, Ozbek H, Demir H. Partial regeneration/proliferation of the β-cells in the Islets of Langerhans by *Nigella sativa* L. in streptozotocin-induced diabetic rats. The Tohoku Journal of Experimental Medicine. 2003; 201(4):213-219.
86. Kaleem M, Kirmani D, Asif M, Ahmed Q, Bano B. Biochemical effects of *Nigella sativa* L seeds in diabetic rats, 2006.
87. Abdelmeguid NE, Fakhoury R, Kamal SM, Al Wafai RJ. Effects of *Nigella sativa* and thymoquinone on biochemical and subcellular changes in pancreatic β-cells of streptozotocin-induced diabetic rats. Journal of diabetes. 2010; 2(4):256-266.
88. Al-Logmani AS, Zari TA. Effects of *Nigella sativa* L. and Cinnamomum zeylanicum Blume oils on some physiological parameters in streptozotocin-induced diabetic rats. Boletín latinoamericano y del caribe de plantas medicinales y aromáticas. 2009; 8(2).
89. Alimohammadi S, Hobbenaghi R, Javanbakht J, Kheradmand D, Mortezaee R, Tavakoli M *et al*. Protective and antidiabetic effects of extract from *Nigella sativa* on blood glucose concentrations against streptozotocin (STZ)-induced diabetic in rats: an experimental study with histopathological evaluation. Diagnostic pathology. 2013; 8(1):137.
90. Asaduzzaman M, Nahar L, Hasan M, Khatun A, Tamanna Z, Huda N *et al*. Hypoglycemic and hypolipidemic potential of *Nigella sativa* L. seed extract in streptozotocin (STZ)-induced diabetic rats. Journal of Plant Biochemistry & Physiology, 2015.
91. Abbas AH. Antihyperglycemic, Antihyperlipidemic Effects of Ethanol Extract of *Nigella sativa* Seeds In Streptozocin/High Fat Diet Induced Hyperglycemic Mice, 2018.
92. Kanter M, Coskun O, Korkmaz A, Oter S. Effects of *Nigella sativa* on oxidative stress and β-cell damage in streptozotocin-induced diabetic rats. The Anatomical Record Part A: Discoveries in Molecular, Cellular, and Evolutionary Biology: An Official Publication of the American Association of Anatomists. 2004; 279(1):685-691.
93. Kanter M. Effects of *Nigella sativa* and its major constituent, thymoquinone on sciatic nerves in experimental diabetic neuropathy. Neurochemical research. 2008; 33(1):87-96.
94. Al-Wafai RJ. *Nigella sativa* and thymoquinone suppress cyclooxygenase-2 and oxidative stress in pancreatic tissue of streptozotocin-induced diabetic rats. Pancreas. 2013; 42(5):841-849.
95. Abbasnezhad Abbasali *et al*. The effects of hydroalcoholic extract of *Nigella sativa* seed on oxidative stress in hippocampus of STZ-induced diabetic rats Avicenna Journal of Phytomedicine. 2015; 5(4):333-40.
96. Satarug S, Baker JR, Urbenjapol S, Haswell-Elkins M, Reilly PE, Williams DJ *et al*. A global perspective on cadmium pollution and toxicity in non-occupationally exposed population. Toxicology letters. 2003; 137(1-2):65-83.
97. Merali Z, Singhal RL. Prevention by zinc of cadmium-induced alterations in pancreatic and hepatic functions. British Journal of Pharmacology. 1976; 57(4):573-579.
98. Klaassen CD, Liu J, Choudhuri S. Metallothionein: an intracellular protein to protect against cadmium toxicity. Annual review of pharmacology and toxicology. 1999; 39(1):267-294.
99. Yau ET, Mennear JH. Pancreatic metallothionein: protection against cadmium-induced inhibition of insulin secretory activity. Toxicology and applied pharmacology. 1997; 39(3):515-520.
100. Kanter M, Coskun O, Gurel A. Effect of black cumin (*Nigella sativa*) on cadmium-induced oxidative stress in the blood of rats. Biological trace element research. 2005; 107(3):277-287.
101. Demir H, Kanter M, Coskun O, Uz YH, Koc A, Yildiz A. Effect of black cumin (*Nigella sativa*) on heart rate, some hematological values, and pancreatic β-cell damage in cadmium-treated rats. Biological trace element research. 2006; 110(2):151-162.
102. Chun TW, Stuyver L, Mizell SB, Ehler LA, Mican JAM, Baseler M *et al*. Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy. Proceedings of the National Academy of Sciences. 1997; 94(24):13193-13197.
103. Chandra S, Murthy SN, Mondal D, Agrawal KC. Therapeutic effects of *Nigella sativa* on chronic HAART-induced hyperinsulinemia in rats. Canadian journal of physiology and pharmacology. 2009; 87(4):300-309.
104. Chandra S, Mondal D, Agrawal KC. HIV-1 protease inhibitor induced oxidative stress suppresses glucose stimulated insulin release: protection with thymoquinone. Experimental Biology and Medicine. 2009; 234(4):442-453.
105. Ziyyat A, Legssyer A, Mekhfi H, Dassouli A, Serhrouchni M, Benjelloun W. Phytotherapy of hypertension and diabetes in oriental Morocco. Journal of Ethnopharmacology. 1997; 58(1):45-54.
106. Laadim M, Ouahidi ML, Zidane L, El-Hessni A, Ouichou A, Mesfioui A. Ethnopharmacological survey of plants used for the treatment of diabetes in the town of Sidi Slimane (Morocco). Journal of Pharmacognosy and Phytotherapy. 2017; 9(6):101-110.
107. Otoom SA, Al-Safi SA, Kerem ZK, Alkofahi A. The use of medicinal herbs by diabetic Jordanian patients. Journal of herbal pharmacotherapy. 2006; 6(2):31-41.
108. Al-Rowais NA. Herbal medicine in the treatment of diabetes mellitus. Saudi medical Journal. 2002; 23(11):1327-1331.
109. Bamosa AO, Ali BA, Sowayan SA. Effect of oral ingestion *Nigella sativa* seeds on some blood parameters. Saudi Pharmaceutical Journal. 1997; 5:126-129.
110. Qidwai W, Hamza HB, Qureshi R, Gilani A. Effectiveness, safety, and tolerability of powdered *Nigella sativa* (Kalonji) seed in capsules on serum lipid levels, blood sugar, blood pressure, and body weight in

adults: results of a randomized, double-blind controlled trial. The Journal of alternative and complementary medicine. 2009; 15(6):639-644.
111. Bamosa AO, Kaatabi H, Lebdaa FM, Elq AM, Al-Sultanb A. Effect of *Nigella sativa* seeds on the glycemic control of patients with type 2 diabetes mellitus. Indian J Physiol Pharmacol. 2010; 54(4):344-54.
112. Kaatabi H, Bamosa AO, Badar A, Al-Elq A, Abou-Hozaifa B, Lebda F *et al*. *Nigella sativa* improves glycemic control and ameliorates oxidative stress in patients with type 2 diabetes mellitus: placebo controlled participant blinded clinical trial. PloS one. 2015; 10(2):e0113486.
113. Heshmati J, Namazi N, Memarzadeh MR, Taghizadeh M, Kolahdooz F. *Nigella sativa* oil affects glucose metabolism and lipid concentrations in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. Food Res Int. 2015; 70:87-93.
114. Hadi S, Mirmiran P, Hosseinpour-Niazi S, Hedayati M, Azizi F. Effect of *Nigella sativa* oil extract on lipid profiles in type 2 diabetic patients: A randomized, double blind, placebo-controlled clinical trial. Iran J Endocrinol Metab. 2015; 16(6):411-8.
115. Hosseini MS, Mirkarimi SA, Amini M, Mohtashami R, Kianbakht S, Fallah Huseini H. Effects of *Nigella sativa* L. seed oil in type II diabetic patients: A randomized, double-blind, placebo - Controlled clinical trial. J Med Plants. 2013; 12(47):93-9.
116. Najmi A, Haque SF, Naseeruddin M, Khan RA. Effect of *Nigella sativa* oil on various clinical and biochemical parameters of metabolic syndrome. Int J Diabetes Dev Ctries. 2008; 16:85-87.
117. Mahdavi R, Namazi N, Alizadeh M, Farajnia S. Effects of *Nigella sativa* oil with a low-calorie diet on cardiometabolic risk factors in obese women: A randomized controlled clinical trial. Food Funct. 2015; 6(6):2041-8.
118. Datau EA, Wardhana, Surachmanto EE, Pandelaki K, Langi JA, Fias. Efficacy of *Nigella sativa* on serum free testosterone and metabolic disturbances in central obese male. Acta Med Indones. 2010; 42(3):130-4.