J. Chem. & Cheml. Sci. Vol.1 (4), 241-248 (2011)

A Review on Therapeutic Applications of Nigella Sativa

R. M. SHRIVASTAVA[1], R. C. AGRAWAL[2] and ZEBA PARVEEN*

[1]Ex. Principal, M. V. M. College and Present Director of Unique College, Bhopal, M.P. India
[2]Lecturer, Jawaharlal Nehru Cancer Hospital and Research Centre, Idgah Hills, Bhopal, M. P. India
*Safia Science College, Bhopal, M. P. India

ABSTRACT

Nigella sativa is widely used medicinal plant throughout India and popular in various indigenous system of medicine like Ayurveda, Siddha, Unani and Tibb. one of the traditionally known herb well known for its healing properties. This review mainly focuses on the pharmacological action of seed extracts, oils and active constituents for their wide spectrum biological properties such as antioxidant, anti diabetic, anti-microbial, anti-cancerous, etc. Very low level of toxicity has been reported through and chronic toxicity studies. Since the N.sativa seeds hold immense therapeutic potential. Nevertheless, more clinical studies are needed to further asses the efficacy and safety in therapeutic applications. The present review is therefore an effort to give a survey of literature on phytochemistry and pharmacological activities of Nigella sativa seed.

Keywords: *Nigella sativa*; Thymoquinone; Antioxidant properties; Oxidative stress; Anti-diabetes; Anti-cancerous activity.

INTRODUCTION

Herbs are vital source of drugs from the ancient time holding the scenario of the Indian *system of medicine*. *Nigella sativa* (NS) belonging to family Ranunculaceae is a spice which is well known for its medicinal properties. It is commonly known as black cumin. NS is an annual flowering plant, native to south west Asia and cultivated in countries like Middle Eastern Mediterranean region, South Europe, Syria, Turkey, Saudi Arabia, Pakistan, India[1]. Seeds of this plant have also been extensively used in the Unani system of medicine ranging from external application to ingestion for diseases such as diabetes, kidney failure[2]. In folk medicine, it has been traditionally used for variety of applications including treatments related to respiratory health, stomach and intestinal health, kidney and liver function, circulatory and immune system support, and for general

overall wellbeing[3]. NS have been extensively in use for centuries in folk medicines, both as herb and for oil by people in Asia, Middle East, and Africa for medicinal purposes. Seeds are used as a new source of edible oils and food applications as spice and condiments in cakes, breads, pastries, curries, pickles and in seasoning etc. Among Muslims, it is regarded as one of the greatest forms of healing medicine available. In the Greco Arab/Unani Tibb system of medicine, black seed has been regarded as a valuable remedy in hepatic and digestive disorders and has been described as a stimulant in a variety ofconditions, ascribed to an imbalance of cold humors. Recent pharmacological investigations have proved the potential therapeutic effects of NS seed as well as its oil through various studies[4]. A number of investigations have tried to elucidate the mechanism of action of these compounds at cellular level. The objective of this review is to compile all this literature systematically to know their effects, mechanism of action and safety for therapeutic applications.

CHEMICAL COMPOSITIONS OF SEED

The variation in nutrient composition of NS varieties from different origin is due to variation of cultivated region, storage condition and maturity stage. NS seeds contain 26.7 % protein, 28.5% fat, 24.9% carbohydrates, 8.4% crude fiber and 4.8 % ash on dry weight basis[5]. The seed is also a good source of many vitamins and minerals particularly Cu, P, Zn and Fe. Fixed oil contains 22% mono unsaturated fatty acids (MUFA) and 50% polyunsaturated fatty acid (PUFA) and it is also rich in linoleic acid and oleic acid. Among sterols, *â*-Sitosterol is the major form, which accounts for 44% and 54% of the total sterols in Tunisian and Iranian varieties of seed oils respectively[6,7], followed by stigmasterol (6.57–20.92% of total sterols). Total poly phenolic content of NS oil was found to be 250-300 mg gallic acid equivalent/kg oil. Essential oil (0.41 to 0.44%) consists of a mixture of monoterpenes as analyzed by GCMS[8]. Nearly 32 compounds have been identified, of which thymoquinone(30-48%), thymohydroquinone, dithymoquinone, p-cymene (7-15%), carvacrol (6-12%), 4 terpineol (2-7%), t-anethol (1-4%), sesquiterpene longifolene (1-8%) and á-pinene are some of the predominant compounds. Other derivatives found in trace amounts include carvone, limonene, citronellol. Many of these compounds are capable of inducing pharmacological effects in humans. Most of the properties of whole seeds or their extracts are mainly attributed to quinine constituents, of which thymoquinone (TQ) is the most abundant as well as the potent pharmacologically active compound which readily dimerises to form dithymoquinone. Seeds contain indazole ring bearing alkaloids such as nigellicine, nigellidine[9] whereas nigellimine and its N-oxides are of isoquinoline alkaloids.

ANTIOXIDANT PROPERTY

NS oil as well as TQ have been shown to prevent oxidative injuries. Incorporation of ethanolic extract of NS seeds in corn oil retarded the oxidative deterioration of triglycerides[11]. These possible antioxidant effects may be related to inhibition of eicosanoid generation,

namely thromboxane B2 and leucotrienes B4 (by inhibiting cyclooxygenase and 5-lipooxygenase respectively), and membrane lipid peroxidation. Oral feeding of NS oil or TQ has protected the methionine induced hyperhomocysteinemia by enhancing the antioxidant status and amelioration of triglycerides, lipid per oxidation and cholesterol concentration in plasma[13]. Intra peritoneal (i.p) injection of NSO and TQ have also shown protective effects on lipid per oxidation process during ischemia reperfusion injury (IRI) in rat hippocampus (14). The attenuation of oxidative stress by radical scavenging properties of NSO has been clearly indicated in pentylenetatrazol (PTZ) induced seizure-kindled mice[15]. TQ is a potent chemo preventive agent and has been shown to suppress the Fe-NTA-induced oxidative stress, hyper proliferative response and renal carcinogenesis in Wistar rats[16]. Oral feeding of the diet containing NS powder at 10% level antagonized the oxidative stress effects induced by hepato carcinogens such as dibutylamine and NaNO3 in Swiss albino rats by normalizing GSH and NO levels[17]. Dietary supplementation of seed powder inhibits the oxidative stress caused by oxidized corn oil in rats[18].Treating with NS for 6 weeks in broiler chicks prevented the liver from oxidative stress by decreasing hepatic lipid per oxidation and increasing the activities of enzymes such as catalase, glutathione-S transferase, adenosine deaminase, myeloperoxidase[19]. Most recently, the antioxidant activities of crude methanolic extract of black cumin seed cake were also investigated and some of the phenolic compounds such as hydroxybenzoic, syringic and pcumaric acids were identified with significant antioxidant properties under *in vitro* systems[20].

ANTI-DIABETIC PROPERTY

Oxidative stress is also believed to play a role in the pathogenesis of diabetes mellitus (DM). Black cumin is one of the most recommended plants for diabetics and the hypoglycemic effect of NSO may be due to extra-pancreatic action as reported by El-Dakhakhny *et al*.,[21]. NS treatment exerts a protective effect in diabetes by decreasing oxidative stress and preserving pancreatic beta-cell integrity. Consequently, NS may be clinically useful for protecting beta-cells against oxidative stress[22]. The insulinotrophic effect of NS is at least partly mediated by stimulation of insulin release and several reports have been published recently in support of this. Kanter *et al*.,[23] have reported that prior treatment of diabetic rats (induced by streptozotocin), with NS, protected the pancreatic B-cells and also decreased the malonaldehyde concentration in pancreas and nitric oxide level in serum. Similarly, Insulinotropic effect of oil has also been demonstrated in streptozotocin plus nicotinamide induced diabetesmellitus in hamsters[24]. Oral treatment of oil for 4 weeks increased the serum insulin level due to stimulatory effect on â cell function, as partly and also decreased the blood glucose level significantly. In an another study, hypoglycemic effect of oil in hamster showed decrease in hepatic gluconeogenesis and immunopotentiating effect through stimulation of macrophage phagocytic

activity either directly or via activation of lymphocytes has been also observed[25]. A clear concentration-dependent increase in insulin release from isolated pancreatic islets was observed for the basic sub-fraction and whole defatted extract[26]. Synergistic effect of NS with human parathyroid hormone (hPTH) showed to be more effective than treatment with NS or hPTH alone in improving bone mass, connectivity, biomechanical behaviour and strength in insulin-dependent diabetic rats[27]. Treatment with NS could be an effective therapy for diabetes as well as diabetic osteopenia. Insulin hormone stimulates two signal transduction pathways through MPAK p42/44erk and PKB/Akt kinases, the later are responsible for enhanced glucose transport into skeletal muscle to form glycogen. From a study, the petroleum extract of NS given for 4 weeks by intragastric gavage in male Sprague-Dawly rats showed a dose dependent activation of these kinases, determined by western blot analysis of kinases from isolated hepatocytes, demonstrated to be in support of treating type II diabetic condition[28]. Oral administration of ethanolic extract of NS seeds (300 mg/kg body weight/day) for 30 days to streptozotocin induced diabetic rats significantly reduced the elevated levels of blood glucose, lipids, plasma insulin and improved altered levels of lipid peroxidation products (TBARS and hydroperoxides) and antioxidant enzymes like catalase, superoxide dismutase, reduced glutathione and glutathione peroxidase in liver and kidney[29]. In a clinical studies, oral administration of NS seed powder (1g/day) for 2 months to hypercholesterolemic patients reduced total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol[31,32]. The mechanism of action for the anti-diabetic property of the TQ is still unclear.

ANTI CANCEROUS PROPERTY

Ethanolic extract of NS has been demonstrated to inhibit the EAT (Ehrlich ascites tumor) tumor growth by reducing the cell count and tumor development[34]. Ethyl acetate fraction from 90% methanolic extract of black cumin exhibited significant growth inhibition of 2 leukemic cell lines and 5 solid tumor cell lines studied under in *vitro* conditions[35]. A decoction prepared from NS seed in combination with *Hemidesmus indicus* and *Smilax glabra* protected diethylnitrosoamine (DEN) induced hepatocarcinogenesis by inhibiting DEN mediated Glutathione S-transferase-P (GST-P) in rat liver[36]. Oral administration of TQ inhibited the benzo(a)pyrene (B(a)P)-induced forestomach carcinogenesis[37] and methylcholanthrene (MC)- induced fibro sarcoma tumor genesis[38] in mice. The molecular mechanism of the TQ has not been well characterized, but in a study inhibition of the growth of HCT-116 human colon cancer cells by TQ was correlated with G1 phase arrest of the cell cycle[39]. Further, TUNEL staining and flow cytometry analysis indicated that TQ triggered the apoptosis in a dose and time-dependent manner with a 2.5-4.5-fold increase in mRNA expression of p53 and the downstream p53 target gene, p21WAF1. In

an *in vivo* study using the DBA2/P815 (H2d) mouse model, results clearly showed that the injection of the essential oil into the tumor site significantly inhibited solid tumor development. Interestingly, the administration of the essential oil into the tumor site inhibited the incidence of liver metastasis development too[40]. The administration of NS reduced the carcinogenic effects of DMBA carcinogen in mammary carcinoma, suggesting a protective role[41]. Kapoor *et al*.,[43] have demonstrated the importance of DNA damage protection properties of NS in preventing the initiation of colon cancer induced by toxic agents such as azoxymethane.

ANTIMICROBIAL PROPERTY

Black seed oil has been shown to be effective against a wide spectrum of organisms-bacteria like *Bacillus cereus, B. subtilis, B.pumilus* S*taphylococcus aureus*, *S.epidermis*, *Echerichia coli*, *Pseudomonas aeuginosa*, *Salmonella abony*[34,35], pathogenic yeast like *candida albicans* etc. *Lysteria monocytogenes* which is one of the fatal food-borne pathogens throughout the world and the inhibitory effect was of NS found to be twice more than the positive control, gentamicin[46, 47]. TQ showed high activity against Gram-positive bacteria and moulds like *Fusarium solani*[48] and *Aspergillus niger* which causes aspergillosis[49]. NS also as a source of antidermatophytes drugs could be used for treatment of fungal skin infection caused by *Trichophyton rubrum Trichophyton interdigitale, Trichophyton mentagrophytes, Ephidermophyton floccosum, Microsporum canis* etc[42]. Antiviral effect of NSO against murine cytomegalovirus (MCMV) infection may be mediated by increasing of Mö number and function, and INF-á production. In tests with 37 isolates of *Shigella* species (*S. deysenteriae, S. flexneri, S. sonnei and S. boydii*), 10 strains of *V. cholerae* and *E. coli*, the volatile seed oil of *N.sativa* showed promising activity against all the strains except *S. deysenteriae*. The minimum inhibitory concentration of the oil was between 50 and 400 µm/ ml for the various strains, demonstrate the therapeutic potential of the seed oil for the treatment of diarrhoea. Methanolic extract of NS showed antibacterial activity tested by disk diffusion method against S. *aureus, pseudomonas aeruginosa, Klebsiella pneumonia Escherichia coli and Bacillus cereus* (21, 22). In an another investigation, antimicrobial effect was demonstrated against some standard and clinical strains such as *Candida albicans*, coagulase-positive *S. aureus* (CPSA) and *Pseudomonas aeroginosa* by agar dilution, cylinder plate and disk diffusion methods(23).

DISCUSSION

Seeds of *N. sativa* seem to possess magical properties and have been worked out extensively. It is a rich source of many important nutrients, selenium, tocopherol, all-trans-retinol, and also a good alternative source of essential fatty acids. Oil as well as

the main active compounds i.e. thymoquinone (TQ) from this plant have been shown to possess beneficial therapeutic potential on human health as it is evident from a many research findings. However, exploration into molecular mechanism for the active compounds need further research in future. Though a number of reports on this herb show great therapeutic values, concern over its usage in food is not much. NS seeds could be used to prepare multi-purpose products for pharmaceutical applications and its usage as dietary source of antioxidant should be considered largely for alleviating and ameliorating disease conditions.

REFERENCES

1. Al-Awadi, F. M., Khatterm M. A., Guma, K. A.: *Diabetolgia*, 28: 432-4 (1985). 1057 (2009).
2. Alhaj, N. A., Shamsudin, M. N., Zamri, H. F., Abdullah, R.: *Am. J. Pharmacol Toxicol*, 3 (4): 225-228(2008).
3. Al-Jabre, S., Al-Akloby, O. M., Al-Qurashi, A. R., Akhtar, N., Al-Dossary, A., Randhawa, M.A.: *Pak J. Med Res*, 42 (2003).
4. Aljabre, S. H. M., Randhawa, M. A., Akhtar, N., Alakloby, O.M., Alqurashi., Aldossary, A.: *J. Ethanophormacol*, 101:116-119 (2005).
5. Al-Othman, A. M., Ahmad, F., Al-Orf, S., Al-Murshed, K.S., Ariff, Z.: *Int. J. Pharmocol*, 2 (1):60-65 (2006).
6. Altan, M. F., Kanter, M., Donmez, S., Kartal, M. E.,, S.: *Acta Histochem*, 109: 304-314 (2007).
7. Anwar, M. A.: *Nigella sativa*: *Malaysian Journal Lib. Infor. Sci,* 10(1): 1-8 (2005).
8. Atta-ur-Rahman., Malik, S., Hasan, S. S., Choudhary, M. I., Ni, C., Clardy, J.: *Tetrahedron Lett*, 36: 1993-1996 (1995).
9. Badary, O.A., Al-Shabanah, O.A., Nagi, M.N., Al-Rikabi, A.C., Elmazar, M.M.: *Eur. J. Cancer Prev*, 8 (5):435–440 (1999).
10. Badary, O.A., Gamal El-Din, A.M.: *Cancer Detect Prev*, 25 (4): 362–368 (2001).
11. Bassim-Atta, M., Imaizumi-K.: *J. Jpn. Oil Chem. Soc*, 47, 5: 475-480 (1998).
12. Benharref, A., Chait, A., Kamal, M., Dalal, A., Zyad, A.: *Braz J. Med. Biol. Res.*, 40(6): 839-847 (2007).
13. Bhatti, I. U., Rehman, F.U.: *W Appl Sci J.*, 6 (8): 1053-1057(2009).
14. Bhatti., I.U., Rehman, F.U.: *W Applied Sci. J.*, 6 (8):1053-1057(2009).
15. Burtis, M., Bucor, F.: *Phytother Res*, 14: 323-328 (2000).
16. Cheikh-Rouhou, S., Besbes, S., Lognay, G., Blecker, C., Deroanne, C., Attia, H.: *J. Food Comp. Anal*., 21(2):162-168 (2008).
17. Damjanova, S., Encheve, R., Stojanova, A., Perofanova, N., Miziiski, F.: Hranitelno Vkusova Promishlenost, 5: 10-11 (2002).
18. El-Aziz, M.A., Hassan, H.A., Mohamed, M.H., Meki, A.R., Abdel-Ghaffar, S.K, Hussein, M.R.: *Int. J. Exp. Pathol*, 86 (6):383-96 (2005).

19. El-Dakhakhny, M., Mady, N., Lembert, N., Ammon, H.P.T.: *Planta Med*. 68 (5):465-466 (2002).
20. El-Daly, E.S. J.: *Islamic Acad. Sci*, 7(2): 93-99 (1994).
21. El-Saleh, S. C., Al-Sagir, O. A., Al-Khalaf, M.I.: *Int. J. Cardiol*, 93:19-23 (2004).
22. Fararh, K. M., Atoji, Y., Shimizu, Y,. Takewaki, T.: *Res. Vet. Sci.*, 73: 279-282 (2002).
23. Fararh, K. M., Atoji, Y., Shimizu, Y., Takewaki, T., *Res. Vet. Sci.*, 77, 123-129 (2004).
24. Gali-Muhtasib, H., Diab-Assaf, M., Boltze, C., Al-Hmaira, J., Hartig, R., Roessner, A., Schneider-Stock, R.: *Int. J. Oncol*, 25 (4):857-66 (2004).
25. Gendy, E., Hessien, M., Abdel Salamm I., Moradm, M. E. L., Magrabym K., Ibrahimm, H. A., Kalifam, M. H., El-Aaser, A. A.: *Turkish J. Biochem*, 32 (1): 5–11 (2007).
26. Gurdip-singh., Marimuthu, P., Heluani, C. S. D., Catalan,. C.S.O.: *J. Sci. Food Agr*, 85(13): 2297-2306 (2005).
27. Gutteridge, J. M. C., Halliwell,: In; Antioxidants confirmed that the root contained high content of in Nutrition, Health and Disease, Oxford University Press, Oxford: 12 (1994).
28. Hosseinzadeha, H., Parvardeh, S., Aslb, M.N.,Sadeghnia, H. R., Ziaee, T., Phytomedicine, 14:621–627 (2007).
29. Iddamaldeniya, S. S., Wickramasinghe, N., Thabrew, Ilhan, A., Gurel, A., Armutcu, F., Kamisli, S., Iraz, : *Neuropharmacology*, 49: 456-464 (2005).
30. Kaleem, M., Kirmani, D., Asif, M., Ahmed, Q., Bano, B.: *Indian J. Exp. Biol*., 44(9):745-8 (2006).
31. Kanter, M., Cosku, N O., Korumaz, A., Oter, S.: Effects of *Nigella sativa* on oxidative stress and B-cells damage in streptozotocin-induced diabetic rats. The anatomical record part A: Discoveries in molecular cellular and evolutionary biology. 299A (1):685- 691(2004).
32. Kapoor, S.: *World J Gastroenterol*, 7; 15(17): 2170-2171(2009).
33. Khan, N., Sultana, S.: *Eur. J. Cancer Prev.*, 14(2):159- 68(2005).
34. Kumar, M., Nair, M., Vasudevan, P., Venkitanarayanan, K.: *Food control*,16: 395-398 (2005).
35. Le, P.M., Andaloussi, A.B., Elimadi, A., Settaf, A., Cherrah,Y., Haddad, P.S.: *J. Ethanophormacol*, 94: 251-259(2004).
36. Mariod, A.A., Ibrahim, R. M., Ismail, M., Ismail, N.: *Food Chem*., 116, 306-312 (2009).
37. Mashhadian, N.V., Rakhshandeh, H.: *Pak J. Med. Sci.*, 21: 1(2005).
38. Mbarek, L.A., Mouse, H.A., Elabbadi, N., Bensalah,M., Gamouh, A., Aboufatima, R.,
39. Meddah, B., Ducroc, R., Faouzi, M., Eto, B., Mahraoui,L.,Benhaddou-Andaloussi, A., Martineau, L. C., Cherrah, Y., Haddad, P. S.: *J. Ethanophormacol*, 121, 3,30: 419-424 (2009).

40. Mehta, B. K., Verma, M., Gupta, M. J.: *Braz. Chem. Soc*., 19, 3:458-462 (2008).
41. Mezayen, R. E., Gazzar, M.E., Nicolls M. R., Marecki.
42. Musa, D., Dilsiz, N., Gumushan, H., Ulakoglu, G., Bitiren, and M.: Bratislava, 59: 735-740 (2004).