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Dual properties of Nigella Sativa: anti-oxidant and pro-oxidant

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Abstract

Nigella sativa (NS) or black seed has been used for the treatment of various disorders for centuries. Experimentally, seed extract or thymoquinone (TQ) which is the main constituent of its oil has been reported to have anti-inflammatory, antineoplastic and anticancer properties. Interestingly, the published data demonstrates that NS acts as anti-oxidant in various diseases simultaneously, it behaves like a pro-oxidant for cancer cells. Here, we have summarized the dual properties of this medicinal plant. Current review is systematic, based on search from PubMed. Pubmed data indicated that NS has both anti-oxidant and pro-oxidant properties in different cell types hence should be used carefully because it acts as a cytoprotective or cytotoxic agent in inflammatory and malignant conditions respectively.

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Introduction

Reactive oxygen species (ROS) and unstable free radicals cause damage to cells hence lead to multiple diseases while anti-oxidants are substances which help to combat ROS or excess of free radicals by donation of electrons making a more stable chemical group [1]. For centuries anti-oxidants derived from plants have remained famous for their therapeutic properties. NS and its major constituent thymoquinone (TQ) have been reported to have anti-inflammatory, cardiovascular, analgesic, anti-neoplastic, anti-cancer and chemo preventive properties. Evidences also showed that Nigella acts as a pro-oxidant for cancer cells. Various TQ action mechanisms have been reported which elucidate it as an anti-oxidant or pro-oxidant at different concentration [2]. Organic extracts of NS seeds induced high expression of pro- and anti- apoptotic genes in HeLa cells [3].

Evidences suggest that NS acts as an anti-oxidant by scavenging ROS [4]. It can ameliorate ischemic reperfusion injury conditions and attenuated ROS in heart [5] intestine [6] and kidney [7]. It is reported that nigella can reduce the toxic effects of anticancer drugs [8] and decreased the viral load in HCV patients [9]. NS has been shown to improve multiple organ toxicity in models of oxidative stress [10-14].

Derivatives of TQ potentially induce apoptosis in cancer cells [15-18]. TQ generates ROS and causes low expression of pro-survival genes, conformational changes in pro-apoptotic proteins hence loss of mitochondrial membrane potential leading to activation of caspase-9, caspase-3, and polyadenosine 5'-diphosphate ribose polymerase cleavage and caspase-dependent apoptosis [19-22].

Here we try to highlight a very important issue that nigella can switch cells towards pro-oxidant or anti-oxidant pathways depending on cell types.

Methods

A systematic search was carried out from PubMed by entering key word "Nigella Sativa" with no filter, 517 articles were found from which only 54 relevant articles were selected.

Discussions

Role of Nigella Sativa as an anti-oxidant

The data of molecular mechanisms involving scavenging of ROS by NS or TQ against multiple inflammatory conditions have been described below.

NLRP3 inflammasome: NLRP3 inflammasome was inactivated partially by inhibition of ROS in melanoma cells by TQ administration. Treatment inhibited the NF-kappa B (NF-κB) activity and proteolytic cleavage of caspase-1 leading to inhibition IL-1β and IL-18 [4].

Multiple organ toxicity: NS was reported to ameliorate multiple organ toxicity in animal model of oxidative stress especially of myocardial and liver necrosis [10]. Oil of NS can protect from lungs damage due to hyperoxia [11]. It ameliorated oxidative stress conditions, reduced tissue damage in

rat ovaries and improved the activities of various enzymes like superoxide dismutase (SOD) and myeloperoxidase (MPO) [13]. Ns can greatly improve plasma and liver anti-oxidant capacity. It protected brain against chronic relapsing experimental autoimmune encephalomyelitis [23], tramadol-induced tolerance and dependence by ameliorating brain intracellular glutathione peroxidase activity [24]. NS oil has been found to be neuroprotective against oxidative stress in epileptogenesis, pilocarpine-induced seizures [25] and opioid tolerance [12].

Ischemic reperfusion: Ischemic reperfusion in heart causes activation of ROS leading to mitochondrial permeability transition pore (MPTP) opening hence cardiomyocyte death. It is reported that NS treatment resulted in substantial recovery of cardiac functions probably through inhibition of MPTP opening [26] improved cardiovascular risk parameters and attenuated ROS [5]. TQ has been ameliorated ischemia-reperfusion injury in intestine [6], kidney [7], gastric mucosa, brain and skeletal muscles. After treatment in skeletal muscles it increased anti-oxidant capacity with declined level of malondialdehyde (MDA) level [27].

Diabetes mellitus: Pathogenesis of diabetes mellitus is considered to be caused by oxidative stress. If NS is provided in these stress conditions, it can decrease lipid peroxidation, serum nitric oxide and also increased anti-oxidant enzyme activity [28,29]. NS oil or TQ improved the neuropathy and oxidative stress in STZ-induced diabetes through a significant decrease in Glutathione S-transferases (GST), Glutathione (GSH) and catalase [30]. When TQ was delivered in pregnancy it inhibited the rate of embryo malformations in diabetic mice through reduction of free radicals [31]. Cyclooxygenase-2 (COX-2) plays an important role in inflammatory conditions of diabetes mellitus induced by streptozotocin. NS treatment was found to suppress COX-2 enzyme, lipid peroxidation MDA levels and increased the level of SOD anti-oxidant enzyme in the pancreatic tissue of diabetic rats [32].

Viral Diseases: A decreased viral load was observed in HCV patients when NS was administered. Furthermore, it was safe and tolerable for the patients and also improved the oxidative stress condition [9]. Nelfinavir is used as one of the highly active anti-retroviral therapy (HAART) regimen which has been found to reduce the death rate of HIV-1 positive patients. An increased generation of ROS and also suppressed cytosolic SOD levels are the drawbacks of using Nelfinavir. It was found that TQ treatment along with HAART resulted in augmentation of ROS production and SOD levels [33].

Hypertension: It is reported that oxidative stress is associated with the pathogenesis of hypertension. Imbalance between anti-oxidant free radical production and anti-oxidant defense mechanisms causes increase in blood pressure. Nitric oxide availability is reduced due to excessive ROS production. This leads to endothelial dysfunction and ultimately results in increased total peripheral resistance. NS may reduce blood pressure due to its anti-oxidant, hypotensive, calcium channel blockade and diuretic properties [34].

Cancer: Anticancer drugs leave toxic effect due to over-production of ROS. NS oil or TQ can potentially up-regulate anti-oxidant mechanisms caused by anticancer drug cyclophosphamide [8]. Radiation therapy of cancer patients activates ROS production which causes unwanted damage to normal tissue. NS seed extracts can protect normal tissue from oxidative damage during radiotherapy of cancer patients [35,36]. NS protects tongue tissue of rats against oxidative stress induced by radiation [37]. NS ethanolic extract exhibited protection of DNA against damage and scavenged free radicals in cell free system. Furthermore its treatment protects mouse splenic lymphocytes against radiation induced oxidative stress hence apoptosis [38].

TQ was demonstrated to attenuate hepatic carcinogenesis induced by diethyl nitrosamine via decrease in oxidative stress. It preserves both mRNA expression and activity of anti-oxidant enzymes [39].

Role of Nigella Sativa as Pro-Apoptotic agent

Besides the above mentioned studies reporting the protection against inflammation induced by cancer cells or anticancer therapy, it can ameliorate various pathogenic conditions by reducing the ROS, it also has been found to act as pro-oxidant and improve cancer pathology by acting as a pro-oxidant i.e. generates ROS to kill cancer cells. The data is quite organized and many detailed molecular pathways have been reported which are involved in the apoptosis of cancer cells.

NF-κB pathway

TQ has been shown to exhibit down regulation of NF-κB expression in lung cancer cells and in osteosarcoma cells [40,41]. It suppressed the activation of NF-κB dependent downstream processes i.e. I kappa B alpha (ikbA) kinase, ikbA phosphorylation, ikb Adegradation, p65 phosphorylation and nuclear translocation. Anti-apoptotic (IAP1, IAP2, XIAP Bcl-2, Bcl-xL, survivin), proliferative (cyclin D1, cyclooxygenase-2, and c-Myc) and angiogenic genes (matrix metalloproteinase-9 or MMP-9) and vascular endothelial growth factor (VEGF) were down-regulated [42]. TQ acted as anti-angiogenic by inhibiting NF-κB and downstream effectors molecules in osteosarcoma. It greatly affected DNA-binding activity of NF-κB, down regulates XIAP, surviving and VEGF with up regulation of caspase-3 and Smac in ostosrcoma cells [41]. Activated B-cell lymphoma (ABC) has the worst survival rate after chemotherapy. TQ causes release of ROS in ABC cells which in turn inhibits NF-κB activity which is activated in pathological conditions. TQ dephosphorylates IκBα and decreases translocation of p65 (a subunit of NFκB) in the nucleus of ABC cells resulting in induction of mitochondrial dependent apoptosis and inhibition of cell viability [43]. NS seed extract has potential to induce apoptosis by activation of p53 and caspases in human cervical cancer cells [44]. In pancreatic cancer cells TQ was found to down-regulate NF-kB, Bcl-2 family, and antiapoptotic genes like X-linked inhibitors of apoptosis, survivin, and COX-2 hence potentiate the apoptosis induced by chemotherapeutic agents gemcitabine and oxaliplatin [45]. TQ up regulated the

expression of p21 and down regulated the histone deacetylase (HDAC) activity and induced histone hyperacetylation causing induction of apoptosis and inhibition of proliferation in pancreatic cancer cell. It also inhibited the activation as well as reduced the transport of NF-kB from the cytosol to the nucleus [46]. TQ has anti metastatic effect on human pancreatic cancer cells by down regulating NF-kBand MMP-9 [47]. TQ exerted strong anti-proliferative and apoptotic effect by caspase 8, 9 and 7in breast cancer cells and down regulated the expression of Bcl-2 and Bcl2L1 with upregulation in ppar-γ activity [48].

Glutathione pathway

TQ can potentially give protection against chemical carcinogenesis and toxicity by increasing the activities of quinonereductase and glutathione transferase [49]. TQ was found to decrease glutathione (GSH) levels in prostate cancer cells resulting in up-regulated expression of GADD45 alpha (growth arrest and DNA damage inducible gene) and AIF (apoptosis-inducing factor-1) and down-regulated expressions of several Bc12-related pro-survival proteins including BAG-1, Bcl2, Bcl2A1, Bcl2L1 and BID [50]. TQ has potential to scavenge free radicals and superoxide radicals and preserve the activity of anti-oxidant enzymes like catalase, glutathione peroxidase and glutathione-S-transferase [51]. TQ caused the apoptosis of tumor cells by modulation of wnt signaling through activation of GSK-3β [52].

JAK-STAT pathway

JAK-STAT pathway involves activation of various cell survival proteins. In cancer conditions this pathway leads to abnormal cell survival and proliferation of cells. TQ suppressed the STAT 3; the signal transducer and activator of transcription which is involved in the abnormal transformation of a number of human malignancies [53]. It generated ROS, modulated multiple molecular targets of cancer therapy including p53, p73, PTEN, STAT3, PPAR-γ, caspases [52]. Phosphorylation of STAT3 by TQled to inhibition of c-Src and JAK2 activation and reduction of the expression of STAT3-regulated gene products (cyclin D1, Bcl-2, Bcl-xL, survivin, Mcl-1 and VEGF) [53].

iNOS pathway

NS suppressed inflammatory response mediated by TNF-α and IL-6 and attenuate iNOS pathway activated in hepatocellular carcinoma [54].

Conclusion

It is concluded that Nigella sativa acts as both anti-oxidant (cells inflammation conditions) and pro-oxidant (cancer cells). It protects against multiple disorder involving inflammation. One drawback we find out after analyzing the data available on PubMed is that the further studies on detailed pathways analysis for anti-oxidant effects are required to enhance importance of NS. It is a potent anti-cancerous agent by exhibiting cytotoxic effects through utilization of various pathways, either activation of apoptotic pathway or inhibition of proliferative or survival pathways. The study necessitates the need of a detail molecular study before using NS or it's derivate for management or treatment of particular disorder. Animal models must be used before

treatment to study its effects on other cells of the disease body.

Competing Interests

The authors declare no competing interests

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