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Antioxidant Properties of *Nigella sativa*

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Abstract

Molecular oxygen (O_2) is essential in all species for the production of energy within mitochondria; a process known as oxidative phosphorylation. The end products of this process include adenosine triphosphate (ATP), water (H_2O) and carbon dioxide (CO_2). In addition, very small amounts of reactive oxygen species (ROS) or free radicals are continuously produced as a consequence of normal metabolism of oxygen but which, on occasions when they become overabundant, may toxically damage cells, and therefore need to be biochemically neutralized or extruded from cells. Antioxidants are defined as substances capable of delaying or inhibiting production of ROS intermediates. Cells can either make these antioxidants endogenously, or receive them through the diet.

Keywords: Molecular oxygen (O_2); Antioxidant; *N. Sativa*

Introduction

The availability of molecular oxygen (O_2) as the final electron acceptor in the electron transport transfer processes within mitochondria represents a crucial component of energy generation within cells. The ongoing electron transport chain is coupled to oxidative phosphrolation process which is eventually converted to the high-energy phosphate bond of adenosine triphosphate (ATP) [1].

The reactive oxygen species (ROS), or free radicals, are nonorganic molecules; examples include the superoxide radical anion (O_2), hydrogen peroxide (H_2O_2) and hydroxyl radicals (HO.), as well as organic molecules such as alkoxyl and peroxyl radicals that are continuously produced within cells as a consequence of the normal metabolism of oxygen. In addtion, reactive nitrogen species such as NO which reacts with the superoxide anion to form peroxynitrite which plays a major role in lipid peroxidation and cell damage. The roles of these end products are not fully understood; however, some authors reported they have important roles in cell signaling and homeostasis [2].

Conversely, antioxidants such as glutathione, superoxide dismutase (SOD), and catalase are defined as substances capable of inhibiting oxidative processes and therefore mask the chemical reaction that transfers electrons or hydrogen to an oxidizing agent [3]. As a consequence, production of ROS will be inhibited and free radical intermediates will be removed [2]. On the other hand, there are some effective antioxidants that maintain normal permeability and cellular composition; examples are vitamin E and ubiquinol [4,5].

The antioxidant system includes both enzymatic and non-enzymatic antioxidants. In addition to glutathione as antioxidant that found in the glutathione system, glutathione peroxidase, glutathione reductase and glutathione-S-transferase are also contribute to this system as enzymatic antioxidants. A brief account on the action of the different antioxidants can be found in [3].

However, if ROS levels increase dramatically, this may result in significant damage or even death to the cell. This is a process known as oxidative stress which occurs as a consequence of an alteration in the equilibrium of the production of reactive oxygen species (ROS) and antioxidative processes, in favor of the overproduction of ROS.

An excessive oxidative stress, and/or inadequate antioxidant defense, may thus occur as the result of a pro-oxidant-antioxidant imbalance, and leading to consequential damage to lipids, carbohydrates, proteins, and DNA. Therefore, maintenance of the balance between the oxidant and antioxidant systems represents a vital aspect both of normal and abnormal cell function and survival.

Damage caused by excess ROS also includes lipid peroxidation, protein modification, and DNA strand breaks, and many mechanisms exist in human body to remove and prevent the generation of these free radicals [6]. For example, the removal of superoxide and H_2O_2 prevents the generation of hydroxyl radicals which are formed by the iron-catalyzed Fenton Reaction, or by the Haber-Weiss-Reaction, and represent the most reactive species within the ROS family [7,8].

Production of Antioxidants in Human Body

Human body synthesizes a variety of antioxidants endogenously, and also receives some of them through diet. One naturally-occurring antioxidant compound is *Nigella sativa* (*N. sativa*), a widely grown

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herbal plant found in different parts of the world, and specifically in the Middle East, Pakistan, India and Far East. It has been used as a promising medicinal plant because of its potent antioxidant effects. In English, *N. sativa* seeds are known as Black Seed, while in Arabic the seeds are known as Habbatul-Barakah (meaning "the seeds of blessing"). Numerous studies show a broad range of biological activities of *N. sativa*, including anti-inflammatory [9,10], anti-diabetic [11], anti-hypertensive [12], anti-histaminic [13] actions, as well as significant anti-neoplastic properties [14,15]. Many active ingredients have been found in the seeds of *N. sativa* [16]. The seeds contain more than 30% fixed oil and 0.4-0.45% (w/w) volatile oil, including [17], 4–24% thymoquinone (TQ) and 46% of many monoterpenes such as r-cymene and a-piene [18-21]. Ghosheh et al. using an HPLC technique, were able to identify four major compounds; thymoquinone (TQ), dithymoquinone (DTQ), thymohydroquinone (THQ), and thymol (THY), in the oil of *N. sativa* seed (NSO) [22]. TQ (Figure 1) is considered as potent anti-oxidant [23], anti-cancer and anti-mutagenic agent [23-25]. Another compound that has been isolated from seeds of *N. sativa* was alpha hederin, a pentacyclic triterpene saponin (Figure 2), which has been reported to have potent *in vivo* anticancer activity [26].

Biological Activity of *N. Sativa* and TQ

Much of the biological activity of *N. sativa* has been shown to be due to TQ, which is now considered the active component of its essential oil. The beneficial medicinal effects of NSO and TQ have been attributed to their radical scavenging (anti-oxidative) activity and their ability to inhibit the production of 5-lipoxygenase products during inflammation [27]. Additionally, an important mechanism clarifying the anti-toxic effects of NSO and TQ is directly linked to its potent antioxidant effects. Oxidative stress requires different lipids (e.g., triglycerides, cholesterol and LDL-cholesterol), which are transported into cells after binding to LDL receptors [28]. In line with previous studies [29,30], recent results in our laboratories showed that cyclophosphamide (CTX) treatment can induce significant increases in plasma levels of triglyceride, cholesterol and LDL cholesterol. This CTX-induced dysregulation in the lipid profile was reversed by NSO and TQ. Two *in vivo* studies in our laboratories confirmed the antioxidant effects of NSO and TQ. Firstly; oral administration of TQ effectively induced an increase in quinone reductase and glutathione transferase activities [31]. Secondly; administration of NSO or TQ in sensitized guinea pigs, inhibited the generation of reactive oxygen species, and increased serum levels of the antioxidant enzymes SOD and glutathione [32].

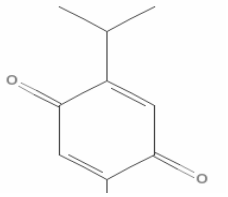

Figure 1: Thymoquinone [source: PubChem- CID 73296].

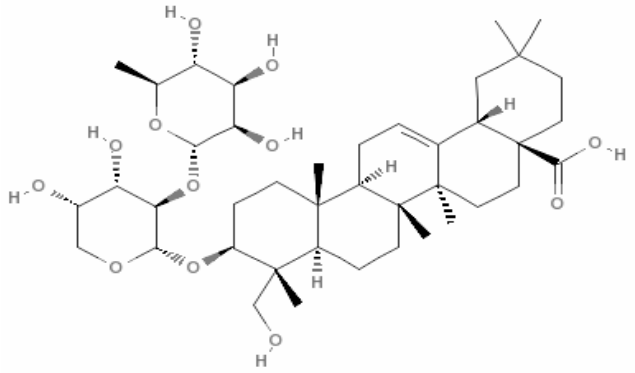

Figure 2: Alpha-hederin (source: PubChem- CID 73296) [24].

The *in vivo* antioxidant effects of TQ observed in our study [33] extended knowledge of the antioxidant effects of NSO and TQ observed in different models [9,34-36]. The pro-oxidant effects of TQ are in accordance with studies showing that TQ is involved in mitochondrial ROS generation in human osteosarcoma and leukemia Jurkat cells [37,38]. The pro-oxidant/antioxidant activities of TQ depend on the milieu where it is present.

The antioxidant activity of TQ has been reported previously, in which TQ was found to act as a scavenger of superoxide, hydroxyl radical and singlet molecular oxygen [23,39-42]. The strong antioxidant properties of TQ may be related to the redox properties of the quinine structure of the TQ molecule, and its unrestricted crossing of morphological barriers, thus gaining easy access to sub cellular compartments and facilitating the ROS scavenging effect [23]. Previous studies have also demonstrated that TQ exhibits an antioxidant effect at low concentrations versus pro-oxidant properties at high concentrations [43,44].

Recently, a unique finding showed that TQ at high concentration (20 μmol/L) had antiproliferative and cytotoxic effects in hepatocyte primary cultures [45]. Similarly, TQ is reported to be a pro-apoptotic agent in the human colon cancer cell line HCT-1 [46] via upregulation of p53 and downregulation of Bcl-2 [47]. In contrast, normal cells and primary mouse keratinocytes are resistant to the apoptotic effect of TQ [48,49].

The high antioxidant potential of TQ has been found to reduce nephropathy-related toxicity, including proteinuria and hyperlipidaemia, associated with nephrotic syndrome [40] gentamicin-induced nephrotoxicity in rats and cyclosporine A-induced injury in rat heart as demonstrated by normalised cardiac histopathology, decreased lipid peroxidation, and improved antioxidant enzyme status and cellular protein oxidation through antioxidant mechanisms [50,51].

Antioxidant of *N. sativa* and Cancer

Moreover, it has also been reported that *N. sativa* oil can induce potent antiviral effects associated with enhanced T-cell responses [52]. Other studies have also found that the anti-toxic effects of TQ in different disease models are associated with inhibition of 5-lipoxygenase products during inflammation, and also with enhanced free radical scavenging activity (antioxidative effect) [53,54]. Studies have reported that TQ can be used in the treatment of forms of cancer. For example, TQ was reported to increase the activities of antioxidant enzymes

and protects cell against various forms of cancer [16]. In addition, El-Mahdy et al. reported that TQ may exhibit an anti-proliferative effect in human myeloblastic leukemia HL-60 cells [55]. Effenberger et al. have studied the derivatives of TQ bearing terpene-terminated 6-alkyl residues that were tested in HL-60 cells and 518A2 melanoma, and found that these derivatives induce apoptosis associated with DNA laddering, a decrease in mitochondrial membrane potential and a slight increase in reactive oxygen species [56]. Other authors have reported that α-hederin also induced death of murine leukemia P388 cells by a dose- and time-dependent increase in apoptosis [26].

Thabrew et al. described cytotoxic activity of *N. sativa* seed in the human hepatoma HepG2 cell line, and found that 88% inhibitory effect on HepG2 was observed after 24-hr incubation with different concentrations (0-50 mg/ml) of the *N. Sativa* extract [57]. Nagi and Almakki have found that the oral administration of TQ was effective in increasing the activities of quinine reductase and glutathione transferase and suggested that TQ may be a useful drug in treating chemical carcinogenesis and toxicity in liver cancer [31].

Swamy and Huat reported the characteristic properties of alpha-hederin from *N. sativa* against lung carcinoma in animal models [26]. Other authors reported that supplementation of diet with honey and *N. sativa* may be of protective effect against lung, skin and colon cancers [58]. However, Rooney and Ryan reported that alpha-hederin and TQ, the two principal bioactive constituents of *N. sativa* enhance neither cytotoxicity nor apoptosis in lung and larynx cancer cell-lines [46].

Antioxidant of *N. sativa* and Diabetes

Interesting studies have confirmed that treatment with *N. sativa* seeds [59] or TQ [53] have an antidiabetic action in streptozotocin-induced diabetes through extrapancreatic and insulin activities [60-63] and activation of the cell signaling molecules MAPK and PKB [64]. Administration of NSO is also able to prevent the chronic elevation of insulin levels induced after treatment with highly active antiretroviral therapy (HAART) [65]. Interestingly, this latter effect (i.e. the hypoglycemic effect of NSO) has been suggested to be due to its ability to decrease hepatic gluconeogenesis [34], to preserve pancreatic beta-cell integrity, to induce lipid peroxidation, and to increase antioxidant defense system activity [66]. However, this latter suggestion may be contradictory as lipid peroxidation is the primary marker of oxidative stress.

At least two groups showed possible biochemical modes of action of TQ via the Akt and NF-kappa B pathways and also p53, STAT3, PPAR-γ [67,68]. Additionally, it might also be worth mentioning the significant effect of TQ on TLR4 expression and PI3K phosphorylation [69,70].

Conclusion

In conclusion, several animal and *in vitro* studies as some studies did not show the presence of antioxidant effects of *N. Sativa* and TQ, and most especially, the antioxidant effects of TQ while still other studies showed cytotoxic effects. Large scale clinical studies in patients are now indicated in those therapeutic areas that involve oxidative stress and/or inflammation as a core physiological component of the development and progression of their condition.

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