Biomedicine & Pharmacotherapy 106 (2018) 390–402

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Thymoquinone: A novel strategy to combat cancer: A review

Muhammad Imran[a,*], Abdur Rauf[b,*], Imtiaz Ali Khan[c], Muhammad Shahbaz[d], Tahira Batool Qaisrani[e], Sri Fatmawati[f], Tareq Abu-Izneid[g], Ali Imran[h], Khaliq Ur Rahman[b], Tanweer Aslam Gondal[i]

[a] University Institute of Diet and Nutritional Sciences, Faculty of Allied Health Sciences, The University of Lahore, Pakistan
[b] Department of Chemistry, University of Swabi, Anbar-23561, Khyber Pakhtunkhwa, Pakistan
[c] Department ofAgriculture, University of Swabi, Anbar-23561, Khyber Pakhtunkhwa, Pakistan
[d] Department of Food science and Technology, Muhammad Nawaz Shareef University of Agriculture, Multan, Pakistan
[e] Department. Agri Engineering &Technology, Ghazi University, DG Khan, Pakistan
[f] Department of Chemistry,Faculty of Mathematics and Natural Sciences, Institut Teknologi Sepuluh Nopember, Kampus ITS-Sukolilo, Surabaya, Indonesia
[g] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Umm Al-Qura University, Makkah, P.O.Box 42, Saudi Arabia
[h] Institute of Home and Food Sciences, Faculty of Science and Technology, Government College University, Faisalabad, Pakistan
[i] School of Exercise and Nutrition, Centre of Advanced Sensory Science, Deakin University, Australia

ARTICLE INFO

Keywords:
Nigella sativa, black seed
Chemical composition
Thymoquinone
Antioxidant
Cancer
Toxicity

ABSTRACT

The higher consumption of fruit, herbs, spices, and vegetables is well known and practical strategy to cure human cancers owing to their presence of bioactive compounds. Among these, *Nigella sativa* is a promising source of bioactive compounds including thymoquinone, monoterpenes, p-cymene and α-piene etc. Thymoquinone has been found effective to inhibit the different cancer stages such as proliferation, migration and invasion. It also acts as anticancer agent against different human cancers such as breast, pancreatic, prostate, blood, oral, bone, head and neck, cervical, liver and lung. It significantly mediated miR-34a up-regulation, enhanced the levels of miR-34a through p53, and down controlled Rac1 expression. Thymoquinone induces apoptosis, regulates the levels of pro- and anti- apoptotic genes. It also has been known to lower the phosphorylation of NF-κB and IKKα/β and reduces the metastasis as well as also lowered the ERK1/2 and PI3K activities. Thymoquinone inhibits the metastasis through activation of JNK and p38. The present review article highlights the anticancer perspectives of thymoquinone in human by various pathways and use of this compound as diet based therapy has proven new pharmacological agent against several types of cancers.

1. Introduction

The *Nigella sativa* seed is also known as black seed in English, 'Alhabba Al-sauda' in Arabic and 'Kalvanji' in Urdu and Hindi languages, is frequently used in many parts of the world, particularly in the middle east and far east countries, for the prevention and treatment of a large number of diseases. Its comprises various active constituents such as thymoquinone, monoterpenes such as p-cymene and α-piene and these compounds possess many pharmacological properties, including antioxidant, analgesic, anti-inflammatory, anti-asthmatic, antipyretic, antimicrobial, antihypertensive, and antineoplastic [1,2,3]. *N. sativa* is promising and significant source of diverse types of bioactive ingredients including 4-terpineol, p-cymene, thymoquinone, dithymoquinone, thymohydroquinone, and t-anethol. It also comprises of other ingredients including carbohydrates, vitamins, fats, proteins, mineral elements, and essential amino acids. Moreover, *N. sativa*seed has been found to consist of nigellimine, nigellidine, saponine, nigellcine, and water soluble triterpenes [4,5,6].

Thymoquinone showed promising role against oxidative damage induced free radical agents, and doxorubicin which is used to induce cardiotoxicity. It exerts suppressive activity on carcinogenesis, eicosanoids production and membrane lipid per-oxidation. Moreover, thymoquinone working as effective chemo-protective phytochemical, as a hyperproliferative actionin rats and also destroys Fe-NTA induced oxidative stress [7,8,9].

Thymoquinone therapy prevents from weakening immune system and protects the human from more susceptible to diseases. It also protects the human healthy cells from oxidative damage and gives long recovery to cells by preventing from toxic side-effects [10,11]. On the other pronounced health perspectives, thymoquinone exhibits antiproliferative effects on different cancer cell lines of ovary, colon, larynx, breast, myeloblastic leukemia, lung, and osteosarcoma, respectively

* Corresponding authors at: Department of Chemistry, University of Swabi, Anbar-23561, Khyber Pakhtunkhwa, Pakistan.
E-mail address: abdurrauf@uoswabi.edu.pk (A. Rauf).

https://doi.org/10.1016/j.biopha.2018.06.159
Received 24 April 2018; Received in revised form 25 June 2018; Accepted 27 June 2018

[12,13,14].

2. Antioxidant potential of thymoquinone

In hippocampal homogenates induced by iron-ascorbate, thymoquinone suppressed the *in vitro* non-enzymatic lipid per-oxidation [27]. Similarly, in hippocampus part subsequent cerebral ischemia-reperfusion damage (IRI), treatment of thymoquinone markedly lowered the concentrations of lipid per-oxidation levels [28]. In another study conducted by [29], they investigated that administration of thymoquinone (9 mg/kg BW) prevented from the liver injury induced by aflatoxin B1 (AFB1) via multiple mechanisms including reduction in serum concentrations of liver marker enzymes for example AST, ALT and ALP, enhancement in glutathione concentrations, and prevented MDA production [29]. Equally, thymoquinone treatments also protected the brain tissues from the radiation-induced nitrosative pressure [30].

in vivo assay by using Wistar rats, orally administrated thymoquinone at the rate of 5 mg/kg body weight (BW) markedly caused reduction in concentrations of lipidperoxidase (LPO), myeloperoxidase (MPO), nitric oxide. Furthermore, it enhanced the concentrations of catalase, and glutathione in collagen produced arthritis (CIA), and depressed the Fe (III) nitrilotriacetic acid (Fe-NTA) induced oxidative stress [31,30]. Thymoquinone provides protection against glucose induced loss of superoxide dismutase activity and fragmentation or cross-linking [32]. Additionally, it determined that Wistar rats treated with thymoquinone and 1,2-dimethylhydrazine (DMH) significantly protected from the leakage of superoxide dismutase, glutathione peroxidase, and catalase in red blood cells and protected the erythrocyte from DMH-induced colon post initiation carcinogenesis [33]. It also has been known as cytoprotective agent against the anti-cancer drugs cyclophosphamide (CTX) via maintaining hemoglobin concentration, normalizing sugar concentrations, lowering alkaline phosphatase, kidney parameters such as creatinine, urea, bilirubin, cholesterol, low density tri-glycerides as well as lipid per-oxidation in the liver [34]. Thymoquinone has also reported to reduce the amyloid-β(Aβ-*42)* produced neurotoxicity by increasing cell viability over powering mitochondrial membrane potential depolarization and production of ROS (reactive oxygen species) in refined hippocampal and cortical neurons. It restores synaptic vesicle recycling inhibition and to incompletely reverse the loss of spontaneous firing action, as well as Aβ1-42 combination *in vitro* [35].

There are consolidated evidences that advocate the anticancer effect of thymoquinone owing to its antioxidative potential. The oxidative stress reducing perspective is considered as the major mechanism behind this effect. However, another school of thought also reported that the thymoquinone caused apoptosis in cancer cells by exerting oxidative damage. The thymoquinone can act as both antioxidant as well as pro-oxidant in dose dependent manner; at lower concentrations act as antioxidant and performed as a prooxidant at higher values [36,37,38,39]. In this context, several *in vitro* &*in vivo* explorations have elucidated that the antioxidant activity of thymoquinone is helpful in controlling rat hepatic carcinoma by diminishing the expression of antioxidant enzymes like glutathione peroxidase, glutathione-s-transferase and catalase [40]. Moreover, thymoquinone exhibited the chemo preventive role by reducing the 1,2-dimethyl-hydrazine (DMH)-induced oxidative stress during the initiation and promotion of colon carcinogenesis in rats [41]. In contrary, findings of some other studies have inferred the oxidative damage perspective of thymoquinone is responsible for its ability to induce apoptosis in cancer cells [42,43]. Another promising study showed apoptosis inducing perspective of thymoquinone in hepatic ischemia reperfusion injury (I/R) and concluding that oxidative diminishing perspective of thymoquinone is the matter (Table 1) of prime consideration [37].

2.1. ROS initiating perspective of thymoquinone

Thymoquinone performs its antitumor role by modulating the various potential targets like p53, p73, NF-Kb, PPAR-γ and reactive oxygen species (ROS). Currently, role of ROS in cancer protection is in lime light; evidences have highlighted the importance of prooxidants in the management of different kind of oncogenic events. Recently, the utilization of ROS generation for the management of resistant tumor cells has been increased [44,45]. In this context, thymoquinone produced ROS generation may cause down regulation in Akt in primary effusion lymphoma cells [46]. Likewise, thymoquinone induced ROS ability is also evident by its action on the mediation of ERK and JNK phosphorylation in human colon cancer cells [46]. Previously, [47] elucidated that the thymoquinone induced ROS production caused activation in the p53 activity, STAT3 activation in pulmonary epithelial cells and B lymphocytes.

The role of thymoquinone in the production of ROS has been well explicated by the investigation carried out by, [47] conducted a clinical trial to investigate the role of thymoquinone induced ROS in the management of breast cancer both *in vivo* and *in vitro*. The results divulged the positive impact of ROS production and tumor suppression by downregulating the expression of involving biomarkers like survivin, XIAP, Bcl-xL and Bcl-2protein. Moreover, the role of the thymoquinone cancer management perspective Via ROS initiation has been further explicated by their ability to induce apoptosis through mitochondrial route by accelerating the oxidative stress. Accordingly, [38] investigate the impact of thymoquinone-induced apoptosis by using mitochondrial route. They utilized the isolated mitochondria from rat liver and treated with dose dependent treatment of thymoquinone.

The results explicated that the thymoquinone dose-dependently acts as a potent inducer of mitochondrial O_2 generation. They were of the view that the thymoquinone owing to its greater lipid solubility and ability to forming a redox couple by reduced and semi reduced forms can incorporate in the inner mitochondrial membrane and easily convert into a mobile electron carrier of the mitochondrial respiratory chain thus initiate the O_2 generation by the leakage of electrons thus cause oxidative damage in mitochondria (Table 2).

In another study, [48] expressed the role of thymoquinone in the management of Acute lymphoblastic leukemia in CEM-ss cell lines and revealed that the thymoquinone performed its action owing to the production of ROS and down regulation of HSP70 and upregulation of Bcl-2.

3. Anticancer perspectives

3.1. Breast cancer

The combining effect of thymoquinone with piperine exhibited the preventive role beside mouse epithelial breast cancer cell lines (EMT6/P) in Balb/C mice *via* lowering VEGF expression and enhancing serum INF-γ levels. Furthermore, it suppresses the angiogenesis, induces apoptosis, and shifts the immune response toward T helper1 response [49]. Recently, [50] reported that thymoquinone caused cell cycle arrest, suppressed the progression from G1 to S phase by targeting cyclin E, cyclin D1, and p27 proteins. It also inhibited the histone deacetylase (HDAC),targeted p21 and Maspin, and induced Bax, down regulated the Bcl-2, up-regulated the EGF, vascular endothelial growth factor (VEGF), and tensin homolog (PTEN) expression [51]. Similarly, Alobaedi et al. (2017) investigated the combining effect of thymoquinone with resveratrol against breast cancer cell lines in Balb/C mice through significantly decreasing tumor size, inducing geographic necrosis, increasing apoptosis, and lowering VEGF expression [50]. The different concentrations of thymoquinone (50, 75, 100, 150 μM) in combination with tamoxifen (2 μM) exerted anticancer role on estrogen negative MDA-MB-231 and estrogen positive MCF-7 human breast cancer cell lines through lowering cell viability and inducing apoptosis [52].