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Review

Therapeutic effects of thymoquinone for the treatment of central nervous system tumors: A review

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ABSTRACT

Background: The aim of this study is to review the effects of thymoquinone (TQ) against central nervous systems (CNS) tumors.

Methods: In this study, we extensively reviewed all articles on the terms of *N. sativa*, TQ, CNS tumors, and different disorders in PubMed, Science Direct, Scopus, and Google Scholar databases between the years 1990 and 2017.

Results: The present study found that TQ has many therapeutic effects due to its antioxidant, anti-inflammatory, and anti-proliferative activities. Experimental studies indicated the protective effects of TQ against CNS tumors. The anti-tumor effects of TQ are mainly caused by inducing G2/M cell cycle arrest, apoptotic pathways, inhibiting autophagy, angiogenesis, invasion, and migration and also by enhancing the efficacy of chemotherapeutic drugs. Although, the study observed no significant toxicity of TQ in the experimental models, more clinical studies are needed to confirm the safety and efficacy of TQ for human.

Conclusions: The present review found that TQ treatment can be considered as a promising therapeutic strategy for human malignant CNS in future.

1. Introduction

Malignant and non-malignant Primary brain and other central nervous system (CNS) tumors have an incidence of 22.36 per 100,000 [1]. Malignant primary brain tumors are recognized as the main cause of death from solid tumors in children and the third cause of death from cancer in adolescents and young adults aged 15–39 years old [2]. The different types of CNS tumors include astrocytic tumors, oligodendroglial tumors, mixed gliomas, ependymal tumors, medulloblastomas, pineal parenchymal tumors, meningeal tumors, germ cell tumors, and craniopharyngioma [3]. The cause of CNS tumors has not fully understood, however; genetic background may increase the risk of CNS tumors [4]. Although the magnetic resonance imaging is essential for early diagnosis of the anatomic extent of the tumor; however, a biopsy is usually needed to confirm the brain tumors [5]. The different types of treatment for patients with CNS tumors consist of the standard (the currently used treatment) and tested in clinical trials [5].The current standard of treatment for CNS tumors includes of active surveillance, surgery radiation therapy, chemotherapy, and targeted therapy [5]. The complementary and alternative medicine are especially interested and have been studied on natural anticancer agents with low side effects [6]. These compounds are safely used at high doses as supplementary treatment in the chemotherapy regimens [6]. Thymoquinone (TQ) is observed in the seeds of *Nigella Sativa*, which is belonging to the *Ranzmculaceae* family[7].TQ was also found in the plants of the *Lamiaceae* family such as *Agastache*, *Coridothymus*, *Origanum*, *Monarda*, *Mosla*, *Satureja*, *Thymbra*, and *Thymus* [8].TQ possesses beneficial properties such as antioxidant, anti-inflammatory, and chemotherapeutic effects [9]. The recent biomedical findings indicated that TQ may be effective against various disorders including Alzheimer's disease, Parkinson's disease, Arthritis, Cardiovascular disease, Diabetes, and various types of cancers such as brain tumors [10]. TQ has been indicated to posse the antitumor effects against several cancer cells, including osteosarcoma, colon, lung, ovarian, pancreas and myeloblastic leukemia [11–13]. The present review has been designed to review the protective effects of TQ against CNS tumors by gathering the scientific literature.

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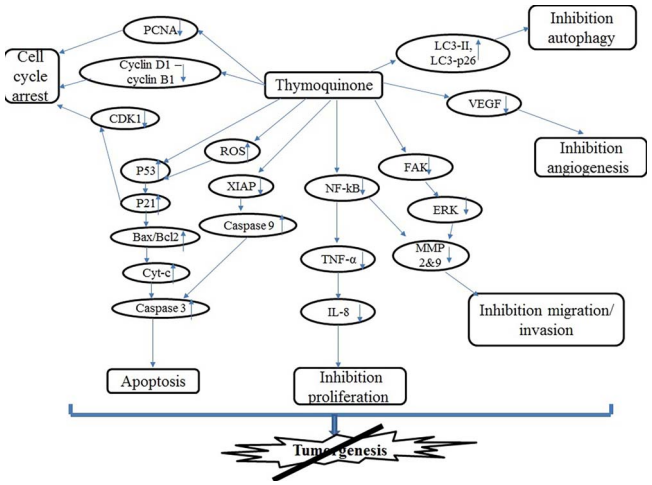

Fig. 1. Cancer pathway targets affected by TQ.

2. TQ and CNS tumors molecular pathways

TQ effects against CNS tumors have been well studied by *in vitro* and *in vivo* assays [7]. TQ triggers many molecular pathways involved in the pathogeneses of CNS tumors such as cellular proliferation [14], immunomodulation [15], autophagy [16], angiogenesis [17], apoptosis [18], invasion [19], and metastasis [20]. Additionally, TQ has been observed to be effective against reactive oxygen species (ROS) generation [21]. A study by Gökce et al., [22] investigated the effects of TQ against spinal cord ischemia-reperfusion injury in rats. TQ treatment ameliorated the neurologic dysfunction and decreased oxidative stress during the reperfusion period. The study suggested that the protective effects of TQ may induce by inhibition of oxidative stress, inflammation and motor neuron apoptosis. In an *in vitro* study of ischemia-reperfusion using PC12 model, TQ was observed to protect neurons from death caused by oxygen/glucose deprivation. The findings suggested that TQ protects the PC12 cells against oxygen/glucose deprivation-induced cytotoxicity through modulating reactive oxygen species (ROS) production [23]. The cancer pathway targets affected by TQ have been indicated in Fig. 1.

3. TQ effect on the G2/M cell cycle arrest

The cell cycle regulation consists of important processes crucial to the cell survival, including the detection and repair of DNA damage and also the control of cell division [24]. The cell cycle molecular pathways are ordered and also directionally occurred in a sequential fashion [24]. The cell-cycle abnormality is one of the typical characteristics of malignant cancers, which leads to proliferation of cancer cells [24]. Recently, it has been tried to show how this cell cycle arrest can occur. Several studies have indicated that many antitumor drugs are effective to inhibit cell-cycle [25]. In this context, it has been observed that TQ is able to induce the G2/M cell cycle arrest and apoptosis. Paramasivam et al. indicated that the G2/M cell cycle arrest might be due to the down-regulate proliferating cell nuclear antigen (PCNA) expression [26]. In the study, the mouse neuroblastoma (Neuro-2a) cell line treated with TQ showed a dose-dependent decrease in protein expression of PCNA by using western blot analysis. Furthermore, it was indicated that TQ had an attenuation ability to decrease the protein expression of cyclin B, CdK1, and also increase the expression of p53, p21 mRNA and protein levels. The results indicated that the pro PCNA plays the main role in TQ-prevented cell death. It was also indicated that p53 expression was up-regulated by TQ treatment in the Neuro-2a cells [26]. Another study indicated that TQ exhibits its anti-proliferative effects by suppression of cyclin D1 and induction of p21. Additionally, it was suggested that TQ suppressed cell growth and cell survival via inducing the cell-cycle arrest in the G2/M phase and apoptosis in the Neuro-2a cells [27].

Cyclins and cyclin-dependent kinases (CDKs) are recognized as two main classes of regulatory molecules through the cell cycle [28]. CDKs-cyclin (CDKCs) regulate the progression of the cell cycle [28]. Cyclin B1 has a main role for promoting cells to enter M phase from G2 phase [29]. During the G2 phase, the levels of cyclin B1 are significantly increased. In mitotic metaphase, the expression of cyclin B1 reaches the peak and is reduced quickly in the anaphase [29]. The cyclin B1 expression directly affects the activity of CDK1. Interaction of cyclin B1 and CDK1 is necessary to initiate the M phase [30]. It has been observed that the down-regulated expression of Cyclin B1 is associated with G2/M cell-cycle arrest [30]. P21 is one of the cyclin-dependent kinase inhibitor (CDKI) families that inhibits the CDK1, CDK2, CDK4, and CDK6 to induce cell-cycle arrest [31]. P53 as a checkpoint protein plays a main role in cell-cycle arrest through DNA repair and apoptosis [32]. P53 activation by anticancer drugs or irradiation causes cell-cycle arrest and/or apoptosis [32]. P53 can block cell-cycle progression by inducing p21 [33]. PCNA is a DNA clamp that is an essential factor for replication [34]. The PCNA involved in replication, repair, recombination and cell-cycle regulation by multiple protein-protein interactions [34]. The PCNA interaction with various CDKCs is required for the progression G1, S, G2 and mitosis phases [34]. PCNA interaction with CDKCs causes a tetramer with Cdc25C and CDK1/cyclin B1, which would promote cells to enter M phase from G2 [35]. The PCNA protein contents increased through the cell-cycle period and remained at a high level in the G2/M phase [35]. Altogether, the present study suggests that TQ treatment induces G2/M arrest in the Neuro-2a cells through direct down-regulating the PCNA, cyclin B, and cyclin D1 expressions. In addition, TQ inhibited CdK1 via up-regulating the expression of p53 that activates p21.

4. TQ effects on the apoptotic pathways

Apoptosis impairment plays important role in the imitation and progression of tumor cell and also its resistance to chemotherapy [36]. The anti-cancer drugs should exhibit strong cytotoxic effects against tumor cells without affecting normal cells [36]. The pervious study indicated that TQ has specific toxicity against the tumor cells, but has no effect on normal cells [37]. Paramasivam et al., showed the protective effects of TQ on the apoptosis pathways in mouse cancerous cell lines. It was reported that TQ (0–70 μM) had cytotoxic effects in the Neuro-2a cells and induced apoptosis in the cell line by elevating the Bax/Bcl-2 ratio [37]. TQ apoptotic effects may be related to the activation of caspase-3, cleavage of Poly (ADP-ribose) polymerase (PARP), and also down-regulation of an X-linked inhibitor of apoptosis protein (XIAP) in the Neuro-2a cells [37]. The molecular pathways of apoptosis are controlled by caspases [38]. Caspase 3 activation and cleavage of PARP are the two main factors in the development of apoptosis [38]. The increased Bax/Bcl-2 ratio changes the permeability of mitochondrial membrane that leads to the release of cytochrome c [38]. Cytochrome c induces caspase 9 that activates the effectors procaspases such as caspase 3, 6 and 7 [38].

However, XIAP is one of the IAP (inhibitor of apoptosis) protein families that inhibits caspase 3 [39]. TQ (0, 20 and 40 μM) also induced apoptosis through modulation of pro-apoptotic (Bax1) and anti-apoptotic (Bcl-xL) genes of the Bcl-2 protein in the Neuro-2a cells [26]. It was also reported that TQ (10, 20, 50, 100 and 200 μM) enhanced the anti-cancer effects of Temozolomide (TMZ) in the human glioblastoma multiforme cell line (U87MG) by intensifying TMZ-induced apoptosis modifications [14]. Medulloblastoma (MB) is the most malignant cerebellum tumor of children that is progressed via the over-expression of NF-κB. NF-κB regulated the expression of IL-8, increased cancer cell growth, and induced resistance to chemotherapy [40]. TQ induced the generation of reactive oxygen species (ROS) that is responsible for the apoptosis induction in the G2M cells. According to the findings, TQ