Review Article

Thymoquinone's Potential Role in Cancer Chemotherapy: A Mini Review

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Abstract

Background: Pollution and genetic factors have increased the likelihood of cancer in the developing world. Cancer is now the leading cause of death in young patients. Scientists are focusing on developing new treatments with a lower risk profile than traditional cytotoxic drugs. Nigella sativa (black seed) has been used for centuries by ancient cultures to treat a variety of ailments. Thymoquinone, the main active compound found in Nigella sativa, is a useful therapeutic agent in various morbidities including cancer. Aim: The review aims to highlight thymoquinone's potential cytotoxic and chemoprotective effects. Methods: The most recent articles were found using reputable websites such as Google Scholar, PubMed, and Research Gate. Many titles, such as thymoquinone, breast cancer, leukemia, colon cancer, osteosarcoma, ovary cancer, and so on, have been used in searches. Then the information from an in vitro studies and animal experiments were collected; the preprint, article review, and meta-analysis study were all excluded. Results: Thymoquinone reduced cell viability and induced programmed cell death in breast cancer, colon cancer, leukemia, osteosarcoma, ovary cancer, and colon cancer. TQ causes cytotoxicity through a variety of mechanisms, including the induction of reactive oxygen species and the inhibition of NF-κB activity in some cancers. Conclusion: Thymoquinone is a promising future cytotoxic agent with fewer side effects than traditional cytotoxic agents.

Keywords: Cancer, Black seed, Thymoquinone, Chemotherapy

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INTRODUCTION

Cancer is a leading cause of death throughout the world. It is associated with a high mortality and morbidity rates; according to the World Cancer Research Fund International in 2008, cancer was responsible for nearly 12.7 million deaths [1]. Despite the lack of sufficient scientific data to support their beneficial effects and safety, natural products have been used to treat a wide range of diseases for decades [2]. The experience of physicians in the field of herbal medicine greatly affected the use of polyherbal preparations. For example, the old nations of America (American Indians) used Podophyllum peltatum for the management of skin cancer and warts [3]. Black seed, which is also known as Nigella sativa, is used worldwide for the treatment of a variety of diseases and malformations. It contains many active substances, including thymoquinone and monoterpenes like p-cymene and α-pinene; they have many pharmacological properties, including anti-inflammatory effects, pain relief, free radical scavenger, bronchodilation, anti-hypertensive effect, and eventually anti-tumor effects [4]. Thymoquinone has been synthesized for decades by oxidizing hydrogen peroxide with thymol. TQ exerts its pharmacological action by altering biochemical and homeostatic processes involved in the production of reactive oxygen species. TQ, as an antioxidant, inhibits the production of superoxide anion and suppresses lipid peroxidation by increasing the activity of antioxidant enzymes such as superoxide dismutase, catalase, glutathione, glutathione transferase, and quinone reductase [5]. TQ has many targets, such as proteins, the cell cycle, PPAR gamma, cytokines, and so on (Figure 1) [3].

Anti-cancer effects of thymoquinone

Cancer is becoming more common each year, with increased mortality and morbidity. Cancer treatment is clearly expensive, and not all patients can afford it; it also places a burden on governments. As a result, numerous studies on the anti-cancer effects of thymoquinone, which is found in Nigella sativa, have been conducted. Thymoquinone inhibits benzo(a)pyrene-induced stomach carcinogenesis and inhibits 20-methylcholanthrene, which leads to fibrosarcoma tumorigenesis in mice. Thymoquinone's ability to inhibit the formation of free radicals has been shown to play an essential role in the prevention of chemical-induced cancers [3]. Cancer hallmarks are the characteristics that normal cells acquire to promote their transformation into cancerous cells [6]. Any drugs that target those hallmarks are likely to be effective therapeutics. Besides the immune defense mechanism, thymoquinone can modulate all cancer hallmarks [5]. The metabolism and antioxidant state of many major organs, including the heart, kidneys, and liver, are modulated by thymoquinone administration; this fact suggests that TQ protects those organs and may be promising for developing less toxic cytotoxic drugs. Furthermore, many cells, including prostate epithelial cells [7], pancreatic ductal cells [8], and normal human intestinal cells [9], are known to be resistant to TQ. To gain a better understanding of TQ's cytotoxic effects and how it modulates cancer hallmarks, we will summarize the most important cancer hallmarks modulated by this fantastic molecule:

Sustaining proliferative signaling

Cancerous cells proliferate rapidly, which is why one strategy for cancer management is to target those cells that proliferate rapidly [10]. Thymoquinone inhibited proliferation by half or 50% in mice with neoplastic keratinocytes at a non-cytotoxic concentration. This compound has been shown to inhibit the proliferation and growth of various cancers such as glioma and glioblastoma, breast cancer, blood cancers such as leukemia, lung cancer and colorectal cancer, pancreatic cancer, and osteosarcoma, but its effect on mouse fibroblast, which is considered a non-cancerous cell, is insufficient. Researchers concluded from these findings that thymoquinone has therapeutic benefits for various types of cancer but has no effect on normal cells [3]. Uncontrolled cell growth is a common feature of cancer, which causes tumor cells to grow in size. Thymoquinone inhibits the growth of tumor cell lines that are resistant to doxorubicin and etoposide [11]. TQ's ability to downregulate both the mitogen-activated protein kinase (MAPK) and protein kinase B (AKT/PKB) signaling pathways has been linked to its anti-proliferative effects in multiple myeloma [12] and squamous cell carcinoma [13]. TQ's effect on MAPK and AKT signaling pathways has
been investigated separately. TQ, as expected, inhibits AKT phosphorylation in breast cancer and effusion lymphoma. TQ also stimulated free radical synthesis and PTEN upregulation [14,15], while blocking ERK phosphorylation by TQ resulted in inhibition of vascular endothelial growth factor [16]. The activation and inhibition of the MAPK protein family are greatly influenced by cell type and TQ dose [5].

**Evading growth suppressors**

Many studies have been conducted to explain the ability of thymoquinone to inhibit the cell cycle in various types of cancer. The cell cycle's transition between G1, S, G2, and M phases is controlled by cyclin-dependent kinases (CDKs) and cyclins themselves. In almost all human tumors, the level of CDKs and cyclin must be deregulated to induce cell cycle gene transcription, enhance mitosis, and avoid checkpoints. TQ effectively targets various CDK inhibitors, CDK, and cyclin, preventing cancer cell evasion. For example, in a study conducted on human colon cancer HCT-116, data analysis showed that G1 phase arrest by TQ arises from blocking the expression of CDK inhibitor p16 and attenuating the level of cyclin D1 [17]. In another study, the researchers documented that inhibition of the G1 phase resulted from the elevation of CDK inhibitor p21 expression [18]. Thymoquinone has been shown to increase p16 synthesis and inhibit cyclin D1, resulting in the arrest of the G0/G1 phase in mouse papilloma carcinoma cells. Moreover, data from various studies revealed that thymoquinone effectively inhibited the G2/M phase in a variety of cancer cells. Thymoquinone, for example, effectively increased p53 synthesis and mitigated cyclin B in a mouse model of spindle cell carcinoma while also arresting the G2/M phase [17]. Thymoquinone has also been shown to inhibit the progression of LNCaP prostate cancer cells from the G1 to the S phase, as well as androgen receptors and E2F1-androgen-regulated proteins such as Cdk-4, Cdk-2, and cyclin A [7]. A new study has been conducted on MCF-7/DOX doxorubicin-resistant breast cancer cells to evaluate the effect of thymoquinone on the cell cycle. The data analysis showed that thymoquinone inhibits the G2/M phase and enhancing the expression of p53 and p21 proteins [14]. These results indicate that thymoquinone can kill cancerous cells by arresting the cell cycle.

**Enabling replicative immortality**

The telomere length controls the number of replications that the cells can undergo. Whenever the telomerase enzyme loses its function, telomeres become shorter and can no longer can protect the cells; eventually, this will trigger programmed cell death (apoptosis). It has been found that in most cancer cells, the telomerase enzyme activity is increased, leading to uncontrolled replication. Nowadays, telomerase is considered a target for cytotoxic drugs [6]. Blocking of the telomerase enzyme together with shortening of the telomere and apoptosis has been documented with thymoquinone in a glioblastoma cell line. Cells with DNA-dependent protein kinase are more sensitive to TQ than cells without DNA-PKcs, according to recent research [19].

**Genome instability and mutation**

Repair defects and mutations arising from genetic instability are the main causes of cancer development and progression. The probability of mutation is increased with increased exposure to carcinogenic chemicals, and the detection and repair of damaged DNA are disrupted in the case of a defective tumor suppressor gene. This fact led many investigators to evaluate the effects of TQ on the tumor suppressor gene p53 very effectively. As a result, patients with faulty P53 are resistant to traditional cytotoxic drugs. TQ-mediated DNA damage is p53 dependent in colon cancer [17], whereas DNA damage is p53 independent in other cancers such as osteosarcoma, leukemia, and the glioblastoma cell line [19]. Enhancing apoptosis by cytotoxic drugs is a critical factor in determining their therapeutic benefit in cancer [3]. Apoptosis, which is a programmed cell death, is induced by thymoquinone in two pathways, P53 dependent and P53 independent, respectively. The dose and duration of treatment have been shown to be essential factors in evaluating the ant apoptotic effect of thymoquinone. For example, in a study conducted on human colorectal cell carcinoma, it effectively stimulated apoptosis while also increasing P21 and p53 expression. In the same study, data analysis revealed that Bcl-2 was inhibited [17]. Thymoquinone's apoptotic effect is not solely dependent on p53; PTEN and STAT3 have also been discovered to play important roles in its apoptotic-stimulating effect. PTEN was up-regulated by thymoquinone in a doxorubicin-resistant breast cancer model, along with significant attenuation of P-Akt [14].

**Tumor promoting inflammation**

About 20% of human tumors are associated with chronic inflammation. Various inflammatory mediators such as prostaglandins, interleukins, and leukotrienes stimulate cancerous cell progression via enhancing cell growth, blood vessel synthesis, cell recruitment, and invasion. There are three studies conducted to determine the anti-inflammatory effects of TQ. In the first one, TQ significantly changed the synthesis and function of those aforementioned inflammatory mediators [5]. In an inflammatory model, thymoquinone attenuated the synthesis of prostaglandins via inhibition of the cyclooxygenase-2 enzyme (COX2) [21]; also, TQ...
mitigated the level of leukotrienes through blocking of the 5-lipoxygenase enzyme [22]. Furthermore, interleukin synthesis such as IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, etc. was decreased by TQ [23].

**Inducing angiogenesis**

Tumor cells require angiogenesis for survival and proliferation [6]. Through oxygen and nutrient supply, VEGF allows cancerous cells to synthesize new blood vessels. TQ inhibited VEGF in vitro, indicating that it has antiangiogenic potential in tumor cells. TQ has been shown to inhibit new blood vessel formation in a variety of cancers, including prostate cancer, multiple myeloma, and the KBM-5 leukemia cell line [24]. Thymoquinone possesses both anti-oxidant and pro-oxidant effects. Many previous studies revealed that thymoquinone enhanced apoptosis via the generation of reactive oxygen species, in contrast to its anti-oxidant and anti-inflammatory effects. It has been found that generation of ROS by thymoquinone in effusion lymphoma cells induces apoptosis and inhibition of Akt, together with an elevated Bax/Bcl 2 ratio [15].

**METHODS**

The rationale for this review was to provide the most updated information about the cytotoxic and chemoprotective effects of thymoquinone and to summarize the mechanisms responsible for its effects. The literature searches were conducted during 1 April 2021 to 14 April 2021. For this article review, published English language studies were considered. Computerized-based databases such as PubMed, Google Scholar, and Research Gate have been used to find the most trustable studies up to April 2021. Key words used for the search were "cancer," "thymoquinone," "cytotoxic effects of black seed," "thymoquinone and lung cancer," etc. Investigations resulted in a large number of published articles. Only seven studies have been used for gathering information regarding the topic. The included articles are in vitro studies and animal-based studies, while the excluded articles are preprint articles, unpublished articles, and article reviews and meta-analyses (Figure 2).

**RESULTS AND DISCUSSION**

*Nigella sativa*, or black seed, was used by Middle Eastern society for more than two thousand years as a natural treatment for various diseases. Thymoquinone is the main active component of *Nigella sativa*, with multiple effects such as anti-oxidant, anti-inflammatory, and anti-cancer effects [1]. In an in vitro model experimental study, Shoieb et al. [25] documented TQ's anti-apoptotic and anti-proliferative effects in 2003. Since then, numerous studies have focused on the therapeutic benefits of TQ in cancer treatment. Thymoquinone has been shown to have anticancer and chemoprotective effects in a variety of cancers, including breast cancer, lung cancer, osteosarcoma, glioblastoma, leukemia, and others [1]. Many studies have been conducted to uncover the molecular mechanism by which TQ has an anticarcinogenic effect in colon cancer, breast cancer, ovarian cancer, lung cancer, and osteosarcoma (Table 1).

**Figure 2:** Schematic presentation of methodology.

Different concentrations of TQ were used in a recent study by Zhang et al. [1] to determine its anti-proliferative effects on a colon cancer cell line. The data were analyzed using one-way ANOVA, and the results showed that at the tested concentration (20 µM), TQ significantly (*p* = 0.013) inhibited HCT116 cell line growth when compared to the control group. Furthermore, TQ at that concentration (40 µM) significantly reduced cell proliferation (*p* = 0.007) in the COLO205 cell line compared to the control group [1]. According to the author, TQ increased the sensitivity of colon cancer cell lines to chemotherapy. The analysis of the data revealed that combining Cisplatin with TQ significantly reduced the cell viability of COLO205 and HCT116 cells. This finding suggests that TQ increased the cytotoxic effect of cisplatin. TQ's cytotoxic effects have been shown to be enhanced when NF-xB inhibitor PDTC [26]. Breast cancer is one of the most dangerous types of tumors, with a high mortality rate. Many anti-cancer drugs have been studied in order to extend the lives of patients suffering from this cancer. Unfortunately, almost all cytotoxic drugs have severe side effects such as myelosuppression, cardiotoxicity from doxorubicin, nausea and vomiting, and so on. Many evidence-based studies support thymoquinone's anti-proliferative effects in various types of cancer.
Table 1: List of publications on the use of thymoquinone in cancer treatment.

<table>
<thead>
<tr>
<th>Cancer Type and Treatment</th>
<th>Model</th>
<th>Author</th>
<th>Description</th>
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<tr>
<td>Colon cancer; Thymoquinone Cisplatin PDTC</td>
<td>In vitro study; Two different colon cancer cell line are used: - COLO205 - HCT116</td>
<td>Zhang et al., 2015</td>
<td>Different concentration of TQ has been used (0, 20, 40, and 60µM). TQ effectively killed Colon cancer cells alone and in combination with Cisplatin and PDTC with ( P&lt;0.05 ) compared to control group. Cisplatin 0.2 µM + TQ (20, 40 µM). COLO205 (( P=0.021 ), 20 µM TQ; ( P=0.003 ), 40 µM TQ) and HCT116 cells (( P=0.038 ), 20µM TQ; ( P=0.004 ), 40µM TQ). Cisplatin 10µM + TQ 4µM + PDCT 50 µM. (( P=0.002 )) and 48 h (( P=0.031 ))</td>
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<tr>
<td>Breast cancer; Thymoquinone doxorubicin, 5-fluorouracil, and paclitaxel</td>
<td>In vitro study; Three different breast cancer cell lines have been used: - MCF7 - MDA-MB-231 - BT-474</td>
<td>Woo et al., 2011</td>
<td>MTT assay has been used to evaluate anti-cancer effects of TQ alone and in combination with other cytotoxic drugs, and also to determine whether it potentiate the effects of other cytotoxic drugs or not. IC50 values of TQ in MCF7 cells after 12 h, 24 h and 48 h of exposure were 48, 40 and 32 µM, respectively. IC50 values after 12 h, 24 h and 48 h TQ exposure in MDA-MB-231 cells were 24, 14, and 11µM, respectively. IC50 values after 12 h, 24 h and 48 h TQ exposure in BT-474 cells were 38, 18, and 21µM, respectively. After 24 hour of treatment with TQ plus doxorubicin, 5-fluorouracil, and paclitaxel; The cytotoxicity of doxorubicin was increased by 2.6 times when administered with 20M of TQ (from 14% to 36%) and of 5-fluorouracil by 2.7 times (from 13% to 35%).</td>
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<tr>
<td>Lung cancer; Thymoquinone</td>
<td>In vitro study; A549 lung cancer cell and MRC-5 have been used.</td>
<td>Samarghian et al., 2018.</td>
<td>Different concentrations of TQ (100, 50, and 25µM) has been used to evaluate anticancer effects on lung cancer cell line (A549 and MRC-5). TQ effectively attenuated synthesis of formazan crystals reflecting that TQ produces anti-proliferative and pro-apoptotic effects on lung cancer cells.</td>
</tr>
<tr>
<td>Lung cancer; Thymoquinone</td>
<td>In vitro study; A549 lung cancer cell has been used.</td>
<td>Yang et al., 2014</td>
<td>Lung cancer cells (A549) were treated with different concentration of TQ for 48 h (0, 5, 10, 20, 40, 80, 160µmol/L). A549 cells were treated with TQ at 40µmol/L for 24, 48, and 72 h. Low TQ concentration (5 µmol/L) shows no significant effect on cell proliferation; while at 40µmol/L TQ anti-proliferative effect on A549 was dramatic and significant (( P&lt;0.01 )). The effects of TQ on cyclin D, PCNA, and p16 were also evaluated. RT-PCR results showed that at 10, 20, 40µmol/L concentrations, TQ mitigate the synthesis of PCNA and cyclin D in a time and concentration-dependent manner (( P&lt;0.01 )); while the concentration of p16 was increased with marked inhibition of the cell cycle.</td>
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<tr>
<td>Osteosarcoma; Thymoquinone 5-fluorouracil, and Oxaliplatin</td>
<td>In vitro study; MG63 OS cell line was used.</td>
<td>Sarman et al., 2016.</td>
<td>-MG63 OS has been treated with 5FU alone and the data showed that 5FU attenuated cell proliferation. Then a combination of TQ at 10 and 20µM were used on MG63 OS. Cell viability were more suppressed by this combination compared to 5FU alone. The inhibitory effect was more visible after 48 and 72 of treatment. After 48 h and 72 of treatment with 1 µM 5FU and 10 µM TQ, the cell viability attenuated significantly (26% and 29%, respectively). MG63 OS has been treated with OXA alone and the data showed that OXA attenuated cell proliferation. Then a combination of TQ at 10 and 20µM were used on MG63 OS. Cell viability were more suppressed by this combination compared to OXA alone. The inhibitory effect was more visible after 48 and 72 of treatment. After 48 and 72 of treatment with 1µM OXA and 10µM TQ, cell viability was attenuated significantly (42% and 42%, respectively). The combination with 10 and 20µM TQ decreased cell viability at rates of 28% and 41% vs. the application of OXA alone at 48 h, and by 38% and 51% at 72 h, respectively.</td>
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<tr>
<td>Ovary cancer; Thymoquinone</td>
<td>Animal study, and in vitro experiments using ID8-NGL cell line.</td>
<td>Wilson et al., 2015.</td>
<td>In ovariann cancer, the expression of NF-kB increases and TQ inhibits the NF-kB pathway. In SRB assays, TQ inhibits proliferation of ID8-NGL cells and NF-kB activity in luciferase assays in a dose-dependent manner. Treatment with TQ for 10 days mitigates NF-kB activity, but the effect was more visible after 30 days. TQ attenuates expression of cleaved PARP and PCNA.</td>
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<tr>
<td>Leukemia; Thymoquinone DOX</td>
<td>In vitro study; Human T-cell leukemia line (Jurkat cells) has been used</td>
<td>Soltani et al., 2017.</td>
<td>Jurkat cells were treated with different TQ concentrations (0-30 µM) for 24, 48, and 72 h. The cell proliferation was attenuated by TQ in concentration and time-dependent manner. IC50 was 19.46±1.14, 17.34±1.95, and 14.12±1.87 µM in 24, 48, and 72 h, respectively. Combination of TQ and DOX produces stronger anti-proliferative effects compared to each drug alone. At dose 0.28 and 16µM, DOX and TQ reduced cell viability by 50% when they are used as monotherapy, but lower dose is required to attenuate 50% of cell viability when a combination of two drugs (DOX and TQ) were used (0.01 µM of DOX and 9 µM of TQ).</td>
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Woo et al. [20] discovered in 2011 that TQ effectively reduced the growth of a cancer cell line when used as a monotherapy and potentiated the cytotoxic effects of doxorubicin and 5-fluorouracil in MCF-7 cells from 14% to 36% and 13% to 35%, respectively. The authors used specific molecular techniques and measured many markers to determine how TQ inhibits the growth of a breast cancer cell line. They found that TQ has pro-apoptotic effects and enhanced cell death in MCF-7 and HL-60 by activating caspases 7, 8, and 9. The data analysis revealed that there is a decrease in Bcl-2 protein and an increase in total Bax/Bcl-2, which could be a mechanism by which TQ induces apoptosis in the MCF-7 cell line [20]. Thymoquinone has been tested for its effect on cell
viability in lung cancer due to its potential anti-cancer effects and safety profile. A recent in vitro study using the A549 lung cancer cell line and the MRC-5 pulmonary fibroblast cell line revealed that TQ significantly reduces lung cancer cell viability in a concentration and time-dependent manner. TQ's inhibitory effect on cell growth and proliferation was more pronounced on the A549 lung cancer cell line than on the MRC-5 [27]. In another study conducted in 2014 by Yang et al. [28] on the A549 lung cancer cell line, they found that TQ possessed an anti-proliferative effect on lung cancer in a time-dependent and concentration-dependent manner, and its inhibitory effect on the growth marker genes PCNA and cyclin D was established with a p < 0.01. The author proposes several mechanisms for TQ's cytotoxic effects on lung cancer, including suppressing the activity and synthesis of MMP-2 and MMP-9. These enzymes are in charge of breaking down extracellular matrix proteins like collagen. Degradation of the extracellular matrix is required for cell recruitment and invasion. TQ's inhibitory effects on the ERK1/2 pathway are another mechanism [28]. Many in vitro and animal studies found that thymoquinone enhanced the anti-proliferative and apoptotic effects of other cytotoxic agents like Oxaliplatin, 5-FU, and doxorubicin, among others. Many researchers have investigated the therapeutic benefits of TQ in osteosarcoma. TQ was tested on the MG63 OS cell line to see how it interacts with Oxaliplatin and 5-FU to see how it affects cell proliferation. When TQ is used as an add-on therapy, a low dose of chemotherapeutic agents is required to inhibit cell proliferation; additionally, the rate of inhibiting cell viability is lower in the monotherapy-treated MG63 OS cell line compared to combinations of TQ and OXA or 5-FU [29]. Ovarian cancer is a leading cause of death in the gynecological field in the United States. TQ's anti-tumor effect has been documented in numerous studies. Wilson et al. [30] conducted one of these studies in 2015. TQ effectively reduced cell proliferation and NF-κB activity, according to the data analysis. The reduction in NF-κB activity was time-dependent; TQ treatment of ID8-NGL for 30 days reduced NF-κB activity more effectively than treatment for 10 days. The author stated that, in addition to the direct anticancer effect, prolonged treatment with TQ-mediated pro-tumorigenic changes in the tumor microenvironment can prolong the anticancer effect [30]. Several studies have been conducted to determine TQ's anti-proliferative effect on leukemia. TQ's cytotoxic effect on PBMC is generally lower than its anti-proliferative effect on cancer cells. In a recent study on the pro-apoptotic and anti-proliferative effect of TQ, Soltani et al. [31] discovered that TQ reduced cell viability in a time- and concentration-dependent manner, with IC50 values of 19.461, 17.342, and 14.123 for 24, 48, and 72 hours, respectively. The author claimed that DOX and TQ had a synergistic effect; additionally, lower doses of both drugs were required to reduce cell proliferation by 50%.

Conclusion

Many evidence-based studies have supported the therapeutic benefits of thymoquinone as cancer chemotherapy and its anti-inflammatory effects. It mediates these effects through various mechanisms. Thymoquinone is a powerful antioxidant while also preserving the activity of different antioxidant enzymes such as glutathione-s-transferase, glutathione peroxidase, and catalase. Many studies have shown that thymoquinone has cytotoxic and chemoprotective effects, such as anti-proliferative effects, cell cycle blocking, induction of programmed cell death, and eventually acting as both an anti-oxidant and a pro-oxidant.

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Conflict of interests

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