



Epigenetic role of thymoquinone: impact on cellular mechanism and cancer therapeutics

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Thymoquinone is a natural product known for its anticancer activity. Preclinical studies indicated numerous mechanisms of action by which thymoquinone exerts its effects on cancer cells. Recent evidence has indicated that thymoquinone can modulate epigenetic machinery, like modifying histone acetylation and deacetylation, DNA methylation and demethylation, which are among the major epigenetic changes that can contribute to carcinogenesis. Moreover, thymoquinone can alter the genetic expression of various noncoding RNAs, such as miRNA and lncRNA, which are the key parts of cellular epigenetics. This review focuses on cellular epigenetic systems, epigenetic changes responsible for cancer and the counteraction of thymoquinone to target epigenetic challenges, which might be among the mechanisms of the thymoquinone effect in cancer cells.

Introduction

The term ‘epigenetics’ was introduced in the early 1940s by Conrad Waddington, who defined epigenetics as ‘the branch of biology, which studies the alterations in genetic expression that are heritable but without any change in DNA sequence’ [1]. Cellular epigenetic characteristics are involved in different biological processes that can switch the expression of a gene ‘on’ or ‘off’ and regulate protein expression [2]. The major epigenetic changes are histone acetylation/deacetylation, DNA methylation/demethylation, nucleosome remodeling and the RNA interferences such as microRNAs (miRNAs), circular RNAs (cirRNAs) and long non-coding RNAs (lncRNAs); and these epigenetic changes have been found to have key roles in the regulatory processes of the activity and expression of genes and/or proteins [3]. Disruption of any of these epigenetic systems leads to the abnormal activation or silencing of genes and/or proteins, resulting in diseases including cancers [4–6]. For this, it is important to counteract the disease-causing epigenetic modifications with high selectivity as the normal cells remain unaffected. Scientific investigations are ongoing

to find out the possible epigenetic treatment by targeting abnormal cells with minimal injury to healthy cells [7,8].

Cancer is the second-leading cause of death after cardiovascular disease and, every year, millions of people are diagnosed with cancer. Although the numbers of cancer survivors are increasing, an estimated 9.6 million of cancer-associated deaths were reported in 2018 [9,10]; and cancer is one of the major health burdens worldwide. For now, the most common treatment options in cancer therapeutics are chemotherapy along with surgery and radiation therapy. Natural products have been regarded as one of the richest sources of chemotherapeutic drug development. Dietary phytochemicals with anticancer properties can alter the genetic expressions of vast numbers of proteins by targeting cellular epigenetic machineries [11,12]. For example, one-carbon metabolites like folate, cobalamin, riboflavin, methionine and pyridoxine can regulate *S*-adenosylmethionine (SAM) levels, a universal methyl group donor, thus affecting the methylation of DNA [11,13]. Some polyphenols like resveratrol can activate the deacetylation reaction of sirtuin; thus, regulating certain miRNAs, which have oncogenic or tumor suppressor roles [14–16]. Another natural compound: curcumin, can directly regulate the activity of DNA methyltransferases (DNMTs). Curcumin induces DNA methylation in leukemia cells and reactivates certain

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tumor suppressor genes in human non-small-cell lung cancer and cervical cancer cells [17,18].

Thymoquinone (chemically known as 2-methyl-5-isopropyl-1,4-benzoquinone) is a natural product phytochemical, mainly found in black cumin or black seed (*Nigella sativa*; family Ranunculaceae), that has been used in different traditional medicinal systems such as in Ayurvedic and Unani systems mainly in Arabian, Mediterranean, South Asian and African regions [19–22]. Thymoquinone was first isolated from black cumin extracts by El-Dakhkhany in 1963 and, afterwards, many preclinical studies were conducted to clarify its pharmacological and medicinal activities [23–25]. Thymoquinone has been shown to exert anti-inflammatory, antidiabetic, antihypertensive, antimicrobial, analgesic, immunomodulatory, spasmolytic, hepatoprotective, renal-protective, gastroprotective, bronchodilatory, antioxidant and antineoplastic effects *in vitro* and *in vivo* [20,26,27]. Thymoquinone causes a selective inhibitory effect on cancer cell growth and it interferes with several other carcinogenic processes, such as cell migration and invasion, angiogenesis, among others, via multiple molecular mechanisms, including influencing epigenetic events in cancer cells [19,20,28,29]. In this review, the epigenetic effects of thymoquinone on cancer cells are discussed comprehensively, which might help researchers in further understanding of its mechanisms of action in cancer cells.

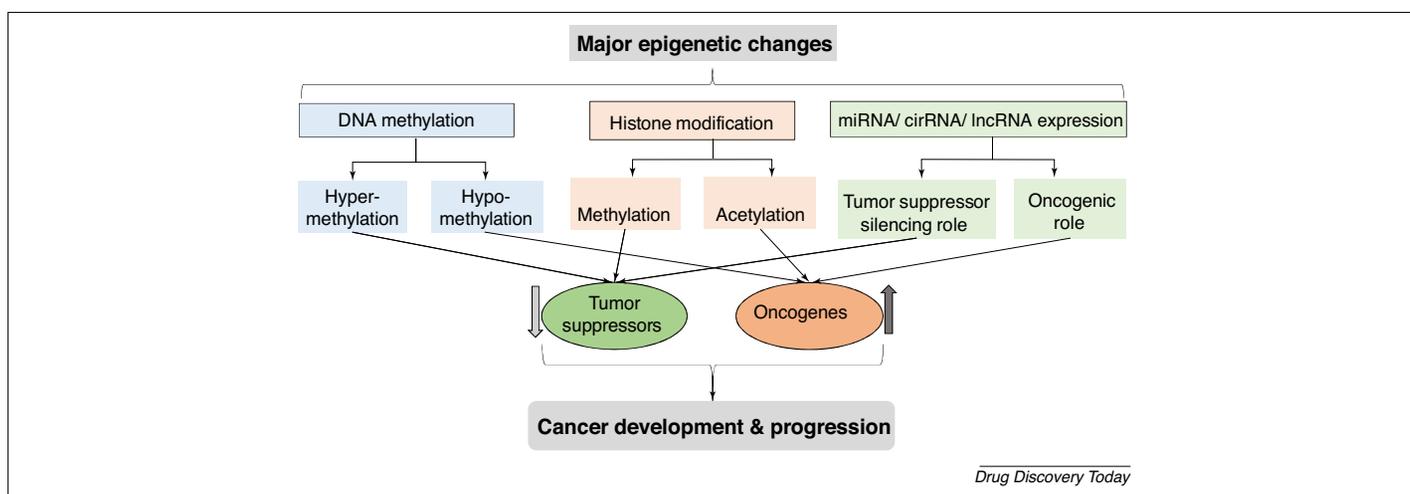
Epigenetic changes and cancer

Epigenetic changes interfere with normal gene regulation and hamper certain cellular processes including DNA repair, replication, differentiation, apoptosis and the cell cycle and, consequently, epigenetic changes, like DNA methylation or chromatin remodeling, can lead to the initiation of carcinogenesis and the development of various cancers [4,30,31]. Fig. 1 presents a schematic diagram of major epigenetic changes contributing to cancer.

DNA methylation is a covalent reaction, where a methyl group is added to DNA and usually stabilizes the chromatin structure. It is

highly specific and the methyl group is added to the cytosine located next to a guanine nucleotide, linked by a phosphate (commonly named as a 'CpG' island). The addition of a methyl group changes the structure and function of DNA, and thus interferes with the instructions for the expression of a gene [7,11,32]. In normal healthy cells, DNA methylation plays a key part in the regulation of gene transcription, inactivation of X chromosome, parental imprinting, repression of oncogenes and, by silencing transposon and repetitive elements, preserving chromosomal integrity [33,34]. In higher eukaryotes, CpG islands are methylated by one of the three DNMT enzymes. DNMT1 recognizes the hemimethylated DNA that is generated during DNA replication, whereas DNMT3 is a *de novo* methyltransferase that establishes the methylation of DNA during embryonic development [35,36]. CpG islands are mostly located in regulatory regions of tissue-specific genes and their methylation status is mainly involved in strict regulation of tissue-specific gene expression [11,33]. Numerous studies showed that hypermethylation of certain regions, more specifically within the promoters of tumor suppressors, causes an inappropriate silencing of transcription, and this aberrant *de novo* methylation is a hallmark of cancer development. Moreover, the increased methylation at the promoter region affects the expression of different noncoding RNAs with important regulatory functions, and thus plays a vital part in cancer metastasis [32,37–39].

Chromatin structure, consisting of DNA, histones and other non-histone proteins, has a vital role in regulating gene expression and DNA replication [40,41]. Histones can be biochemically modified by two main methods: methylation and acetylation reactions catalyzed by specific enzymes. Histone methyltransferases (HMTs) and histone demethylases (HDMs) regulate the methylation process, whereas histone acetyltransferases (HATs) and histone deacetylases (HDACs) mediate histone acetylation and deacetylation reactions, respectively. Acetylation of histones is associated with



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FIGURE 1

Epigenetic changes in cancer progression. Epigenetic changes result in aberrant gene expression via the methylation of DNA, modification of histone and noncoding RNAs. Most often, DNA hypermethylation contributes to cancer progression when tumor suppressor genes become silenced. By contrast, DNA hypomethylation contributes to oncogenesis when previously silenced oncogenes become transcriptionally activated. Histone modifications also have important roles in cancer development. Histones can become methylated or acetylated on specific amino acid residues that are connected by silencing discriminating tumor suppressor genes and enacting oncogenes. Another mechanism of epigenetic alteration is mediated by noncoding RNAs. The miRNAs, cirRNAs and lncRNAs can contribute to cancer progression by interfering with the expression of tumor suppressors and by acting as oncogenes [38,46,50,53,56].

chromatin activation and deacetylation is associated with inactivation of heterochromatin [40,42,43]. Among other epigenetic changes, phosphorylation, ADP ribosylation, ubiquitinylation and sumoylation are important, contributing to cancer initiation and progression, mainly via chromatin remodeling [44,45]. Modifications of DNA and histones alter the chromatin structure by interfering with noncovalent interactions between and within nucleosomes; when histones are modified, they can regulate gene expression by determining chromatin structure [40,43,46]. They can also act as the docking sites for specific proteins that can recognize chromatin modifications. Many of these proteins also contain several 'reader' domains, which recognize distinct post-translational modifications of histones. After recognizing the modifications, the chromatin readers recruit remodeling enzymes and chromatin modifiers, which can further act as the effectors of modification [36,47,48]. Defects in chromatin modifiers and remodelers have been found to be responsible for the etiology of various types of cancer [4,39].

The noncoding RNAs can regulate the gene expression by interfering with the translation process of mRNA into proteins. Among noncoding RNAs, miRNAs have been studied more extensively, and they play an important part in heritable changes of gene expression, without making any change to the genomic DNA sequence. An abnormal expression or aberrant regulation of miRNAs is responsible for tumor initiation and development in different human cancers by triggering histone covalent modifications and DNA methylation [8,49–51]. Some circulating microRNAs, for example miR21 and miR422a, have been found to be associated with the development and progression of different cancers, and even with cancer metastasis [52–54]. Also, the lncRNAs can regulate cellular processes by interfering with gene expression epigenetically, as well as by targeting transcriptional and post-transcriptional steps and translational processes. Multiple lncRNAs have tumor-suppressor role or oncogenic function [55–57].

Mechanism for thymoquinone action in cancer therapeutics

For thousands of years, black cummin has been used in different traditional systems of medicine, and thymoquinone, dithymoquinone, thymohydroquinone and thymol are the active ingredients found in black cummin seeds. Several studies have indicated that thymoquinone has notable activities in the prevention and treatment of various types of diseases including cancers by targeting different biochemical, molecular and physiological pathways [20,29]. It has been evident that thymoquinone can inhibit DNA synthesis and proliferation in cancer cells by interfering with the structure of DNA [58–60]. In pathogenesis of different cancers, oxidative stress has vital roles. Usually the antioxidant systems prevent oxidative DNA damage by scavenging free radicals, and the antioxidant activity of thymoquinone to protect cellular damage is well documented [22,61–63]. Thymoquinone can up-regulate proapoptotic genes and proteins, such as Bax/Bak, or downregulate antiapoptotic genes and proteins, such as Bcl-2, Bcl-xL, among others, as well as modulating the caspase pathway, and thus controlling cancer cell growth by inducing apoptosis [24,26]. It is also evident that thymoquinone induces apoptosis by interfering with the activity and expression of various other molecular targets, such as p53, peroxisome proliferator-activated

receptor (PPAR)- γ , phosphatase and tensin homolog (PTEN) and signal transducer and activator of transcription (STAT)3, and through the generation of reactive oxygen species (ROS) [64]. Certain tumor suppressor genes and proteins have been found to be overexpressed or activated by thymoquinone; for example, p53, PTEN, p21, p27 and breast cancer type 1 susceptibility protein (BRCA1), among others, whereas certain oncogenic signaling molecules and pathways, like phosphoinositide 3 kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK)/ERK, have been found to be inhibited by thymoquinone [21,24,29,65–67].

In addition to inhibiting cancer cell growth, thymoquinone has potential to control cancer cell metastasis by targeting different molecular pathways. For example, thymoquinone reduces ERK phosphorylation and matrix metalloproteinase (MMP) secretion by downregulating focal adhesion kinase (FAK) [68]; it downregulates Twist1 and Zeb1 transcription factors, and thus inhibits epithelial to mesenchymal transition (EMT) and subsequently inhibits cancer metastasis [19,69]. Also, thymoquinone can inhibit angiogenesis by interfering with essential steps of neovascularization, such as suppressing proangiogenic vascular endothelial growth factor (VEGF)-induced ERK activation, and inhibition of tube formation [70,71]. Polo-box domain (PBD) of polo like kinase 1 (Plk1) was indicated as one of the important targets of thymoquinone. Plk1 is an important inducer of the cell cycle and thymoquinone distorts its function, consequently halting the cell cycle [72,73].

Epigenetic mechanism of the anticancer activity of thymoquinone

The genetic and epigenetic alterations cause the aberrant gene expression and protein function, which are the hallmarks of cancer. Natural compounds are excellent candidates in cancer prevention and therapeutics, because scientific evidence has shown that these compounds can directly or indirectly target and regulate genetic expression by interfering with genetic and epigenetic machineries [11,74,75]. Thymoquinone is a promising anticancer molecule because it can target different cell signaling pathways involved in carcinogenesis, including modulation of epigenetic traits of cancer cells, such as histone acetylation or deacetylation and DNA methylation or demethylation [76,77].

Histone acetylation/deacetylation

It is evident that thymoquinone can improve the total cellular HDAC activity in cancer cells [78]. HDACs are usually overexpressed in MCF-7 breast cancer cells, and thymoquinone can act as a HDAC inhibitor (HDACi) that potently induces apoptosis through inducing acetylation of histones and inhibiting deacetylation of histones. Also, thymoquinone reactivates HDAC target genes (p21 and Maspin), inducing the upregulation of Bax (proapoptotic gene) and downregulation of Bcl-2 (antiapoptotic gene), thus arresting the G2/M phase of the cell cycle [77,78].

The NAD⁺-dependent HDAC: silent mating-type information regulator 2 homolog 1 (SIRT1), has vital roles in different biological and cellular processes, including the aging process, oxidative stress and apoptosis. SIRT1 can alter the cellular apoptosis process by rendering deacetylation of the acetylated p53, where acetylated p53 can promote oxidative-stress-induced apoptosis [79–81]. Deleted in breast cancer 1 (DBC1) can bind with SIRT1 and to prevent its activation. The activation of crucial cellular energy sensor AMP-activated protein

kinase (AMPK) can promote SIRT1–DBC1 dissociation that leads to SIRT1 activation, and activation of SIRT1 deacetylates p53 and attenuates the transcriptional process of p53 [80,82]. It has been reported that thymoquinone can upregulate SIRT1 expression in neonatal rat cardiomyocytes and consequently deacetylates p53; thus, it can act as an apoptosis inducer [83,84]. Lu *et al.* [85] also reported that thymoquinone activates SIRT1, suppressing p53 acetylation in cardiomyocytes. Velagapudi *et al.* [86] reported that thymoquinone inhibits the activation of neuroinflammation in BV2 microglia via the activation of AMPK and SIRT1. They showed that thymoquinone reduces cellular ROS generation and increases nuclear accumulation of SIRT1 and increases NAD⁺. The activation of NAD⁺/SIRT1 and AMPK possibly makes a contribution in deacetylation-induced activation of target proteins, like FOXO3a, and inhibition of neuroinflammation in BV2 microglia [86].

DNA methylation/demethylation

Thymoquinone has been suggested as a modulator of the methylation process in DNA and, interestingly, thymoquinone can possibly act as a methylating and a demethylating agent [87]. Numerous *in vitro* and some *in vivo* studies indicated that thymoquinone can interfere with the epigenetic processes by targeting and binding to the enzymatic center of DNMT1 and/or inducing the disruption of the transcription of DNMT1. It has been evident that thymoquinone binds to the catalytic site of DNMT1, leading to its downregulation via interference with the Sp1–miR29b loop, which consequently results in decreased methylation of DNA [88,89]. Pang *et al.* [89] exposed leukemia cells to thymoquinone and found that DNMT1 downregulation through Sp1–NF-κB complex dissociation from the

DNMT1 promoter induced a decrease of colony formation and increased cellular apoptosis by caspase activation. The *in vivo* study also demonstrated that thymoquinone administration induced leukemia regression in leukemia-bearing mice and inhibited metastasis in the lung and liver [89]. Collectively, they suggested that thymoquinone induces methylation of DNA via binding with DNMT1 and suppressing its expression, indicating thymoquinone as a novel compound in leukemia therapy that acts through DNA hypomethylation [89].

Aberrant DNA methylation and histone modification have been found to be linked to chemoresistance of doxorubicin in MCF-7/DOX cells, and these changes affect the expression profile of different target genes; for example, inducing the upregulation of KRAS, BCL6 and NOTCH1 and downregulation of BRCA1, PTEN and RB1 in MCF-7/DOX cells [90]. Interestingly, there is the possibility of counteraction of epigenetic changes by thymoquinone in MCF-7/DOX cells through the upregulation of PTEN, subsequently arresting the cell cycle and inducing apoptosis by disrupting the mitochondrial membrane potential, caspase activation and cleavage of poly(ADP-ribose) polymerase (PARP) [77].

The transcription factors that affect EMT (EMT-TFs) such as Twist1, Zeb1, Snail1 and Slug play essential parts in metastasis through different signaling cascades in cancer cells [91,92]. It is evident that thymoquinone treatment inhibits the expression of Twist1 and Twist1-induced N-Cadherin; and increases the expression of Twist1-repressed E-Cadherin in BT549 triple-negative breast cancer (TNBC) cells [19]. Interestingly, the methylation of the Twist1 promoter was found to be increased by thymoquinone treatment in certain cell lines, and there is a possibility that thymoquinone

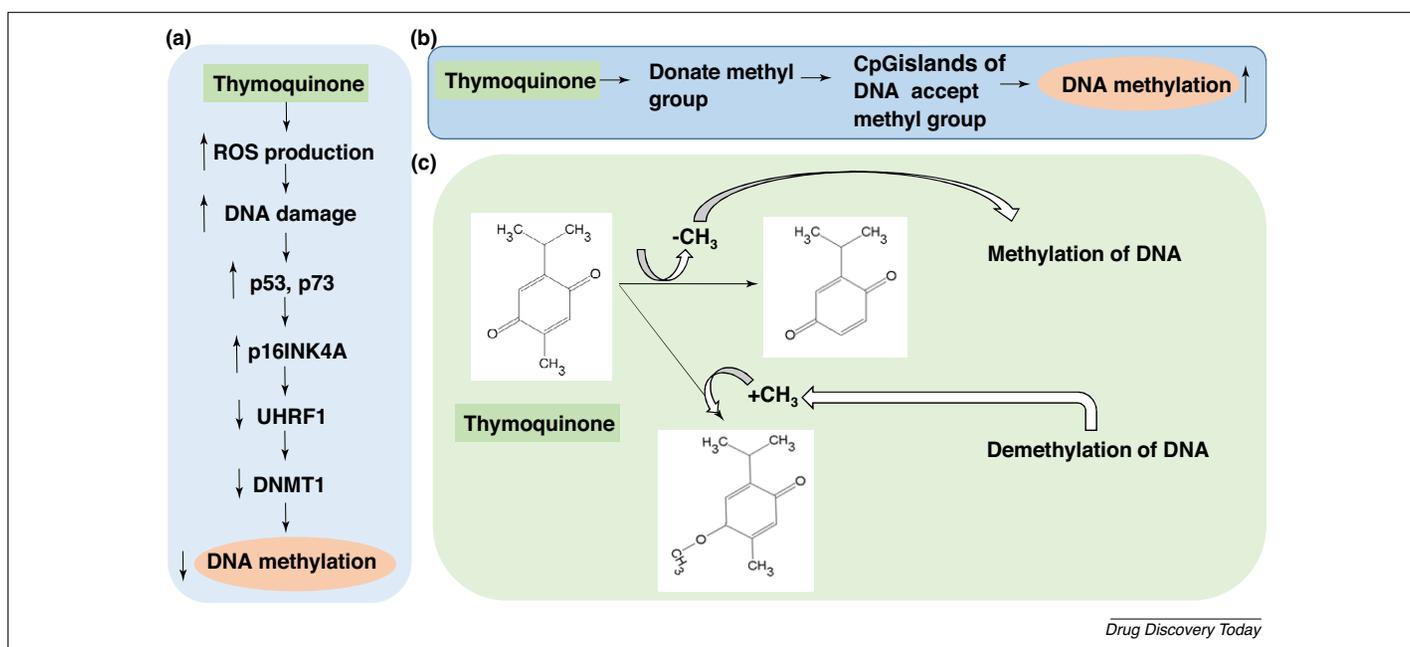


FIGURE 2

The role of thymoquinone in DNA methylation/demethylation. (a) Upregulation of ubiquitin-like-containing plant homodomain (PHD) and ring finger domain 1 (UHRF1) influences cancer cells to repress tumor suppressor genes through their promoter hypermethylation during cell proliferation. Thymoquinone can suppress UHRF1 and, thus, might be able to repair epigenetic aberration in cancer cells through a DNA demethylating process, probably involved in downregulation of DNA methyltransferase (DNMT)1. Downregulation of UHRF1 by thymoquinone can lead to normal expression of tumor suppressor genes and upregulation of negative regulators, like p53, p73 and p16INK4A, allows cancer cells to undergo apoptosis or G1/S arrest [93–96]. (b) Thymoquinone can also donate a methyl group directly to methylate CpG islands of genomic DNA (more specifically, promoter regions) [19]. (c) The chemical structure of thymoquinone also creates the possibility to donate or accept a methyl group to or from DNA, and thus can act as a methylating and demethylating agent (proposed mechanism, which can be investigated experimentally).

downregulates Twist1 by an epigenetic mechanism (i.e., hypermethylation of the Twist1 promoter) [19]. A similar report on downregulation of Twist1 and Zeb1 via promoter methylation in cervical cancer cell lines CaSki and SiHa also exists [69].

Ubiquitin-like-containing plant homodomain (PHD) and ring finger domain 1 (UHRF1) is an important part of a macromolecular complex that includes other molecules like DNMT1, HDAC1, HAUSP and Tip60, and is responsible for the duplication of the epigenetic code after the replication of DNA. UHRF1 is a putative oncogene and upregulation of UHRF1 helps the cancer cells in maintaining pathologic repression of tumor suppressor genes through their promoter hypermethylation during cell proliferation. UHRF1 usually recognizes and binds to the methylated promoters of tumor suppressor genes and, by interacting with DNMT1, UHRF1 regulates the expression of tumor suppressor genes [93,94]. Thymoquinone has been found to inhibit UHRF1 expression and probably able to repair this 'wrong' epigenetic code by targeting the epigenetic integrator UHRF1 in cancer cells through the DNA demethylating process. Thymoquinone activates p73-dependent mitochondrial signaling and cell-cycle checkpoints that subsequently target UHRF1 [95]. This downregulation of UHRF1 by thymoquinone might be a mechanism of thymoquinone in cancer prevention and therapy, because this repression might lead to the re-expression of tumor suppressor genes, as well as upregulation of certain negative regulators, like p16INK4A, p53 and p73, and thus allow cancer cells to undergo cell cycle arrest and apoptosis in the p53-deficient Jurkat cells (acute lymphoblastic leukemia cell line) and HeLa cells (cervical cancer cell line) [93,96]. A recent study reported that thymoquinone decreases the expression of some important epigenetic proteins like DNMT1,3A,3B, G9A, HDAC1,4,9, KDM1B, KMT2A,B,C,D,E and UHRF1 in Jurkat cells, and also decreases the expression of DNMT1, G9a and HDAC1 in MDA-MB-468 breast cancer cells [97]. The chemical structure of thymoquinone can further explain its dual role in methylation and demethylation. Thymoquinone can probably donate a methyl group ($-CH_3$) or accept $-CH_3$ group from DNA (a possible mechanism of thymoquinone action in DNA methylation/demethylation is shown in Fig. 2).

Activating and deactivating noncoding RNAs

Imani *et al.* [98] indicated that inactivation of EMT-TFs by the epigenetic process, more specifically by using miR34a, might be a promising therapeutic approach against metastasis of breast cancer cells *in vitro*; and thymoquinone can be an enhancer of miR34a action. Experimental evidence showed that co-delivery of thymoquinone and miR34a can downregulate EMT signaling pathways by targeting Twist1 and Zeb1 directly in TNBC cell line BT549 [98]. Thymoquinone also affects the expression patterns of miRNAs. Meral *et al.* [99] reported that overexpression of miR206b-3p induces oxidative stress and necrosis in liver and contributes to developing Ehrlich acid solid tumors in model mice, which was counteracted by thymoquinone treatment. They intraperitoneally injected 10 mg/kg thymoquinone into male BALB/c mice for 5 days per week and treated them in this way for 4 weeks, and then Ehrlich acid tumor cells were administered subcutaneously into mouse neck to induce the formation of solid tumors, with continuing thymoquinone treatment. The results indicated that thymoquinone treatment inhibits the oxidative stress, minimizes the necrosis, increases regeneration and downregulates miR206b-3p expression in liver tissue [99]. Another microRNA, miR146a, which is usually highly expressed in the hippocampal region of *Status epilepticus* (SE) rats, is involved in inhibition of inflammatory cytokines via the NF- κ B pathway [100], and thymoquinone treatment was found to downregulate the expression of miR146a and thus might limit the inflammatory reactions by interfering with the NF- κ B pathway.

In another study, thymoquinone was encapsulated into nanoparticles (PEG4000-Tq-Nps) and its effects were observed in breast cancer cell metastasis [101]. Experimental results indicated a potent antimigratory effect, which could be caused by the increased expression of miR34a induced by thymoquinone, as well as the downregulation of cytoskeletal actin polymerization via the inhibition of Rac1 expression [101]. Table 1 presents some miRNAs targeted by thymoquinone in cancer cells.

Future research

Usually, the abnormal epigenetic changes occur in the early stages of cancer development and, so, they are thought to be the potential targets in cancer chemotherapeutics. Hypothetically, epigenetic defects could be reversed easily, and this has inspired researchers

TABLE 1

Action of thymoquinone in regulating miRNAs in cancer

Thymoquinone-targeted miRNA	Normal expression in cancer	Experimental model	Mechanisms of action	Refs
miR34a (upregulation)	Downregulated	Human breast cancer cells	Thymoquinone upregulated miR34a activity and inhibited breast cancer cell metastasis by targeting EMT-associated transcription factors Nanoparticle-derived thymoquinone delivery upregulated miR34a activity that directly downregulated Rac1 expression and induced actin depolymerization and disruption of actin cytoskeleton in cancer cells by inhibiting Rac1	[98] [101]
miR206b-3p (downregulation)	Upregulated	Ehrlich acid mouse solid tumor model	miR206b-3p upregulation is linked with increased necrosis and oxidative stress, which was prevented by thymoquinone probably via the downregulation of miR206b-3p	[99]
miR146a (downregulation)	Upregulated	<i>Status epilepticus</i> rat model	miRNA146a inhibits inflammatory cytokines through NF- κ B pathway, which was counteracted by thymoquinone	[100]

to identify novel chemotherapeutic compounds that can potentially reverse or protect abnormal epigenetic changes [3,36,102,103]. Recent data suggest that thymoquinone might potentially interfere with the epigenome and regulate the genomic expression related to different carcinogenic pathways. Further studies are needed to verify this hypothesis and to investigate the link between thymoquinone-induced epigenetic changes, alteration of genetic expression and different phenotypes [29,70,89]. Importantly, a systematic study to define crucial genes for carcinogens, and their epigenetic repair by thymoquinone in cancer cells and animal models, should be conducted; focusing on deciphering precise molecular mechanisms of thymoquinone in DNA methylation and histone acetylation is also important. Another important point to be noted is about the anticancer therapeutic potential of thymoquinone. There has not yet been a successful clinical trial by the US government for thymoquinone usage. The pharmacokinetic background of thymoquinone is mostly responsible for this, because the bioavailability of thymoquinone is comparatively lower than currently used chemotherapeutic drugs, which we have discussed in previous work [20]. In addition to understanding the molecular mechanism of thymoquinone action, researchers should focus on chemical properties of thymoquinone and increase its bioavailability.

Concluding remarks

Cancer is a major health problem worldwide that can be initiated and driven by genetic abnormalities as well as epigenetic alterations. Alterations of normal epigenetic machineries

are regarded to be among the hallmarks of cancer, and these alterations hamper normal regulation of genes, and obstruct normal cellular and molecular processes, including DNA repair, apoptosis and the cell cycle. Epigenetic aberrations usually lead to the inhibition of tumor suppressor genes and/or activation of oncogenes in cancer cells, and thus epigenetic modifications might be useful biomarkers for prognosis and prevention or treatment of cancer. The current conventional therapy used for cancer treatment has some adverse effects and might not be applicable in all patients. Because of its interesting chemical formula, and its capability to target different biomolecules (genes and proteins), thymoquinone is a potential therapeutic option in the prevention and treatment of cancer. More investigations are necessary to further clarify the functional outcome of thymoquinone in cancer-associated epigenetic variations at the molecular level to develop thymoquinone as a pharmaceutical preparation in a cancer management system.

Conflicts of interest

There are no conflicts of interest regarding this article.

Acknowledgments

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