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Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network

REVIEW ARTICLE BIOSCIENCE RESEARCH, 2021 18(3): 2381-2387. **OPEN ACCESS**

Therapeutic role of Thymoquinone against different types of cancer

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According to many surveys it is noticed that cancer is possibly the most common disease in both men and women. Many other chemotherapies and radio therapies are used to overcome this disease which harm the body side by side, on the other hand organic supplies are generally harmless, operative, and easily accessible replacements of cancer treatment. Many previous studies proved the therapeutic effects of thymoquinone and also verified the best option for the inhibition of cancer. *Nigella sativa* has been used as a common medicine for many years in ancient time. There are many chronic diseases which are cured by using crude oil of *Nigella sativa* including cancer, cardiovascular complications, diabetes, asthma, kidney disease. Thymoquinone is very capable against leukemia, lung cancer, renal carcinoma, hepatic cancer, prostate and breast with greatly protection. The current review article has summarized the effects of *Nigella sativa* against various types of cancer.

Keywords: *Nigella sativa*, Thymoquinone, Carcinoma, Alpha-hederin, Anti-oxidant, Proliferation, Apoptosis, Mechanism.

INTRODUCTION

Cancer is considered second ranked life threating disease in the world after the myocardial infarction, in each year; lots of people are detected with cancer. Luckily, cases of cancer patients are increasing day by day, especially due to the presence of developed, fast recognition and innovative dealing policies. A study has been reported that higher than 15.5 billion Americans with the cancer history are thriving since January 2016(Siegel et al. 2016). Presently, chemotherapy is the most communal management for cancer therapy, but its complications are unavoidable. Other scientific study showed that thymoquinone, main ingredient of *Nigella sativa* has potent to prevent cancer via inactivation and initiation of molecular pathways (Aggarwal et al. 2015).

Western Asia, in Middle Eastern countries and in the Konya region in Turkey, these are the famous sites for the cultivation of black seed (Lord et al. 2014).The Ranunculacea (Buttercup) family is that family which contains the black cumin, *Nigella sativa* which is commonly well-known as black seed (Güllü et al. 2013).

The *Nigella sativa* seed, contains volatile (0.40%–0.45%) and non-volatile (32%–40%) oils, protein content is (16.00%–20.85%), carbohydrates are approximately (31.0%–33.9%), fibre content is (5.50–7.94%), alkaloids, tannins, saponins

many minerals such as iron, calcium, potassium, magnesium, zinc and copper (1.79%– 3.44%). Many Vitamins which are present in black seeds are alpha, beta carotenoids and ascorbic acid, niacin, thiamine, pyridoxal phosphate and folic acid, these nutritional values may be varying depending upon the region where they cultivated (Güllü et al. 2013) and (Al-Mahasneh et al. 2014)
Many forms of *Nigella sativa* are used for therapeutic purposes, such as a grinded form, crude oil or extract (Heshmati et al. 2015).Other analyses on seeds have reported the amount of thymoquinone is 52.6 mg/100g and 20.13 mg/100 g that provides its major composition(Tüfek et al. 2015). phosphorus (Ph) Salama, (2016).
. Bitter cumin (B. persicum) is a type of cumin seeds which consist of 0.5 to 1.6 per cent essential oil, specifically limonen-6-one (carvone) proportion is (45%–60%) and p-cymene which is another main type of essential oils of bitter cumin (Sultan et al. 2009)

Phytochemicals are bioactive compounds which are present in many fruits, vegetables, herbs, and several other plants. About 10,000 phytochemicals have been recognized for their medicinal properties such as anti-inflammatory and anticancer. Oxidative stress is an imbalance state in free radicals and antioxidants of body containing oxygen molecules with a bumpy number of electrons. The odd number permits them to easily respond with extra molecules. They alter oxidative stress phase and inflammatory signaling, hence performing antioxidant and anti-inflammatory activities, further they prevent angiogenesis by modify the gene expression (Kang, H. (2019).

There are two major bioactive components or phytochemicals of black seeds are Thymoquinone and Alpha hederin. Thymoquinone (2-Isopropyl-5-methyl-1,4-benzoquinone) is the bioactive component of the from black seeds oil which is volatile in nature (Majdalawieh et al. 2017) .It has been broadly investigated for its wide-range of medicinal, pharmacological and therapeutics effects including anti-inflammatory (Taka et al. 2018), anti-oxidant (Armutcu et al. 2018), antitumor (Singh et al. 2018), and analgesic (Amin and Hosseinzadeh (2016).

A recent study conducted to prove the alpha hederin as a new autophagy inhibitor and hypothesized that it has ability to promote the killing effect on NSCLC cells. Treatment through alpha hederin reduced non-small cell lung cancer (NSCLC) proliferation and speedup the NSCLC cell apoptosis (Zhan et al. 2018)

Unrestricted species are the components containing oxygen molecules with a Cancer states a stage of large number of diseases categorized by the progress of abnormal cells that split wildly and able to infiltrate and destroy normal body tissue. Cancer is too much powerful to scatter throughout body. Additionally, some malignancies occur due to chronic inflammatory states, while others are due to disruption and conversion in immune response as part of advancement and metastasis (Hegde et al. 2020).

Anti-oxidant and cytotoxic effects

One of the latest studies conducted to see the consequences of thymoquinone on the hepatic cells of Dawley rats suffering from liver carcinoma, proved that different doses of *Nigella sativa* (one dose is 0.01 g/kg body weight which was low dose, the second dose was normal dose 0.1 g/kg body weight and third dose was high potential dose 1.0 g/kg body weight) giving to normalized the Alanine Transaminase (ALT) and Aspartate Aminotransferase (AST) level in rats' liver, display efficient result by reducing the levels of both liver enzyme (ALT & AST) in medicated rats in comparison with control group(Dollah et al. 2013).

Pre-treatment through thymoquinone opposed the enhanced the level of lipid peroxidation and amplified enzymatic tasks that aid antioxidant action of thymoquinone in the erythrocyte throughout 1,2-dimethylhydrazine-administration during the condition of colon carcinogenesis in Wistar rats (Jrah Harzallah et al. 2012).

Latest investigational works recommended antioxidant property of *Nigella sativa* is multiple investigations described that thymoquinone initiate apoptotic activity in onco cells via applying oxidative injury(Dergarabetian et al. 2013)

Additional hypothesis suggested that thymoquinone performance as an antioxidant is less powerful as compared to prooxidant activity of thymoquinone which is at higher level (Zubair et al. 2013).

Anti-proliferative and pro-apoptotic effects

A study conducted to reveal the improving abilities of black seeds for liver carcinoma illustrated that, ethanolic extracts form when administered to the patient of liver cancer; these extract gave amazing results to improve the cell changes occurring in liver due to diethylnitrosamine (DENA) treatment (Fathy and Nikaido, (2013)

In another parallel study, the same results are obtained as the given amount of methanolic

extracts for the changes in albino rat model with liver cell cancer of glyco-regulatory enzymes (Khan et al. 2014) Liver cancer was initiated in an albino rat by giving intraperitoneal injections of DENA and carbon tetrachloride (CCl4), this administration increases the comparative liver weight, the amount of a specifically best for its preventive activities for cancer; but fetoprotein (AFP) and the functions of hexokinase glyceraldehyde phosphate dehydrogenase, and G6P dehydrogenase in medicated rats' serum (Abdel-Hamid et al. 2013).

Anti-inflammatory effects

A study which was conducted to report anti-inflammatory action of thymoquinone on LPS-stimulated BV-2 murine microglia cells, where thymoquinone was efficient in decreasing nitrate with equivalent debility of inducible nitric oxide synthase (iNOS) protein expression proved (Taka et al. 2015)

In another study, dose of thymoquinone (5 mg/kg body once daily for 21 days) given via oral route to the collagen-induced arthritic Wistar rats for its anti-arthritic activity, this experiment shown marvelous effect of thymoquinone to reduce the level proinflammatory mediators [IL-1β, IL-6, TNF-α, IFN-γ, and PGE2] and enhanced IL-10 (Umar et al. 2012).

Immunomodulatory activities of thymoquinone

It is also reported that thymoquinone can defeat the signaling of NF-κB and vanquishes the IL-8 expression in children suffering from the brain tumor medulloblastoma (Ashour et al. 2016).

It is observed in an analysis that by treating the head and neck squamous cell carcinoma (HNSCC) with thymoquinone, thymoquinone efficiently initiated the autophagy progress (Chu et al. 2014). Active component of thymoquinone has the potential to enhance the permeability of mitochondrial membrane and exhibit an imperative role in stimulation of JNK and p38 in CPT- 11-R LoVo colon cancer cells. Further it can induce cell death which is independent of caspase (are a family of protease enzymes playing 29.which is independent of caspase (are a family of protease enzymes playing primary roles in programmed cell death) (Chen et al. 2015).

Role of *Nigella sativa* in prevention of cancer

Nigella sativa perform many functions as it acts as an antioxidant, anti-mutagenic, cytotoxic, pro-apoptotic, antiproliferative, and anti-metastatic agent. Essential oil from is also used as an anti-inflammatory agent by reducing inflammatory status in the blood and also protects the tissue of colon from ulcerative colitis which leads to colon cancer (Majdalawieh et al. 2016).

Blood cancer

One of the most common neonatology malignancies is the cancer of blood tissues. Multiple experiments were done to observe the effects of *Nigella sativa* on lymphoblastic leukemia for 40 treated children. In the study twenty patients of first group were under doxorubicin therapy and *Nigella sativa* oil fixed doses as eighty milligram per kg per dose distributed into3 doses primary and continuous for one week later every doxorubicin dosage and remaining 20 subjects of second group were taken under doxorubicin and placebo for one week following each doxorubicin dosage. It was noted that black seed oil improves pulse activities in children suffering from lymphoblastic leukemia who were medicated with Doxorubicin and Thymoquinone (Hagag et al. 2020).

Breast cancer

The investigations have also revealed that the extract of oil (Black Seed Oil, BSO) and the bioactive constituent thymoquinone can give effective and curable effects against breast cancer in female rats. It was observed that active component of thymoquinone and black seed oil (BSO) minimize the proportion of lump indicators (intensity of Multiple discriminant analysis (MDA) and lactate dehydrogenase (LDH) additionally alkaline phosphatase level (ALP) and AST functions), repressed the structural modifications and turn down the utterance of the genes of mammary gland such as Brca1, Brca2, Id-1 and P53 alterations in feminine rats initiated by treating an immunosuppressor and also a laboratory carcinogen, Dimethylbenz[a]anthracene (DMBA) (Linjawi et al. 2015)

Colon cancer

One of the several experiments done to explore the anti-cancer results of thymoquinone against colon cancer explained that, the treatment through 20 μM thymoquinone resulted in a substantial decrease in cell feasibility in HCT1116 cells when compared with the control group. Additionally, when controlled group treated with 40 μM thymoquinone, the treatment gave significantly result by decreasing cell capability in COLO205 cells. Cytotoxicity assays specified that

thymoquinone dose-dependently reduced cell probability of the COLO205 and HCT116 colon oncocell lines. The work confirmed thymoquinone resulted in cell death of colon cancer cells and made the colon cancer cells more sensitive to Cisplatin therapy by suppressing NF-κB activation (Zhang et al. 2016)

Another work investigated that 150 μM of thymoquinone was capable to efficiently reduce the invasiveness of human Colon oncoCells (HT-29) HT-29 cells about 8 fold as compared with those were not treated with active constituent of the *Nigella sativa* oil Tokay, (2020).

Hepatic cancer

Another plan conducted on rats suffering from induced hepatocarcinogenesis exposed thymoquinone dosage of four milligram per kg per day mixed with drinking water was capable to neutralize the hepatic carcinoma induced by diethylnitrosamine known as DENA. Mostly, thymoquinone brought back the biological and chemical worth and the distortion of hepatic cells due to liver carcinoma (Bimonte et al. 2019) Another experiment done to demonstrate the functions of thymoquinone against proliferation on rats tolerated hepatocarcinogenesis instigated through N-nistrodiethhylamine commonly known as NDEA, 0,01% with drinking water, thymoquinone slowdown cancer initiation process by imposing the G1/S phase cycle progression (Bimonte et al. 2019)

Pancreatic cancer

An inspection on rats with hepatic carcinoma elaborated the effect of thymoquinone against pancreas cancer. In the analysis of cell cycle profiles were checked through cytometric of PI stained cellular DNA content at 24 and 48 h after treating MiaPaCa-2 and AsPC-1 cells with thymoquinone (30 and 50 μM). After monitoring the genetic histograms, it proved the lump of dead cells within 24h.

By giving thymoquinone 30 μM, it was noticed that the percentage of apoptotic cells improved from twenty nine percent at forty eight hours. Thymoquinone acts as a multitarget agent, has a clinical will power to combat with cancerous cells (Relles et al. 2016).

Lung cancer

In a scientific investigation on human lung cancer, the A549 cells were handled by giving multiple quantities of thymoquinone for three days. Feasibility of cell was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide assay. Programmed cell death was noted during the analysis.

Thymoquinone reduced the feasibility and enhanced cell ability for programmed cell death in A549 human plural carcinoma cells. Management through thymoquinone outstandingly elevated the ratio of Bax/ Bcl-2 in the cells with plural carcinoma (Samarghandian et al. 2019).

Renal cancer

In another examination conducted to verify the effect of thymoquinone on hypoxic renal cancer noted that thymoquinone enhanced HIF-1α protein degradation. Thymoquinone suppressed the activities of transcription factors for cancer genes, such as nuclear factor-κB (NF-κB). On the other hand, thymoquinone deregulated the enzymes that aids metabolization of carcinogens, such as cytochrome p4501A2 (CYP 1A2) and cytochrome p450 3A4 (CYP 3A4) (Mostofa et al. 2017).

Thymoquinone has been appreciated as a new HIF-1α inhibitor. Thymoquinone-facilitated the suppression of angiogenesis through HIF-mediated VEGF Vascular endothelial growth factor expression. A research has shown that thymoquinone significantly down regulated the levels of proteins such as HIF-1α in the deoxygenated tumor cells of kidney. In a study on human cells with renal cancer, cell numbers after apoptosis were investigated through quantitative measures by the use of Muse™ Annexin V and Dead Cell kit. On temporary bases the cells of Caki-1 and A498 (1 × 105 cells/well) were incubated after seeding them for about twenty four hours. After the treatment with thymoquinone, the incubated cells were stained with reagents for duration of twenty minutes at room temperature. After analyzing it was noted that thymoquinone increased the population of apoptotic cells in which mostly were cancerous cells (Lee et al. 2019).

Prostate cancer

A scientific experiment was done to exhibit the effect of thymoquinone to suppress the expression of PC3 cells during prostate cancer. It was noted that thymoquinone significantly reduced the amount of PC3 cells after giving the treatment with specific dose of thymoquinone (623.63 μg/ml); catalase activity was efficiently reduced in PC3 cells by giving thymoquinone dose (Mahdy et al. 2020)

The results of a scientific work on prostate

cancer confirmed that the growth of prostate cancer DU145 and PC3 cells at a density >90% was remarkably suppressed with thymoquinone treatment at concentrations ≥10.0 μM (Kou et al. 2017).

Cervical cancer

One of the recent investigations on cervical cancer has proved consequences of thymoquinone for circulation of Siha and C33A cells measured by the MTT assay. By giving several quantities of thymoquinone (10-60μM) cancer cells were treated for twelve and twenty four hours. The study exhibited that thymoquinone noticeably decreased the feasibility of cancer.

Another experiment recognized the mechanisms of anticancer property performed by thymoquinone against cervical carcinoma by using HPV-16-positive cervical cancer cell line discovered that thymoquinone remarkably decrease the feasibility of both the C33A and Siha cells (Ichwan et al. 2014)

CONCLUSION

Thymoquinone which is an important component of black seed is an excellent molecule which has potential against cancer agents because it regulates many molecular mechanisms. It is also famous as therapeutic agent to treat different types of cancer. Due to its marvelous function it can be used as clinical trials, it can be used in nutraceuticals, in the form of mixture with other cancer preventing drugs. For the present, surveys of medical lab should continue so that scientists gain improved knowledge about whole mechanism of thymoquinone to target the cancer cells, also make sure the appropriate drug delivery system.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

ACKNOWLEGEMENT

This work was submitted in the partial fulfillment of the requirements for the Bachelor's degree in Human Nutrition and Dietetics for Afro Asian Institute Affiliated with Government College and University, Faisalabad.

AUTHOR CONTRIBUTIONS

Neelam Sabar, Rabia Shabbir conceptualization-Equal, writing-original draft-Equal. Neelam Sabar, Muhammad Imran writing original draft-Equal, writing-review & editing-equal

Saram Ali, Zara Batool writing-review & editing-Equal. Arooj Saeed, Awais Raza conceptualization-Equal,Writing-original draft-Equal. Saram Ali, Visualization-Equal. Rabia Shabbir, Arooj saeed writing-review 7 editing-Equal

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