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ROLE OF BLACK CUMIN'S ACTIVE COMPONENT-THYMOQUINONE IN CANCER

***Shahnai Basharat[1], Syed Amir Gilani[2], Muhammad Mustafa Qamar[3], Ayesha Basharat[3], Waqas Ahmad [3], Nyla Basharat[4]**

[1]University Institute of Diet & Nutritional Sciences, The University of Lahore;
[2]Dean, Faculty of Allied Health Sciences, The University of Lahore, Pakistan;
[3]Department of Allied Health Sciences, Sargodha Medical College, University of Sargodha, Pakistan;
[4]Research Assistant, University of Saskatchewan, Canada.

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Abstract:

Used for its medicinal properties from the early times, black cumin (Nigella sativa) has evolved to be a herb of great importance. Thymoquinone has come forth as significant phytochemical due to a range of beneficial constituents. The thymoquinone is having a positive impact against numerous ailments; black cumin has come to be of great importance by researchers in the field of Medical Nutrition Therapy (MNT). Thymoquinone showed to be useful not just as an anti-inflammatory, antidiabetic, antimicrobial, antibacterial, and antiseptic but also as a potent anticancer agent. Cancer becomes the second leading cause of death worldwide; it is an ever-increasing concern. By exhibiting strong antioxidant properties, thymoquinone has shown to have great potential against several cancers such as breast, lung, colon, gastric and bladder cancer. It is effective in inhibiting different stages of cancer such as invasion, migration and proliferation. Thymoquinone works against cancer through different modes of action. Its role is facilitated by different mechanisms such as apoptosis induction, anti-proliferation, anti-metastasis/anti-angiogenesis and cell cycle arrest. Its primary purpose is to reduce oxidative stress in order to bring about apoptosis of the cancer cells. Many studies have concluded that the anticancer effect of thymoquinone could be enhanced when it works in coordination with some chemotherapeutic agents and has also been found to minimize their lethal side effects. With more research, thymoquinone could become an integral part of not only a regular diet but also the pharmaceutical world in combating cancer.

Keywords: *Black Cumin, Nigella Sativa, Thymoquinone, Cancer*

Corresponding author:
Muhammad Mustafa Qamar,
Sargodha Medical College, University of Sargodha, Pakistan.
mmustafaqamar@gmail.com

QR code

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INTRODUCTION:

Herbal medicine has been used as a cure for multiple basic medical ailments by the majority of the population (about 80%) in developing countries. The reason would be that when compared to allopathic medicine, herbal medicine is non-toxic, harmless, inexpensive, easily available and most of all, effective. Nigella Sativa is an example of such medicinal plants.[1] Black Cumin or black seed, scientifically known as Nigella Sativa.[2] It cultivated popularly in the Middle Eastern Mediterranean region, Saudi Arabia, Iran, Turkey, Syria, Pakistan, Northern India, and Southern Europe. Nigella sativa seeds and their oils have quite a history of folklore usage in the form of food as well as medicine by the Arabian and Indian culture.[3] With quite a religious and historical importance, viewed as a miracle herb.[1]

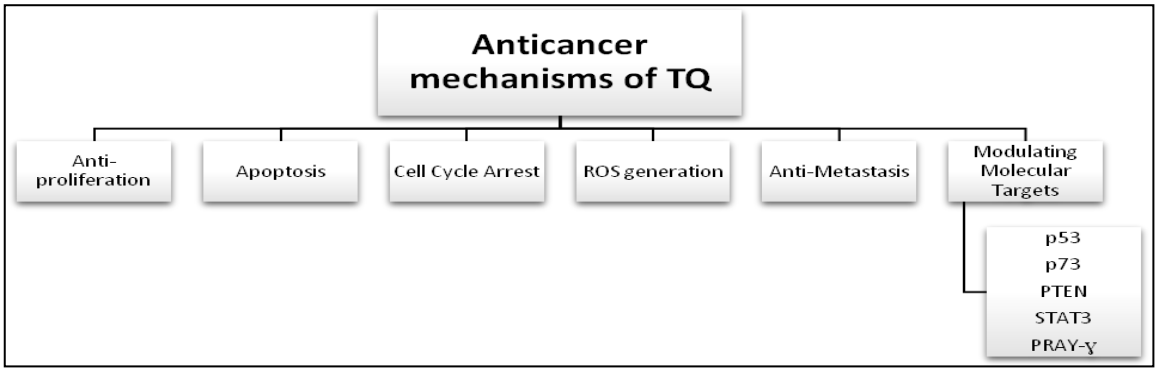
Nigella Sativa consists of a range of constituents including vitamins, minerals, carbohydrates, proteins (eight of the nine essential amino acids), oil and moisture. Among the constituents obtained from the volatile oil, thymoquinone is identified as the principal active component.[4]

Essential oils obtained from Nigella sativa is of great value due to its volatile oil composition of thymoquinone and monoterpenes including thymohydro quinone, thymoquinone, thymol, α pinene, and p-cymene. [4] Black cumin seeds also contain a terpene, diterpene, and triterpene alkaloids. Two types of alkaloids were identified from the methanolic extract of black cumin seeds while thymoquinone was the chief active component obtained from the crude oil of black cumin.[5]

The seeds of black cumin consist of unsaturated FA for example oleic acid (twenty %), eicosadienoic acid (three %) linoleic acid (fifty-five %), and dihomolinoleic acid (ten %), and saturated FA (like palmitic acid (fourteen %) and stearic acid (three %). N. sativa seeds have found to comprise of vitamins like niacin, ascorbic acid, folic acid, pyridoxine, and thiamine, plus crude oil, and some minerals, like P, Ca, Fe, Zn, Na, and Cu. Furthermore, some chemical compounds are said to be isolated from the seed oil of N.sativa that are steryl glucosides, free sterols,steryl esters, and acylatedsteryl glucosides.[6]

Black cumin is considered to stimulate menstruation and increase the production of milk in females.[7] Nigella sativa's antimicrobial actions were due to the presence of thymoquinone, thymohydroquinone, longifolene (sesquiterpenes), p-cymene (monoterpene).[8] There is a link between usage of black cumin and a significant decrease in the levels of triglycerides, and LDL-cholesterol.[9] Cancer commencement and progression has been linked with oxidative stress[10] caused due to cell proliferation, genome instability and a greater number of DNA mutations or induced DNA damage, and thus antioxidant agents might inhibit carcinogenesis.[11]

Studied indicate that diet represents 30-35% of the risk factors leading to cancer. Certain foods and dietary patterns have been associated with the danger of several cancers.[12] The existing epidemiological information is not reliable for several foods, and the relations with cancer risk remain uncertain.[13] In 2017, 1,688,780 new cancer cases and 600,920 cancer deaths were projected to occur in the United States. The cancer incidence rate is 20% higher in men than in women, while the cancer death rate is 40% higher.[14] Globally, lung cancer was diagnosed as most common cancer (11.6% of total cases) and also categorised as the leading cause of death. The statistic of female breast cancer is 11.6%, prostate cancer- 7.1%, colorectal cancer - 6.1%, stomach cancer - 8.2% and liver cancer 8.2%.[15] Breast cancer is the most common in Pakistan. Ten years of data from 2000-2009, about 28,740 cancer patients were evaluated in which 6,718 were of breast cancer, 46% were located in Lahore with age of 47 + 12 years, less than 1% were at stage 0 and 10, 32, 35, 23% were at stage I, II, III, IV. [16] Recent experimental researches show TQ to be a potent chemoprotective agent regarding its action in the suppression of tumour metastasis, growth and development for many cancers.[17] The cytoprotective and antioxidant properties of black cumin and TQ might be related to their beneficial actions along with their influence on the mediators of inflammation.[18,19]



Anticancer Mechanism of Thymoquinone: There are a large number of researches that have been done for the purpose to find out the effectiveness of thymoquinone on cancer cells by controlling some biological activities that play an active part in the pathogenesis of tumour cells. It has been found that a molecular target of thymoquinone that works in opposition to frequent cells causing cancer or retardation of the growth of cancerous cells. In the modulation of angiogenesis, protein kinase, tumorigenesis and nuclear factor-kappa B.[20] Thymoquinone works against cancer through different modes of action; its role is facilitated by different mechanisms such as ROS generation, apoptosis induction, anti-proliferation,anti-metastasis/anti-angiogenesis and cell cycle arrest. Moreover, thymoquinone has been found to work against cancer with the help of multiple molecular targets such as PPAR-activation of caspases, p53, PTEN, p73, RSS generation and STAT3.[21] Many studies have concluded that the anticancer effect of thymoquinone could be enhanced when it works in coordination with some chemotherapeutic agents and has also been found to minimize their lethal side effects.[22]

Constituents mainly responsible for cancer are the free radicals that are tremendously reactive species and are responsible for the breakdown of DNA strands; initiate the peroxidation of various compounds, cause protein damage hence leading to numerous health complications and some diseases such as accelerated ageing, inflammation, cancer, and atherosclerosis. Some plants such as N.sativa are known well for their potential anticancer elements, comprising of tannins, lignins, and flavonoids . These compounds play a very noteworthy role in health advancement.[23] Glutathione is regulated by N.sativa that prevents oxidative stress and hinders free radical production. Aerobic respiration produces radicals like superoxide (0_2), hydroxyl (0H), and hydrogen peroxide (H_2O_2) and their production is said to be decreased by black cumin.[24] ROS production produces excess harm to normal tissue of the patients going through radiation therapy. So black cumin extracts play a very significant role by protecting normal tissue from the damage that occurred during therapy. Hence, protection of DNA against damage and free radicals can be controlled by black cumin ethanolic extract. The products of thymoquinone prompt apoptosis in cancer cells. Changes in pro-apoptotic proteins and generation of ROS are carried out by thymoquinone. Thus it leads to the activation of caspase-dependent apoptosis - caspase-3 and caspase-9. [25] Cysteine-aspartic proteases or cysteine dependent aspartate-directed proteases (CASPASES) belongs to a family of cysteine proteases that are effective as catalysts for the necrosis, inflammation, and hydrolytic reactions of apoptosis. The main result of releasing pro-apoptotic proteins is the initiation of Caspase-9. Active effector caspases, effectors 7,6,3, cause the inactivation of proteins that play an important role in protecting living cells from apoptosis, for example, the DNA repairing protein.[26] The possible effects of thymoquinone on tumour suppressor gene p53is reported in a study. The growth suppression of tumour is caused by a specific gene called p53 gene. Mainly human cancers have been caused due to the functional loss of p53 gene.[27]

The term apoptosis is defined as the course of programmed cell death (PCD), mostly affecting dispersed cells relatively rather than every cell in a specific region. Thus, apoptosis could be defined as a gene-regulated phenomenon responsible for the changes of cells like nuclear fragmentation, cell shrinkage, alteration of the cell's morphology, chromosomal DNA fragmentation, global mRNA decay, and chromatin condensation. Apoptosis has a significant part in many autoimmune disorders' neurodegenerative diseases, and also in AIDS and cancer. Varying stimuli may induce apoptosis such as heat, anticancer drugs, radiation, ROS, and hypoxia.[26]

According to a study, black cumin was used to treat human ***breast cancer*** cells or to reduce the no of deaths caused by MCF-7 cells in breast cancer. Methanolic extract of black cumin was given to MCF-7 cells. Gene expression was also characterized for few apoptosis-related genes

(Caspase - 3, - 8, - 9 and p53 genes). 50 microliter and 100 microliters of black cumin were given to MCF-7 cells for 24 hr., 48 hr., 72 hr. moreover, examination was done with a microscope. Caspase - 3, - 8, - 9 and p53 genes was also increased according to time and dose. Black cumin induced cell death in MCF-7 cells. This result promotes further use of black cumin for breast cancer therapy.[28]

A study was conducted to study the cure of ***breast cancer*** or to reduce breast carcinogens in 90 female rats by treating it with thymoquinone (TQ). Female rats get 1, 4-Dimethyl-2, 3-benzphenanthrene dose (65 mg/kg) a day through the intra-gastric tube to induce breast cancer. For the treatment of these animals, the medication was given orally with 10 mg/kg of TQ. This medicine was given for three times a week for four months. From this experiment, it was concluded that TQ has a considerable effect in reducing or in treating breast cancer in female rats.[29]

A study conducted by Motaghed, addressed the anticancer of thymoquinone against human ***breast cancer*** cell lines MCF-7. MCF-7 cells were treated with TQ concentrations ranging from 25-300 micromoles/L for 24-72 hr. their growth rate was monitored. A substantial difference was noted between the untreated and treated cells by the MTT assay. Using Flow cytometry, the apoptotic percentage was analyzed. The minimal dosage of thymoquinone and long-term treatment presented significant inhibition of breast cancer cell.[30]

The anticancer actions of TQ were analyzed in a study conducted by Woo CC et al. on ***breast cancer*** cells. Western blot, annexin V-propidium iodide staining, and MTT assay were used to analyze the effects of TQ. After inducing with carcinogen for two weeks, mice were treated with 4-8mg/kg for 2 weeks. TQ was seen to not only suppress the growth of tumour but also to inhibit the anti-apoptotic gene of breast cancer cells. Therefore, the results indicated that TQ induced pro-apoptotic effects mediated through ROS generation.[21]

The effect of thymoquinone on ***breast cancer*** cells (MCF-7) was studied by Dasteerjee MCF-7 cells were cultured and treated with 25 micromol/L of thymoquinone for 24, 48 and 72 hr. Flow cytometry was used to perceive the percentage of apoptotic cells. The results showed that by the up-regulation of the p53 gene in breast cancer cells, thymoquinone could cause apoptosis.[31]

In a study, thymoquinone's effect as an important component in treating ***colon cancer*** was studied.48 rats were divided into six groups. Once a week for 18 weeks, they received carcinogen through subcutaneous injection. Treatment groups received a diet of 2-4% black cumin for 6 months results showed positive effects in the treatment of colon cancer cells.[32]

The aim of a study was to treat ***colon cancer*** by using TQ. In the study, TQ is used in a high amount to treat the colon cell line growth of 12 mice, identified by the immunoblotting method. Low amount of TQ throughout the process was given to the mice for 30 days. Amount of 20 micromol/L of thymoquinone was suitable for killing cancer cells of the colon. Conclusion for this experiment proves TQ is very effective in the apoptosis of colon cancer cells.[33]

Kundu J et al.; conducted a study to analyze the activity of TQ in reducing the human ***colon cancer*** HCT116 cells. The cell was treated with TQ (10-50 micromol/L) for 24 hrs. TQ triggered activation of caspase -9 -7 -3. Cells of colon cancer died due to TQ stopping the cleavage of caspase -3. Conclusion for this experiment was that TQ has a considerable effect against human colon cancer cell.[34]

Purpose of a study conducted was to analyze the action of TQ on topotecan (popular anticancer medicine for ***colorectal cancer***). After obtaining the optimal mix (0.6 micromol/L topotecan and 40 micromole/L thymoquinone), using the Western blot method, expression levels protein caspase -8, -3, -9, p21 and p53 were analyzed. Furthermore, propidium/annexin iodide and cell cycle analysis staining were done. Through the p53-independent mechanism, cell death occurred. In conclusion, the effectiveness of topotecan was increased by TQ through the inhibition of proliferation and decreasing the toxicity.[35]

A study was conducted on thymoquinone to treat *ovarian* ***cancer*** **cell** (Caov-3 cells). The inhibiting activity of TQ was regulated using methyl thiazolyl tetrazolium (MTT), and the cell death was inspect using flow cytometry. Cells of ovarian cancer were treated with TQ for 24hr., 48hr., and 72 hr. It was found that TQ triggers the pathway of apoptosis and cell oxidative pressure. The outcomes suggested that TQ might be a potential agent for ovarian growth medication improvement.[36]
Zhu conducted a study to study apoptosis of ***gastric cancer*** cells by thymoquinone treatment. Human gastric cancer cells were treated with TQ (0, 10, 100, 125 micromol/L). The time duration for this process was 12hrs, 24 hrs. Moreover, 36hrs, moreover, the growth rate was observed. Cell death was determined with flow cytometry. Apoptosis of gastric cells was perceived after Hoechst Staining. TQ cause the death in HGC27 cells, which were

seen by Annenin V-flourserinisothiocynamate (FITC) and Hoechst 33258. This study provided strong evidence that TQ induces apoptosis in gastric cancer.[37]A study was conducted to study the effect of thymoquinone on the treatment of ***bladder cancer*** cells. The cell of bladder cancer was inserted in 16 mice. After two weeks, mice divided into two groups (a) control, (b) TQ (5mg/kg daily by intragastric intubation). In the seventh week, the weight and inhibition of cancer cells were measured, and results were effective. Flow cytometry (FCM) was used to conclude the cellular apoptosis. Apoptosis rate induced by thymoquinone was more substantial than that of the control. Conclusion for this experiment was that TQ is effective against a cell of human bladder cancer.[38]

Further evidence of thymoquinone's anticancer activity was seen in a study conducted by Attoub S et al. demonstrating TQ's effect of ***lung cancer*** cells (LMN35). Mice were inoculated with LMN35 lung cells. They were then treated with 10mg/kg of TQ for 18 days. Results showed inhibition in tumour growth by 39%. This was capitalized by the increase in activated caspase -3. Hence, these demonstrations indicate thymoquinone as a potential anticancer agent in the future proceedings.[19]

CONCLUSION:

Cancer has become a leading cause of death worldwide. This article analysed the benefits exhibited by black cumin and its active component thymoquinone. In light of previous studies, the extensive thymoquinone impact in the improvement of cancer complications that helped to promote its use in targeting the different types of cancer and improve the overall health of cancer patients.

Dietary Element	Studied	Duration	Effect On Cancer	References
Thymoquinone (10 mg/kg)	LMN35 (mice)	18 days	Inhibited growth	Attoub S *et al.*,[19] 2013
Thymoquinone (4-8mg/kg)	Breast cancer cells	4 weeks	↓oxidative stress	Woo CC *et al.*,[21] 2013
Thymoquinone (50-100 microliter)	MCF-7 cells	24hr.,48hr.,72hr.	Induces apoptosis	Al Hazmi*et al.*,[28] 2014
Thymoquinone (65 mg/kg)	MCF-7 cells 90 female rats	3 times a week for 4 months	↓oxidative stress	Linjawi*et al.*,[29] 2015
Thymoquinone (25-300 micro mol/L)	MCF-7 cells (mice)	24-72 hr.	Induces apoptosis	Motaghed M *et al.*,[30] 2013
Thymoquinone (25 micro mol/L)	MCF-7 cells	24hr., 48hr., 72 hr.	Induces apoptosis	Dastjerdi MN *et al.*,[31] 2016
Thymoquinone (2-4% of diet)	Colon cancer cells (48 rats)	Once a week for 18 weeks	Induces apoptosis	Dadkhah Aa *et al.*,[32] 2014
Thymoquinone (20 micro mol/L)	Colon cancer cells 12 mice	30 days	Induces apoptosis	Hsu HH *et al.*,[33] 2014
Thymoquinone (10-50 micro mol/L)	HCT116	24 hr.	Induces apoptosis	Kundu J et al.,[34] 2014
Thymoquinone (40 micro mol/L)	Colon cancer cells	24 hr., 48 hr.	Induces apoptosis	Khalife R et al.,[35] 2016
Thymoquinone (0-50 microgram)	CaoV-3 cells	24 hr.,48 hr., 72 hr.	↓oxidative stress	Taha MM *et al.*,[36] 2016
Thymoquinone (0-125 micro mol/L)	Gastric cancer cells	12-36 hr.	Induces apoptosis	Zhu WQ *et al.*,[37] 2016
Thymoquinone (5mg/kg)	Bladder cancer cells (16 mice)	2 weeks	Induces apoptosis	Mu HQ *et al.*,[38] 2012

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