European Journal of Therapeutics
DOI: 10.5152/EurJTher.2017.368
Original Research

Investigation of the Protective Effects of Nigella Sativa Oil and Thymoquinone in Radiation Exposed Rats

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ABSTRACT
Objective: It is not always possible to treat early and late side effects due to radiotherapy. In this study, the effects of free radicals on the oxidant antioxidant system were investigated in comparison with the clinical use of WR-2721 in the prevention and treatment of side effects caused by free radicals.
Methods: According to the experimental protocol, rats were randomly assigned to five groups: Control Group (K; n=10), Radiotherapy Group (R; n=10), Nigella sativa oil Group (NSO; n=10; 2.4 g/kg/day), Nigella sativa oil+Radiotherapy Group (R+NSO; n=10; 60 min; 2.4 g/kg/day), Radiotherapy+Amifostine Group (R+WR-2721; n=10; 200 mg / kg / day; 60 min before 60 min. Radiotherapy was applied to the rats using radioactive cobalt-60 teletherapy machine in a single dose of 8 Gy to the whole body area as SSD 40 cm. The study was completed in 72 h following radiation application, and the rats were sacrificed by decapitation. Oxidative Stress Index (OSİ) Total Oxidative Stress (TOS) Total Antioxidant Status(TAS) malondialdehyde (MDA), nitric oxide (NO), myeloperoxidase (MPO), superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT) parameters were measured.
Results: According to these results, WR has more positive effects on MPO and CAT values when NSO on MDA values. There was no statistically significant difference in TOS, OSI, NO, TAS, SOD, CAT values between the R + NSO and K Groups. Compared to the R Group, TOS, OSI, NO, MDA levels significantly decreased and TAS, SOD, GSH, CAT levels significantly increased in the R+NSO Group.
Conclusion: In this study, we have shown that Nigella sativa oil is effective in radiation-induced damage on the liver oxidative stress and nitrosative stress. Further studies should be conducted to investigate different tissues, with different radiation intensities and different concentrations of Nigella sativa oil.
Keywords: Nigella sativa oil, cancer, radiation

INTRODUCTION

Cancer is the second highest cause of death in Turkey following cardiovascular diseases. Even though no concrete solution has been found for the disease, it is important to improve the effects of the progress of the disease, and increase, or at least improve, the quality of life (1).

Radiotherapy (RT) has been commonly and effectively used in the treatment of cancer for over a century. RT is mostly administered by using high energy photon rays and electron rays such as X rays or gamma rays. The objective of this treatment method is the elimination of tumor tissue, as well as the protection of normal tissue. Damage in the normal tissues is related to the sensitivity of that tissue to radiation, and it may not always be possible to treat it. The risk of complications increases as the dose is increased in RT. Besides this, the risk increases more as the critical organ volume within the treatment site increases. Each organ's resistance to radiation is different (2, 3).

The biological effects of radiation occur directly or indirectly in normal tissues. Direct effect is the effect of radiation directly on the target molecule DNA in the cell. Indirect effect, on the other hand, causes the formation of free radicals with the radiolysis of water molecules due to the effect of radiation. Anti-oxidants are the most effective components against free radicals (3, 4).

It may not always be possible to treat the early and late adverse effects that emerge as a result of radiotherapy. Researchers have used various agents that reduce the cellular toxicity of ionized radiation in normal tissues to prevent early and late complications caused by ionized radiation in organs such as the peripheral nerves, heart, bladder and kidney (5). It has been reported that compounds containing sulfur have the most protective effect. The most commonly investigated agent is aminothiol (cysteine, cystamine, WR-2721, glutathione) compounds. Amifostine demonstrates its effect by converting into WR-1065, which is its metabolite. It is pointed out in the literature that WR-2721 and

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Received: 25.01.2018 • **Accepted:** 12.02.2018

WR-1065, which are claimed to have selective cytoprotective effects in normal cells compared to cancer cells (6), are the most feasible radio-protectors for humans and have started to be used in the clinical setting (7).

Commonly known as black seed, Nigella sativa L. belongs to the Ranunculaceae family, and is an annually flowering plant that is grown commonly in many countries, mostly Eastern Mediterranean ones (8). Nigella sativa seeds consist of 0.4-0.45% essential oils, and more than 30% fixed oils. Thymoquinone (TQ) accounts for 18.4-24% of the essential oils. TQ's structure is 2-isopropyl-5-methyl-1.4-benzoquinone, and its molecular formula is $C_{10}H_{12}O_2$. It has been determined that Nigella sativa is made up of 22.6-26.7% protein, and 32.7-40.0% carbohydrates (9). In a study focused on articles written in English between 2000-2016 which was conducted on some popular search engines such as PubMed, Science Direct, Scopus and Web of Science, Nigella sativa (NS) and Trigonella foenum-graecum were the most frequently mentioned plants in the treatment of cancer (10).

In a review on the anti-oxidant, anti-inflammatory, anti-cancer, anti-diabetic, gastro-protective, hepato-protective, antimicrobial and antihistaminic effects of TQ, the main chemical compounds of the NS plant, a set of therapeutic benefits were emphasized under different *in vitro* and *in vivo* conditions (11).

Anti-cancer effects of TQ were observed in several preclinical studies where it was used for the diverse pharmacologic effects of NS (12). TQ prevents a wide range of tumorigenic processes, as well as carcinogenesis, malignant growth, invasion, migration and angiogenesis, due to its versatile nature (13).

Cisplatin (CP) is an effective anti-cancer drug that causes significant toxicity in the kidneys, the proximal tubules in particular, by producing reactive oxygen derivatives. It has an excellent content for use as functional food or combinatorial nutraceuticals in the CP chemotherapy to cure nephropathy accompanied by long-term NS and TQ cancer chemotherapy (12). In another study, it was shown to suppress metastatic phenotype, and reverse the epithelial mesenchymal transition (EMT) of the prostate cancer cells. These findings give rise to the idea that thymoquinone is a potential therapeutic substance against prostate cancer that acts by targeting the transforming growth factor-β (TGF-β) (14).

In this study, the effects of nigella sativa oil on the oxidant/anti-oxidant system have been examined, which have antitumoral, anti-inflammatory, anti-oxidant characteristics in the prevention and treatment of adverse effects created by free radicals. For this purpose, the potential protective effects of the nigella sativa oil were examined from oxidant parameters Oxidative Stress Index (OSİ) Total Oxidative Stress (TOS) malondialdehyde (MDA), nitric oxide (NO), myeloperoxidase (MPO) and anti-oxidant parameters superoxide dismutase (SOD), glutathione (GSH), catalase (CAT) and Total Antioxidant Status (TAS) in rats exposed to single dose of 8 Gy ionized radiation.

METHODS

Ethics committee approval was received for this study from the ethics committee of Gaziantep University Animal Experiments Local Ethics Committee with the decision no. 4/4 dated 06.02.2012.

The study was performed at the Gaziantep University Faculty of Medicine; Department Biophysics, Department of Physiology, Department of Biochemistry and Clinical Biochemistry and Oncology Hospital, Department of Radiation Physics.

Sprague Dawley 50 female rats weighing about 150-250 gr were used in this study, and divided into 5 groups.

Radiotherapy was administered to the whole body of these rats in a single dose at 8 Gy fraction with a Co 60 teletherapy device so that SSD was 40 cm.

Rats were quarantined at least one week before the radiotherapy. The care and feeding of rats were performed under 21±2°C ambient temperature, 55-60% moisture and 12:12 hours of light-darkness cycle conditions. The weight of the animals was 200±50 gr, and they were fed with standard rat food. In the examination conducted before the study, rats in a poor condition of health were excluded from the study.

In accordance with the study protocol, rats were randomized into a total of 5 groups, namely: Control Group (C; n=10), Radiotherapy Group (R; n=10), Nigella Sativa Oil Group (NSO; n=10), Nigella Sativa Oil+Radiotherapy Group (R+NSO; n=10), Radiotheapy+Amifostine (R+WR-2721; n=10).

The 1st Group (Control Group I): This control group was fed with normal feed and water for 72 hours.

The 2nd Group (Radiotherapy Group): Throughout Day 1, 0.25 mL normal saline was administered to these rats in this group intraperitoneally 30 minutes before a single dose of 8 Gray (Gy) radiotherapy. Then they were fed with normal feed and water for 3 days. At the end of Day 3, their blood and liver tissues were collected.

The 3rd Group (Nigella Sativa Oil Group): The rats in this group received 2.4 g/kg/day nigella sativa oil on Day 1 by means of gavage. They were fed with normal feed and water for 3 days. At the end of Day 3, their blood and liver tissues were collected.

The 4th Group (Nigella Sativa Oil + Radiotherapy Group): On Day 1, 2.4 g/kg/day nigella sativa oil was given to the rats in this group by means of gavage 60 minutes before a single dose of 8 Gy radiotherapy. Then they were fed with normal feed and water for 3 days, and at the end of Day 3, their blood and liver tissues were collected.

The 5th Group (Radiation+Amifostine Group) 200 mg/kg WR-2721 was administered intraperitoneally 30 minutes before a single dose therapy. Then they were fed with normal feed and water for 3 days. At the end of Day 3, their blood and liver tissues were collected.

Except for the control group, rats in other groups were anesthetized with 50 mg/kg/ip of ketamine and put on the radiotherapy

equipment in face down position. Radiotherapy was administered to the whole body of these rats in a single dose at 8 Gy fraction with a Co 60 teletherapy device so that SSD was 40 cm. The study was completed within 72 hours following radiotherapy, and then the rats were decapitated.

Surgical procedures of the study were carried out under sterile conditions and deep anesthesia. At the end of hour 72, 50 mg/kg/ip. Ketamine HCL (Ketalar) and 10 mg/kg Xylazin HCl (Rompun) mixture was administered intraperitoneally for anesthesia. Half of the liver tissue samples were spared for pathologic examination in a 10% neutral buffered formalin solution, and the remaining part was stored at -85°C for biochemical measurements.

The blood's 1000 g that was collected in the tubes without anti-coagulants was centrifuged at $^{+}4^{0}$C for 10 minutes after keeping at room temperature for 30 minutes. 1000g of blood samples collected in the tubes with heparin was centrifuged at $^{+}4^{0}$C for 10 minutes. Erythrocyte packages were prepared and portioned after separating the plasma, and kept at -85°C until the time of analysis.

Total antioxidant status, TOS, OSI, MDA, NO, MPO, SOD, CAT and GSH parameters were measured. Tests were performed on serum samples using the myeloperoxidase ELISA method. Glutathione, Superoxide Dismutase, Malondialdehyde, Nitrate, and Catalase were analyzed in the liver tissue on an ELISA reader using the colorimetric method. Total oxidant level was tested in the auto-analyzer device using spectrophotometric method. TAS and TOS were measured using the Rel Assay commercial kits. OSI which is considered as an indicator of Oxidative Stress is expressed in percentage ratio of TOS and TAS. MDA was measured with colorimetric method at 532 nm using Cayman commercial kit (item no: 10009055). Results were expressed in nmol/mL. SOD was measured with colorimetric method at 450 nm using Cayman commercial kit (item no: 706002). Results were expressed in U/mL. Nitrate was measured with colorimetric method at 540 nm using Cayman commercial kit (item no: 780001). The results were expressed in μM. Myeloperoxidase was determined with ELISA method at 405 nm using the Immundiagnostik (REF K 6631B) commercial kit. The results were expressed in ng/mL.

RESULTS

In the comparison of R and C groups, it was seen that TOS, OSI, NO, MDA, and MPO parameters increased in a statistically significant manner, whereas TAS, SOD, GSH, CAT levels decreased.

In the NSO group, MPO levels increased, creating a significant difference as compared to the C group. SOD decreased in the R+WR group in a statistically significant manner as compared to the C group.

Total antioxidant status, GSH and OSI a value was observed between the C and R groups in NSO, R+NSO and R+WR groups, respectively. This value shows a statistically significant difference between the two groups. Similar MDA results were obtained in NSO, R+NSO, R+WR groups.

According to the comparison with R+NSO group, there was a decrease in CAT values in NSO and R+WR groups. When compared to the R+NSO group, MDA was higher and MPO was lower in the R+WR group. However, MDA and OSI parameters were lower and TAS parameter was higher in the NSO group as compared to the R+NSO group. These changes show a statistically significant difference.

In the comparison between R+NSO and C groups, GSH was lower in R+NSO whereas MPO and MDA were lower in C group. These values show a statistically significant difference. TOS, OSI, NO, TAS, SOD, and CAT values did not demonstrate a statistically significant difference in the R+NSO group compared to the C group.

In the comparison between R+NSO and R groups, it was seen that TOS, OSI, NO, MDA parameters decreased in a statistically significant manner whereas TAS, SOD, GSH, CAT levels increased in the R+NSO group. No statistically significant difference was seen in MPO value in the R+NSO group as compared to the R group (Table 1).

Table 1. Mean TAS, TOS, OSI, NO, MPO, CAT, GSH, SOD, MDA levels in experiment and control groups (Mean±SD)

	C	R	NSO	R+NSO	R+WR
TAS	1.15±0.09	0.81±.04[a,c]	1.31±0.15[a,b,c]	1.04±0.14	1.02±0.18
TOS	24.79±1.73	37.87±3.6[a,c]	24.97±1.35	25.37±1.43	27.38±1.11
OSI	21.67±2.22	46.82±4.49[a,c]	19.24±3.03[c]	24.78±4.48	27.62±5.41[a,b]
SOD	0.73±0.01	0.67±0.01[a,c]	0.73±0.008	0.72±0.02	0.7±0.02a
NO	1.05±0.13	1.39±0.12[a,c]	1.03±0.12	1.14±0.07	1.19±0.21
GSH	57.53±1.49[c]	45.81±1.53[a,c]	57.06±2.78	52.83±4.86[a,b]	56.69±4.6
MPO	0.77±0.13[c]	1.43±0.52[a]	1.14±0.17a	1.32±0.19[a]	0.92±0.06[c]
CAT	228.74±5.81	192.66±3.64[a,c]	230.96±1.74[c]	223.55±6.11	234.84±1.73[a,b,c]
MDA	32.74±1.04[c]	48.1±1.5[a,c]	28.68±0.75[a,b,c]	35.7±1.91[a,b]	44.28±1.43[a,b,c]

[a]p<0.05: In comparison to C group, [b]p<0.05: In comparison to R group, [c]p<0.05: In comparison to R+NSO group
TAS: total antioxidant status; TOS: total oxidative stress; OSI: oxidative stress index; NO: nitric oxide; MPO: myeloperoxidase; CAT: catalase; GSH: glutathione; SOD: superoxide dismutase; MDA: malondialdehyde

DISCUSSION

Various agents that reduce the cellular toxicity of ionized radiation in normal tissues have been used before application to prevent early and late complications caused by ionized radiation in organs such as peripheral nerves, heart, bladder and kidneys (15).

WR-1065 is an aminothiol that has selective cyto-protective effects in normal cells as compared to cancer cells, and used for protection of tissues against the harmful effect of chemotherapy drugs (8).

In a study, radiation-related harmful effects of 2- (3-aminopropylamino) ethylsulphonyl phosphonic acid (WR-2721) and peptidoglycan (PGN) on the intestines and bone marrow peptidoglycan both as a single agent or a combination therapies. WR-2721 was given in a dose of 3 mg per rat 30 minutes after the 10 Gy radiation, and 30 ug PGN per rat was injected intraperitoneally 24 hours after radiation. Application of WR-2721 with PGN had both a re-increasing effect in hematopoietic and intestinal cells, and a synergistic effect on survival in rats exposed to radiation, however it caused a certain degree of disorder in immunity (16).

The studies conducted showed the antibacterial, anti-inflammatory immunomodulator, gastroprotective antiviral (11), antiasthmatic (17), antidiabetic (18), antihelminthic (19), antifungal (20), antitumoral (21), antihistaminic (22) effects of the nigella sativa.

As the main bioactive compound of nigella sativa, Thymoquinone shows an anti-cancer activity via various mechanisms of action by intervening with the DNA structure that shows a selective antioxidant and oxidant activity, and affecting the carcinogenic signal molecules/pathways, paths and immunomodulation. In vitro activity of thymoquinone was affected more in animal cancer models; however there has not been any proven clinical practice yet (23).

In our study, MDA and CAT values rose in a statistically significant manner in the R+WR group as compared to the R+NSO group. MPO value, on the other hand, decreased in a statistically significant manner. According to these results, in the comparison of NSO and WR, NSO was effective on the MDA value, but WR created more positive effects on the MPO and CAT values.

In a study, antioxidant, blood pressure-decreasing diuretic characteristics of NS and its active compounds were investigated (24).

In some models, it led to a hepatoprotective effect on liver toxicity. Effects of NSO were investigated on rats infected with Schistosomiasis Mansoni in a study. Two doses of oil was given (2.5 and 5 mL, two weeks, oral / kg) in a single dose or combination with Praziquantel (PZQ) which is preferred in the treatment of schistosomiasis.

The role of nigella sativa against the changes caused by S. mansoni infection is thought to be partly due to its antioxidant effect, and the improvement of immunologic main system (25).

Additionally, nigella sativa has been shown to have antioxidant, anti-inflammatory and anti-ulcer activity under various conditions. In a study, the effects of an extract containing nigella sativa fluid on gastric acid secretion were investigated in isolated rat stomachs. It was supported that nigella sativa has a gastroprotective effect since it decreases the gastric acid secretion (26).

In a study on the antioxidant effects of nigella sativa against the effects of radiation on rat tongues, oxidative stress index, total oxidant state and lipid hydroperoxide levels were statistically higher in R group, C, CN (sham) and RN groups. It has also been emphasized that NS oil might be a beneficial substance in the protection against isolated radiation therapy-induced tissue damage (27).

In a study, rats were orally given NSO at a dose of 1 g/kg/day 1 hour before the 5 gray radiation for 10 days, and NSO was concluded to have antioxidant effects that increase the antioxidant capacity in the liver tissue of rats, and to be effective on reduction of oxidative stress indicators (28).

In our study, 2.4 g/kg/day nigella sativa oil was given to the R+NSO group by means of gavage 60 minutes before a single dose of 8 Gy radiotherapy on Day 1. In the comparison of R and C groups, it was seen that oxidative stress indicators, TOS, OSI, NO, MDA, MPO parameters increased in a statistically significant manner whereas levels of antioxidant parameters TAS, SOD, GSH, CAT decreased in R group.

In an article on the effects of nigella sativa on the treatment and complications of diabetes, it was stated that nigella sativa and its compounds decrease the oxidative and nitrosative stress, increase the antioxidant capacity, and thus reduced the diabetic complication risks (29).

A single dose was administered in our study at a fraction of 8 Gy. While NO levels increase remarkably in the RO group as compared to the C group, there was some decrease in the R group as compared to R+NSO group; however, no statistically significant difference was seen.

In a study on rats investigating the effects of NSO pre-treatment on the ethanol-related hepatoxicity, hepatic MDA levels were observed to have decreased, but an increase was seen in GSH levels (30).

Similar to the study mentioned, GSH was lower and MDA was higher in a manner to demonstrate a statistically significant difference in the R group as compared to the R+NSO group in our study. According to the comparison with R+NSO group, CAT and TAS values were higher in the NSO group. However, MDA and OSI parameters decreased in the NSO group. These changes show a statistically significant difference.

Besides, TOS, OSI, NO, TAS, SOD, CAT values did not demonstrate a statistically significant difference in the R+NSO group in our study as compared to the C group. In the comparison of R+NSO and R groups, it was seen that TOS, OSI, NO, and MDA parameters decreased in a statistically significant manner whereas TAS, SOD, GSH, and CAT levels increased in the R+NSO group.

Nigella sativa was observed to create clear changes in GSH and MDA parameters. According to our overall results, we think that nigella sativa is effective on TAS, TOS, NO, MPO and SOD parameters by decreasing the oxidative stress and supporting the increase in antioxidants.

CONCLUSION

Damaging and eliminating the tumor tissue are the main problems in treating common diseases such as cancer. The main factor that accompanies this problem and makes the treatment process difficult is the protection of healthy tissue against the damages of radiation. This study showed that nigella sativa oil is effective on the radiation-induced damage in the liver in case of oxidative stress and nitrosative stress. It would be worth conducting further studies with different tissues, different radiation severities, and different Nigella sativa oil doses.

Ethics Committee Approval: Ethics committee approval was received for this study from Gaziantep University Animal Experiments Local Ethics Committee with the decision no. 4/4 dated 06.02.2012.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.D.; Design - C.D.; Supervision - C.D.; Resources - C.D., H.G.; Data Collection and/or Processing - M.A., C.D.; Analysis and/or Interpretation - M.A., M.T.; Literature Search - H.G.; Writing Manuscript - C.D., H.G.; Critical Review - C.D., H.G.

Acknowledgements: We would like to extend our gratitude to the Gaziantep University Scientific Research Projects Management Commission for their support.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: This project was supported by the Gaziantep University Scientific Research Projects Management Commission through TF.13.07 [d6] project.

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How to cite:

Demirel C, Gözen H, Akan M, Tarakçıoğlu M. Investigation of the Protective Effects of Nigella Sativa Oil and Thymoquinone in Radiation Exposed Rats. Eur J Ther 2018; 24(4): 224–8.