ORIGINAL ARTICLE

# The Influence of *Nigella sativa* on the Increase of IFN-γ and Quality of Life in Lung Cancer Patients Undergoing Chemotherapy

**Reza Aditya Mahendra[1]*, Suryanti Dwi Pratiwi[1], Teguh Rahayu Sartono[1], Sastia Rakhma[2], Nanik Setijowati[3]**
[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
[2]National Cheng Kung University, Tainan, Taiwan
[3]Department of Family Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.

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**ABSTRACT**

**Introduction:** In vitro and animal model studies have shown that *Nigella sativa* reduces cancer cell proliferation and improves chemotherapy effectiveness. Cellular activation triggers the production of IFN-γ by natural killer (NK) cells. This study examined the effect of *Nigella sativa* supplementation on IFN-γ levels and quality of life in lung cancer patients before and after interferon therapy.
**Methods:** This study used a non-equivalent control experimental design involving 21 lung cancer patients undergoing initial chemotherapy at Dr. Saiful Anwar General Hospital, Malang, in 2023. The patients were divided into two groups: one group received standard chemotherapy, and another group received a combination of chemotherapy and *Nigella sativa* supplementation at a dose of 2x500 mg for nine weeks. The effects of this intervention were assessed by measuring IFN-γ levels using an enzyme-linked immunosorbent assay (ELISA) kit and evaluating quality of life using the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QLQ-C30) questionnaire before and after the fourth cycle of chemotherapy.
**Results:** The results showed a significant increase in IFN-γ levels in the combination group undergoing chemotherapy and receiving *Nigella sativa* supplementation (6140.44±2233.89) compared to the standard chemotherapy group (3827.08±1722.79), with a p-value of 0.015. Quality of life improved in both groups, with scores of 53.70±6.05 before and 65.74±14.70 after chemotherapy (p=0.000).
**Conclusion:** This study found that *Nigella sativa* supplementation can enhance IFN-γ levels and quality of life in lung cancer patients after four chemotherapy treatment cycles. These findings indicated that *Nigella sativa* could be a beneficial supplement for lung cancer patients.

## INTRODUCTION

Cancer is a global disease that is characterized by the transformation of normal cells into tumor cells through various stages of development, ranging from precancerous conditions to cancer.[1] Lung cancer is the most significant cause of cancer-related death in both males and females globally.[2] The high mortality rate associated with lung cancer is often attributed to delayed diagnoses, as many new cases are detected at advanced stages.[3]

The quality of life of cancer patients reflects their ability to perform daily activities, including physical, psychological, and social functions, as well as its impact on their professional lives.[4] It is significantly influenced by the type of cancer and the treatment they receive, particularly in relation to physical function and the levels of fatigue they experience.[5] The side effects of chemotherapy can reduce health-related quality of life, making the selection of an appropriate chemotherapy regimen critical to improving therapy effectiveness.[6,7] Evaluating the quality of life of patients with chronic diseases is crucial for outpatient, inpatient, and rehabilitation patients.[8] To facilitate this, the National Institute of Cancer and the European Organization for Research and Treatment of Cancer (EORTC) has developed the EORTC Core Quality of Life (QLQ-C30) questionnaire, which has been used in various clinical

*Corresponding author: rezaadityam@student.ub.ac.id

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trials.[9]

Various immune cells in the human body can recognize and eliminate tumor cells. Among these, natural killer (NK) cells play a role in identifying and destroying tumor cells by rapidly reducing MHC-I expression through a "missing self" recognition process. Additionally, NK cells release various cytokines and chemokines, such as IFN-γ, IL-10, CCL3, CCL4, and CCL5, which link the innate and adaptive immune systems to enhance the immune response against cancer.[10] In particular, IFN-γ plays a crucial role in improving the ability of NK cells to recognize and kill cancer cells.[11] High levels of IFN-γ production by NK cells and the presence of NKp30 are associated with favorable prognosis for long-term survival in cancer patients.[10]

Despite remarkable efforts to discover methods for controlling and curing cancer, millions of people continue to succumb to various types of cancer annually. Over the past century, medical science has significantly advanced to prevent this disease, yet a universally effective treatment remains elusive. In the search for innovative therapies, scientists are now integrating traditional and herbal medicines with modern treatment approaches. One promising traditional remedy is black cumin (*Nigella sativa*), which has been used for medicinal purposes for centuries.[12]

Thymoquinone, an active compound found in black cumin, has been studied for its potential anticancer effects. This compound works by inducing cancer cell death, obstructing the formation of new blood vessels that supply tumors with nutrients, and reducing inflammation and oxidative stress that contribute to cancer cell growth.[13] Thymoquinone exhibits immunomodulatory and anti-inflammatory effects by inactivating cytokines such as interleukins (IL-5, IL-4) and interferon-gamma (IFN-γ).[1]

Based on the aforementioned background, evaluating the quality of life of cancer patients undergoing chemotherapy using the EORTC QLQ-C30 questionnaire and using the traditional medicine *Nigella sativa* is necessary. This study assessed the impact of chemotherapy on cancer patients' quality of life. Additionally, this study examined the potential of *Nigella sativa*, specifically thymoquinone, in supporting cancer therapy by reducing chemotherapy side effects and improving patients' quality of life. This study provided new insights into cancer treatment approaches combining conventional medicine to enhance patients' overall well-being.

## METHODS

The sample consisted of patients with lung cancer at Dr. Saiful Anwar General Hospital, Malang, who had not previously undergone chemotherapy and met the inclusion and exclusion criteria. The inclusion criteria were patients aged 18 years and older with a diagnosis of primary lung cancer at stages IIIB, IVA, and IVB who were willing to participate in this study and provided informed consent. The exclusion criteria comprised patients with primary lung cancer originating from outside the lungs, those who had previously undergone chemotherapy, those who were pregnant or breastfeeding, and those with limitations that hindered data collection.

All experimental procedures were approved by Dr. Saiful Anwar General Hospital, with certificate number 400/063/K.3/102.7/2024. This study was conducted from August to November 2023. The patients were divided into two groups: the first group was the control group that received standard lung cancer therapy (chemotherapy), and the second group was the treatment group that received a combination of chemotherapy and oral intervention with *Nigella sativa* capsules. This study lasted nine weeks, and outcomes were assessed using the computed tomography (CT) Response Evaluation Criteria in Solid Tumors (RECIST). Additionally, the function of NK cells was assessed by measuring IFN-γ levels before the intervention (H0) and nine weeks after the intervention (H84). Blood serum samples were collected at the end of the treatment period, and IFN-γ levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit by Elabscience® (USA, Catalog No E-EL-H10108).

Patients' quality of life was assessed using the EORTC QLQ-C30 questionnaire, translated and validated in Indonesia for research purposes involving cancer patients in Indonesia. This questionnaire consists of 30 items that include five functional scales (physical function, role function, emotional function, cognitive function, and social function), three symptom scales (fatigue, pain, and nausea or vomiting), one scale measuring global health status or overall quality of life, and six single items addressing various symptoms (shortness of breath, insomnia, loss of appetite, constipation, diarrhea, and the impact of financial difficulties).[14] The EORTC questionnaire evaluates four criteria, namely the EORTC functional score (FS), the EORTC symptom score (SS), the EORTC global health score (GHS), and the EORTC lung cancer score (LCS).

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26. The Shapiro-Wilk was used to evaluate the normality of the data. A paired t-test was used for normally distributed data, while non-normally distributed data used the Wilcoxon test, with a significance level of $p \leq 0.05$. To evaluate the effect of black cumin administration on IFN-γ levels and quality of life, a multivariate analysis of variance (MANOVA) was conducted.

## RESULTS

This study involved 21 patients divided into two groups: the treatment group (12 individuals; 57.1%) and the control group (9 individuals; 42.9%). Most of the respondents in this study were males (57.1%), with an average age of 59.14±8.83 years old. The three most common occupations among the respondents were housewives (33.3%), private employees (19%), and retirees (14.3%). Most respondents did not have comorbid diseases (78.2%). Among the five patients with comorbid diseases, most had a single type of comorbid disease (76.2%). Additionally, most patients (81%) had controlled lung cancer, and the majority (52.4%) did not smoke. Of the 10 patients who smoked, most smoked 12 cigarettes per day (70%) and had smoked for an average of 13.18±16.04 years. Based on histopathological examination, the most common type of cancer among the respondents was non-small cell lung carcinoma, which includes adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and adenosquamous carcinoma.

**Table 1.** Demographic profile of the patients

| Characteristics | Mean±Standard Deviation | Min-Max |
|---|---|---|
| Age (years old) | 59.14±8.83 | 45.00-78.00 |
| Smoking duration (years) | 13.81±16.04 | 0.00-40.00 |
| **Characteristics** | **Frequency** | **Percentage (%)** |
| Group | | |
| Treatment | 12 | 57.1% |
| Control | 9 | 42.9% |
| Sex | | |
| Male | 12 | 57.1% |
| Female | 9 | 42.9% |
| Occupation | | |
| Retired | 3 | 14.3% |
| Housewife | 7 | 33.3% |
| Private employee | 4 | 19.0% |
| Trader | 2 | 9.5% |
| Teacher | 2 | 9.5% |
| Civil servant | 1 | 4.8% |
| Construction worker | 1 | 4.8% |
| Indonesian National Armed Forces | 1 | 4.8% |
| Comorbid disease | | |
| Absent | 16 | 76.2% |
| Present | 5 | 23.8% |
| Number of comorbid diseases | | |
| One type of comorbidity | 4 | 80% |
| Two types of comorbidities | 1 | 20% |
| Three types of comorbidities | 0 | 0.0% |
| Control | | |
| Controlled | 17 | 81.0% |
| Not controlled | 4 | 19.0% |
| Smoking history | | |
| Smokers | 11 | 52.4% |
| Non-smokers | 10 | 47.6% |
| Number of cigarettes per day | | |
| Six cigarettes/day | 2 | 20.0% |
| Ten cigarettes/day | 1 | 10.0% |
| Twelve cigarettes/day | 7 | 70.0% |
| Anatomical pathology | | |
| Small cell lung cancer | 4 | 19.0% |
| Non-small cell lung cancer | 17 | 81.0% |

**Comparison of Quality of Life between the Treatment and Control Groups**

This study observed an increase in the average score of the EORTC QLQ-C30 questionnaire after the administration of black cumin. Comparative analysis conducted using the t-test and Wilcoxon test yielded a p-value of less than 0.05, indicating a significant improvement in the quality of life among lung cancer patients receiving black cumin supplementation. The EORTC questionnaire assessed four criteria: the EORTC FS, the EORTC SS, the EORTC GHS, and the EORTC LCS.

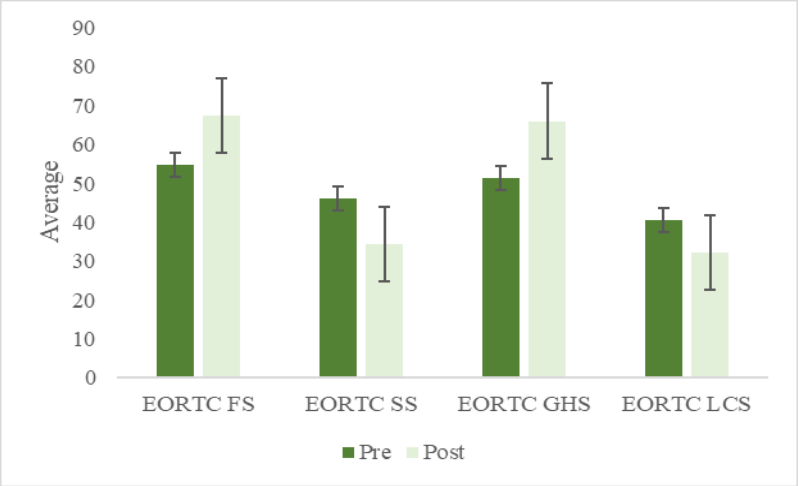


**Figure 1.** The European Organization for Research and Treatment of Cancer (EORTC) in the control group. EORTC functional score (FS) refers to the quality of life based on individual functioning; EORTC symptom score (SS) refers to the quality of life based on individual symptoms; EORTC global health score (GHS) refers to the quality of life based on overall condition; and EORTC lung cancer score (LCS) refers to the quality of life based on lung cancer-specific symptom.

In the control group, significant changes were observed between the pre- and post-intervention assessments. The EORTC FS and EORTC GHS scores increased from 54.78 to 67.41 and from 51.39 to 65.97, respectively, indicating improvements in function and quality of life. On the other hand, the EORTC SS and EORTC LCS scores decreased from 46.15 to 34.39 and from 40.5 to 32.17, respectively, indicating a reduction in symptoms and cognitive issues. These findings suggested an overall improvement in various aspects of health after the intervention (Figure 1).

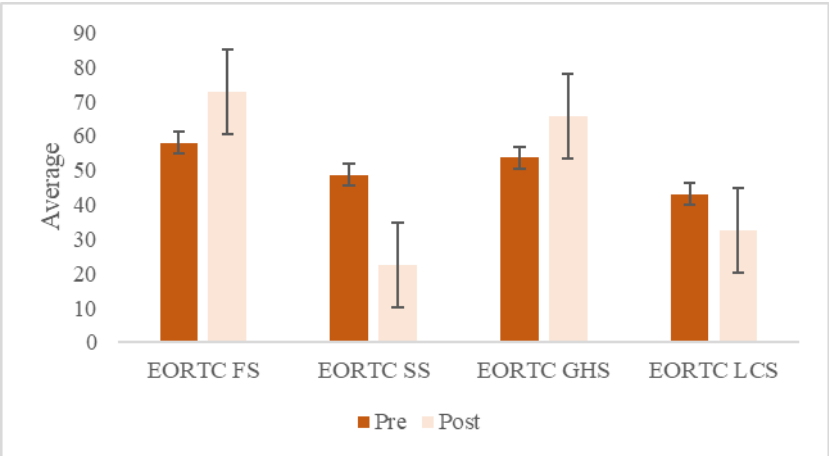


**Figure 2.** The European Organization for Research and Treatment of Cancer (EORTC) in the treatment group**.** EORTC functional score (FS) refers to the quality of life based on individual functioning; EORTC symptom score (SS) refers to the quality of life based on individual symptoms; EORTC global health score (GHS) refers to the quality of life based on overall condition; and EORTC lung cancer score (LCS) refers to the quality of life based on lung cancer-specific symptom.

Similarly, significant changes were observed between the pre- and post-intervention in the treatment group. The EORTC FS and EORTC GHS scores increased from 58.03 to 72.72 and 53.7 to 65.74, respectively, indicating improved function and quality of life. Meanwhile, the EORTC SS score dropped significantly from 48.71 to 22.5, indicating a significant reduction in symptoms. The EORTC LCS score decreased from 43.1 to 32.4, indicating improved cognitive issues. These findings suggested an overall improvement in various aspects of health after the intervention (Figure 2).

### Comparison of IFN-γ Levels between the Treatment and Control Groups

Comparative analysis of IFN-ɣ levels before the administration of black cumin between the control and treatment groups yielded a p-value of 0.654 (p>0.05), indicating no significant differences in IFN-ɣ levels between the two groups. However, after the administration of black cumin, a comparative analysis of IFN-ɣ levels between the control and treatment groups yielded a p-value of 0.015 (p<0.05), indicating significant differences in IFN-ɣ levels between the two groups.

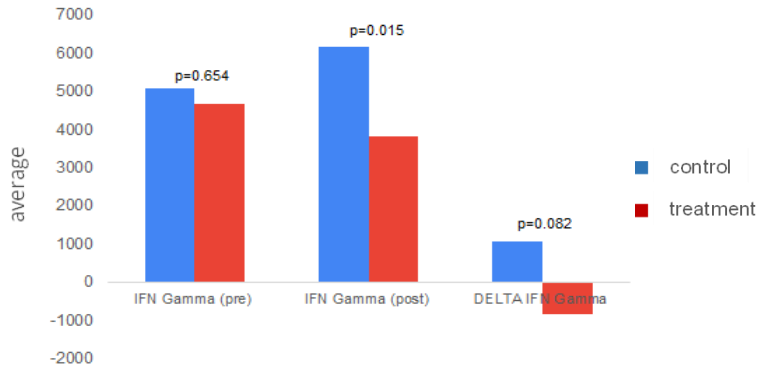


**Figure 3.** Comparison of IFN-γ levels**.** Delta IFN-ɣ represents the difference between IFN-ɣ levels pre- and post-intervention.

## DISCUSSION

### Demographic Profile of the Patients

In this study, most respondents were males (57.1%), with no significant difference between males and females. This finding is consistent with a previous study showing that 68.52% of lung cancer patients were males.[15] Males are at approximately twice the risk of being diagnosed with lung cancer due to smoking, although the prevalence among females is gradually increasing.[16,17]

The average age of the respondents was 59.14±8.83 years old. Lung cancer is most commonly found in the 51-60 years old age group.[18] It typically occurs after several decades of smoking and can be influenced by biological aging, telomere shortening, and diminished cellular deoxyribonucleic acid (DNA) repair capacity. In terms of occupation, this study found that housewives (33.3%), private sector employees (19%), and retirees (14.3%) were the most common types of occupation. Occupational and environmental exposures were identified as significant etiological factors in lung cancer development, particularly indoor air pollution, which poses a primary risk for non-smoking females in Asia. This factor is associated with high-temperature cooking methods, unrefined cooking oils, and poor home ventilation. Epidemiological studies also indicated that proximity to pollution sources can increase the risk of lung cancer.[18–20]

The majority of respondents (78.2%) did not have comorbidities. This finding contrasts with a previous study indicating that 67% of lung cancer patients had comorbid conditions.[21] Common comorbidities included hypertension, chronic obstructive pulmonary disease (COPD), and diabetes. This contrasting result may be attributed to differences in the age distribution of patients.[22,23] Comorbidities are associated with lung cancer survival as they can obscure symptoms, lead to delayed diagnosis, and affect therapy choices.[21,22]

In addition, the majority of respondents (52.4%) were non-smokers, although lung cancer rates are also increasing among non-smokers. Passive smoking, air pollution, and infections such as tuberculosis can elevate the risk of lung cancer.[24,25] In this study, 47.6% of respondents were smokers, with 70% smoking 12 cigarettes per day. Tobacco contains numerous carcinogens that can damage DNA.[16,17]

Based on histopathological examination, the most commonly identified cancer type was non-small cell lung cancer/NSCLC (81.0%). Lung cancer is divided into two main groups, with NSCLC accounting for 85% of all cases. Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR) mutations are the most prevalent, particularly in adenocarcinoma, which is commonly found among East Asian ethnicities and females.[18,26,27]

### *Nigella sativa* and Quality of Life

This study demonstrates an improvement in the quality of life following the administration of *Nigella sativa* to lung cancer patients. Although no specific studies directly address this issue, existing research has yielded varied results. For instance, Irmak, *et al.* (2019) reported that *Nigella sativa* did not enhance the quality of life of cancer patients undergoing chemotherapy.[28] Conversely, Afhsar, *et al.* (2023) found that administering 5 grams of *Nigella sativa* daily could reduce febrile neutropenia, shorten hospital stays, and improve the quality of life of children with brain tumors.[29]

Alternative medicines and supplements, including *Nigella sativa*, may also enhance the quality of life of lung cancer patients by providing a sense of calm and increasing motivation for treatment adherence. Furthermore, *Nigella sativa* has beneficial effects on conditions such as osteoarthritis, attributed to its anti-inflammatory properties, mainly through thymoquinone. However, according to Bodaghi, *et al.* (2019), *Nigella sativa* did not enhance the quality of life of patients with ulcerative colitis, which differences may influence dosage.[29–31]

### *Nigella sativa* and IFN-γ Levels

This study observed an increase in average IFN-γ levels following the administration of *Nigella sativa*, although this was not statistically significant. A decrease in host immunosurveillance capability is believed to contribute to cancer progression. IFN-γ is a cytokine with antiviral, antitumor, and immunomodulatory functions, playing a crucial role in regulating immune responses. In the tumor microenvironment (TME), IFN-γ regulates antitumor immunity by inducing apoptosis in tumor cells through interactions with granzyme B and perforin.[32,33]

Various cytokines and tumor antigens stimulate IFN-γ production. *Nigella sativa* exhibits anti-inflammatory and immunomodulatory effects that can enhance T cell populations and increase IFN-γ levels. The active compound thymoquinone in *Nigella sativa* acts as an immunomodulator by inhibiting enzymes involved in arachidonic acid metabolism. Studies indicated that *Nigella sativa* could elevate IFN-γ levels and had the potential to inhibit carcinogenesis.[32,33]

The administration of ethanol extracts of *Nigella sativa* at specific doses can enhance IFN-γ levels, and combinations with *Curcuma xanthorrhiza* further increase IFN-γ secretion. The rise in IFN-γ levels is associated with increased cytotoxic activity of NK cells. Additionally, macrophages can produce IFN-γ in response to certain stimuli.[32,34] Furthermore, granzymes A and N-acetyl-β-D-glucosaminidase, two crucial enzymes involved in target cell death, were released more significantly when NK cells were treated with *Nigella sativa* extract. These findings suggested that *Nigella sativa* increases the cytotoxic capacity of NK cells, potentially facilitating immune system modulation. This helps to explain the anticancer properties of *Nigella sativa*, which have been observed both in vitro and in vivo.[35]

This study has a limitation, namely administering the same dosage of black cumin to all patients, making it impossible to determine the dose-effect relationship between *Nigella sativa*, IFN-γ levels, and quality of life.

## CONCLUSION

The results indicated that combining chemotherapy and *Nigella sativa* (black cumin) supplementation significantly enhanced IFN-γ levels and the quality of life in lung cancer patients compared to the group undergoing chemotherapy. These findings highlighted the potential of *Nigella sativa* as an adjuvant in cancer therapy and paved the way for further research to understand its mechanisms of action and long-term benefits in lung cancer management.

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### Conflict of Interest

The authors declared there is no conflict of interest.

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### Authors' Contributions

Drafting the manuscript: RAM, SDP, TRS, NS. Collecting data, analyzing data, and preparing the manuscript: RAM, SDP. Compiling the research design: RAM, TRS, NS. Revising the final manuscript for publication: RAM, SDP, TRS, NS, SR. Giving final approval: RAM, SDP, TRS, NS, SR. All authors contributed and approved the final version of the manuscript.

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