Moestopo International Review on Societies, Humanities, and Sciences (MIRSHuS)
Vol. 4, No. 2 (2024) pp. 156-169
ISSN: 2775-9601

THE EFFECT OF BLACK CUMIN *(NIGELLA SATIVA L.)* ON THE IMMUNE SYSTEM FOR ORAL HEALTH

Komang Krisna Dewi*
University Prof. Dr. Moestopo (Beragama), Jakarta, Indonesia
Solva Yuditha
University Prof. Dr. Moestopo (Beragama), Jakarta, Indonesia
Lukas Kusparmanto
University Prof. Dr. Moestopo (Beragama), Jakarta, Indonesia
Winda Asha Purwoko
University Prof. Dr. Moestopo (Beragama), Jakarta, Indonesia

*Correspondence: komangkrisnadewi@gmail.com

ARTICLE INFO
Article History:
received: 20/06/2024
revised: 19/08/2024
accepted: 09/09/2024

Keywords:
Immune system; Black cumin; *Nigella Sativa L.*; Oral Health

DOI:
10.32509/mirshus.v4i2.82

ABSTRACT
The immune system is a system that is able to protect the body from microorganisms that cause disease. This system can limit microbial colonization in the oral cavity and prevent the penetration of harmful substances. The immune system is related to health problems in the oral cavity. Black cumin (Nigella sativa L.) has the main active component, namely thymoquinone. Thymoquinone has an immunomodulatory, anti-inflammatory, analgesic, and antioxidant effect that shows an important role in oral disease management and also in oral health. Research shows that the substance thymoquinone in black cumin has an effect on increasing the immune system in the oral cavity. The research analyzed was research on the effect of black cumin on the immune system for oral health. The use of black cumin containing *thymoquinone* is effective for increasing the immune system in the oral cavity, if used at a concentration of 0.1%-0.2% and applied directly to the area that is experiencing inflammation. So it can be concluded that black cumin has an effect on increasing the immune system in the oral cavity.

INTRODUCTION

Black cumin *(Nigella Sativa L.)* is a plant that thrives in the tropics. Another name for black cumin is *Habbatussauda* which comes from Arabic, from the word *'habbah'* which means seed and *'sauda'* which means black. Black cumin is also known as black cumin or black seed. This plant belongs to the *Ranunculaceae* family, which is a seed plant. Black cumin is also classified as a weed that grows seasonally. The morphology of the black cumin plant can be seen in Figure 1 (Ahmad et al., 2013; Suciyati et al., 2020)

Figure 1. Black Cumin Plant
(Ahmad et al., 2013).

The black cumin plant grows in the Eastern Mediterranean region to India and Southeast Asia including Indonesia and can grow in the highlands of Indonesia (1,315 meters above sea level) with a maximum minimum temperature range of 15.48-

26.26℃. Black cumin has been used as a traditional medicine for more than 2000 years. Black cumin seeds have long been utilized as a medicinal plant and as a seasoning in the Middle East (Herlina et al., 2017; Suciyati et al., 2020).

Based on research the content in black cumin consists of; 1) Fatty Acids. Black cumin seeds contain *oleic* acid, *linoleic* acid, *linolenic* acid, *arachidonic* acid, *palmitoleic* acid and *stearic* acid which are fatty acids. Unsaturated fatty acids when consumed can provide considerable health benefits (Ahmad et al., 2013; Ijaz et al., 2017; Tutuncu, 2020). 2) Carbohydrates. Black cumin contains monosaccharides in the form of glucose, *mannose,* and *xylose* and has *non-starch polysaccharide* components that are a source of dietary fiber(Assi et al., 2016). 3) Vitamins. Black cumin seeds contain carotene which will be converted into vitamin A by the liver, and contain other vitamins such as B1 (*Thiamine*), B2 (*Riboflavin*), B6 (*Pyridoxine*), PP (*Niacin*), and *folic* acid. Therefore, black cumin seeds can be recommended as a nutritious food supplement (Assi et al., 2016; Ijaz et al., 2017). 4) Amino Acids. Black cumin contains amino acids that make up the components of proteins. Essential amino acids cannot be synthesized by the human body so they are required from food.(Assi et al., 2016). 5) Essential Oils. The most important essential oil content in black cumin is *thymoquinone* which has immunomodulatory, analgesic, anti-inflammatory,antioxidant, antibacterial and antifungal effects. *Thymoquinone* compounds are reported to improve immune performance by maintaining T cell immune response, T cell reproduction, and increasing T cell circulation. The anti-inflammatory properties of *thymoquinone* are mediated through inhibition of the biosynthesis of important mediators in the inflammatory process. Thymoquinone also reduces proinflammatory *cytokines* such as *interleukin* (IL) and *Tumor Necrosis Factor* (TNF). *Thymoquinone* in black cumin acts as an immunomodulator in cellular and humoral immunity and plays a role in increasing chemokinesis, chemotaxis, phagocytic activity, antibody levels and immunoglobulin hemagglutination (Ahmad et al., 2013; Ijaz et al., 2017; Yazdi et al., 2018). For this reason, black cumin *(Nigella Sativa L.)* is one of the herbal ingredients that can be used as a source of nutrients for the immune system, plays a role in the management of the treatment of several diseases (such as flu, hypertension, rheumatism, and treating various bacterial infections) and also plays a role in oral health (Sulistiawati & Radji, 2014).

Several studies have shown that the substance *thymoquinone* in black cumin has an effect in improving the immune system in the oral cavity and a potential therapeutic effect for oral and dental diseases. Giving gel or mouthwash containing thymoquinone showed a significant decrease in *Plaque Index* (PI), *Gingival Index* (GI), *Probing Depth* (PD), *Clinical Attachment Level* (CAL), and a decrease in IL-1β levels in *Gingival Crevicular Fluid* (GCF) and an increase in the amount of antioxidant capacity or *Total Anti-oxidant Capacity* (TAOC) in GCF after scaling and root planing treatments. However, there are still differences in results regarding the effect of black cumin (*Nigella Sativa L.)* on the immune system for oral health in a number of studies. For this reason, a more in-depth study is needed regarding the benefits of black cumin, how to administer, and the dose of administration of black cumin so that it is effective for increasing the immune system and directly affects oral health.

METHOD

This literature review is based on the analysis of several articles according to the *Preferred Reporting Item Guidelines for Methods of Systematic Review and Meta Analysis* (PRISMA). The analysis was obtained from relevant reference sources and obtained from journals and textbooks using keywords; Immune system, Black cumin, *Nigella Sativa L.*, Oral health, accessed through the PubMed database, Elsevier, NCBI, textbooks and accredited national

journals. The journals taken were research and descriptive journals published in 2013-2023. The selection process of scientific articles can be seen in the PRISMA diagram in Figure 2.

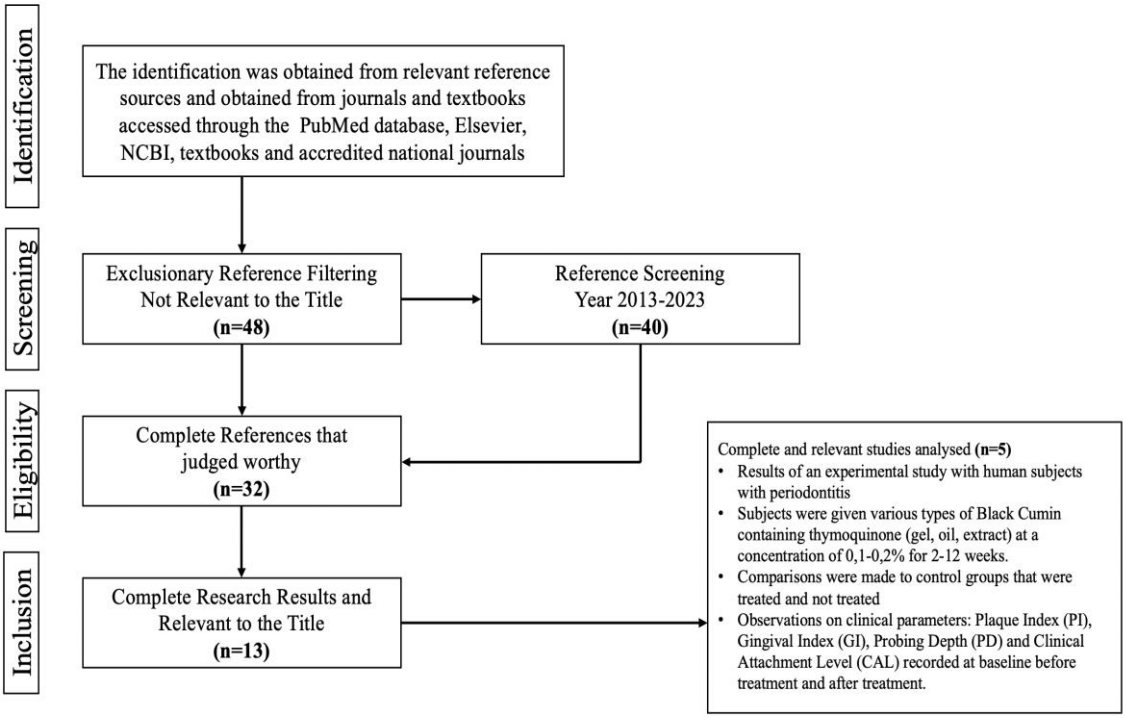

Figure 2. Literature Review Database Analysis Flowchart

RESULT

Research related to the effect of black cumin on the immune system for oral health has been studied among others by Alaaeldin et al. in 2017 with 68 subjects consisting of women and men with an age range of 25-58 years, 48 subjects had chronic periodontitis and 20 other subjects had no abnormalities. The subjects were divided into three groups, group I consisted of 20 healthy subjects (control group), group II consisted of 24 chronic periodontitis subjects who only received scaling and root planning (SRP) treatment and group III consisted of 24 patients with chronic periodontitis who received *scaling* and *root planning* (SRP) treatment combined with *thymoquinone* 0.1% gel treatment. The gel was administered *intrapocket* right after completion of SRP treatment using a blunt sterile needle until the gel was visible at the gingival margin and reapplied after 48 hours, then the gel treated area was covered with a *periodontal pack* for 7 days. Patients were instructed to maintain oral hygiene, avoid brushing the area covered with *periodontal pack,* after the periodontal pack was removed, the treatment area was cleaned with sterile saline.[9]

Preparation of *thymoquinone* 0.1% gel was carried out by preparing *thymoquinone* > 99% derived from *Nigella Sativa* or black cumin, as well as gelation ingredients, namely *Poloxamer 188* and *Carbopol 934*. The gel was prepared by adding a minimum amount of water to *Poloxamer 188* (2%) at 5°C and stirring gently until it formed a gel. *Thymoquinone* was added with a small amount of ethanol and then incorporated into the *Poloxamer* solution. A mixture of water and Carbopol 934 (5%) was stirred in a separate beaker, then added to the stirred Poloxamer and *thymoquinone* solution for 1 hour, adjusting the preparation to 25 ml, after which 2 g of *thymoquinone* gel was placed in a 100 ml beaker on a low temperature thermostat water bath. The gel was prepared and stirred

at 50 rpm by increasing the temperature and rate by 5°C/5 minutes which is the gelation temperature that indicates the magnet stops moving as a sign of gelation, then prepare the final concentration of *thymoquinone* gel of 0.1% (Alaaedin et al., 2017).

Clinical and biochemical parameters were observed in the study of Alaaeldin et al. in 2017. The clinical parameters used included *Plaque Index* (PI), *Probing Depth* (PD), *Gingival Index* (GI), and *Clinical Attachment Level* (CAL) recorded before treatment, 4 weeks and 12 weeks after treatment in groups II and III. Gingival Crevicular Fluid (GCF) was collected on the first day, 4 weeks and 12 weeks after treatment to look at changes in oral immune cells using the biochemical parameters of periodontitis IL-1β and TAOC levels in GCF. IL-1β and TAOC levels in GCF were examined and tested using a commercially available *Enzyme linked immunosorbent assay* (ELISA). The results showed that both study groups II and III were significant in the clinical parameters of PD, GI, and CAL from baseline to 4 and 12 weeks after treatment, the results of the study can be seen in Table 1 (Alaaedin et al., 2017).

Table 1. Clinical Parameters After *Thymoquinone* 0.1% Gel Administration

Groups	**GI**		**CAL**		**PD**	
	4 weeks	12 weeks	4 weeks	12 weeks	4 weeks	12 weeks
Groups II	47.96+0.2 %	71.9+ 0.15 %	21.71+ 0.50 %	47.7+0.35 %	29.19+ 0.043%	50.93+0.02 %
Groups III	49.95+0.05 %	75.27+0.83 %	27.72+0.03 %	58.5+0.081 %	33.94+0.2 %	56.9+0.13 %

Changes in mean IL-1β values at baseline and at 4-week and 12-week intervals in groups I, II and III are shown in Table 2. This study showed a significant decrease in IL-1β after 4 weeks of treatment in the group that received *scaling* and *root planing* combined with 0.1% *thymoquinone* gel (group III) compared to the group that received *scaling* and *root planing* treatment only (group II), P value <0.0001(Alaaedin et al., 2017)

Table 2. Comparison of IL-1β Levels After *Thymoquinone* 0.1% Gel Administration

IL-1 β	**Groups I**	**Groups II Average ±SD**	**Groups III Average ±SD**	***P value* (II compared to III)**
Baseline	103. 2±12.5	230.49±24.73	233.99±25.11	0.6
4 weeks	102.42±10.4	153.26±27.31	125.54±19.21	<0.0001
12 weeks	102.1±11.25	106.04±9.51	103.95±10.84	0.4

The examination of TAOC in GCF in the study of Alaeeldin et al. showed a significant increase in the group that received *scaling* and *root planing* treatment combined with *thymoquinone* 0.1% gel (group III) compared to the group that received only *scaling* and *root planing* treatment (group II), P value <0.0001. Results can be seen in Table 3 (Alaaedin et al., 2017).

Table 3. Comparison of TAOC after *Thymoquinone* 0.1% Gel.

TAOC	Groups I	Groups II Average ±SD	Groups III Average ±SD	*P-value* (II compared to III)
Baseline	843.33±22.52	644.22±17.02	647.37±22.06	0.5
4 weeks	840.43±11.5	723.91±12.62	739.54±15.88	<0.0001
12 weeks	838.2±20.3	762.96±12.84	773.73±14.68	0.01

Alaeeldin et al. research is in line with research conducted by Khalil et al. in 2019 with 68 female and male subjects with an age range of 25-58 years, 48 of whom had chronic periodontitis. 68 subjects were grouped into three groups, group I consisted of 24 patients who received SRP treatment combined with *thymoquinone* gel (0.1%), group II consisted of 24 patients who only received SRP treatment, and group III consisted of 20 healthy subjects as a control group. *Thymoquinone* gel 0.1% was applied *intrapocket* right after the completion of SRP treatment with a blunt sterile needle until the gel was visible at the gingival margin. The gel was reapplied after 48 hours and covered with *periodontal pack* for 7 days. The method of making 0.1% *thymoquinone* gel in this study is by adding water to *acetic* acid, then the pre-weighed *thymoquinone* powder is gradually added to the *acetic* solution and allowed to expand, add water and mixed to form a final concentration of 1.8%. The gel formed was allowed to stand for 24 hours at room temperature, after which about 5.5 ml of aqueous *thymoquinone* suspension was prepared and dispersed to give a final *thymoquinone* concentration of 0.1% (Khalil & Alaeeldin, 2019).

Clinical parameters including PI, GI, PD and CAL were recorded at baseline before treatment, at week 4 and 12 after treatment. Biochemical parameters namely IL-1β and TAOC levels in GCF were recorded at baseline before treatment, at week 4 and 12 after treatment. The results showed that subjects with SRP treatment combined with *thymoquinone* 0.1% gel (group I) had a significant reduction in clinical parameters. Significant results were also shown in biochemical parameters, namely the level of IL-1β and TAOC in GCF. In patients with SRP treatment combined with *thymoquinone* 0.1% gel (group I) there was a significant decrease in the level of IL-1β in GCF at week 4. The results can be seen in Table 4 (Khalil & Alaeeldin, 2019).

Table 4. Comparison of IL-1β Levels After *Thymoquinone* 0.1% Gel Administration.

IL-1 β	Groups I Average ±SD	Groups II Average ±SD	*P value* (II compared to III)
Baseline	233.99±25.11	230.49±24.73	0.6
4 weeks	125.54±19.21	153.26±27.31	<0.0001
12 weeks	103.95±10.84	106.04±9.51	0.4

Research by Alaeeldin et al. and Khalil et al. both show that the administration of 0.1% *thymoquinone* gel in patients with oral health disorders, namely chronic periodontitis after SRP treatment is effective in activating and increasing immune system cells both innate immune system and adaptive immune system. The difference obtained from the two studies is the method of making *thymoquinone* gel, but the results shown are still significant.

The above study applied *thymoquinone* gel in the gingival sulcus which often experiences chronic periodontitis resulting in periodontal pockets. The gingival sulcus is part of the periodontal tissue which is one of the components of the immune system in the

oral cavity which has many defence elements including the gingival epithelium which prevents bacterial adhesion by continuously releasing keratinocytes into the oral cavity and becomes a defence against the invasion of pathogenic microorganisms. This tissue is susceptible to acute and chronic inflammation caused by plaque bacteria that accumulate in the space between the teeth and gums (gingival sulcus). The gingival sulcus is moistened with a serum exudate called gingival crevicular fluid (GCF) (*British Society for Immunology. Immune Responses in the Oral Cavity Category: Organs and Tissues*, 2022). GCF can play a role in the pathogenesis of periodontal disease or disorders, so measuring the presence of inflammatory mediators in the gingival crevicular fluid can be used to evaluate risk factors for gingival attachment loss and alveolar bone destruction. An increase in GCF indicates inflammation in periodontal tissue (Newman et al., 2018). IL-1β is a pro-inflammatory *cytokine*, in patients with periodontal disease the level of IL-1β in GCF shows high results, therefore IL-1β can be used as a biomarker in individuals with periodontal disease (Gomes, 2016). *Thymoquinone* in black cumin has anti-inflammatory properties so that it can play a role in reducing pro-inflammatory cytokines such as IL-1β.

Total antioxidant capacity (TAOC) is an integrated parameter that reflects the cumulative action of non-enzymatic antioxidants present in plasma and body fluids, measuring TAOC can provide information about the balance between oxidants and antioxidant systems. TAOC in individuals with periodontitis is lower than in individuals with healthy periodontal (Baser et al., 2015). The studies of Alaeeldin et al. and Khalil et al. both showed a significant increase in TAOC in periodontitis patients who were administered *thymoquinone* gel. This indicates that thymoquinone can help in the healing process of periodontal disease.

Another study was conducted by Hassan et al. in 2020 with 40 subjects who experienced chronic periodontitis with an average age of 36 years consisting of 22 male subjects and 18 female subjects. The subjects were divided into 2 groups, namely the control group and the study group. The control group consisted of 20 subjects who were given normal saline as a placebo, and the study group consisted of 20 subjects given black cumin oil (Nigella Sativa L.). Using the randomized controlled trial research method, both groups randomly received 80 ml each of normal saline (UNISOL-NS®, Pakistan) and black cumin oil (Kalonji oil-Marbaha®) mouth rinses in amber bottles. The mouth rinses were administered after scaling and root planing treatments before the start of the clinical trial. Saliva samples of all subjects were taken on day 0 and day 15 (week 2) to check the level of IL-1β. Saliva collection was carried out by collecting 5ml of unstimulated saliva in a sterile tube through passive drooling technique in the morning between 08:00-09:00 am. Participants were instructed not to eat and drink and were not allowed to perform oral hygiene measures for at least 1 hour before saliva collection. Subjects were asked to rinse their mouth with distilled drinking water for 1 minute, then debris was removed with a sterile cotton pellet, and saliva was collected. The collected saliva samples were placed on ice in eppendorf tubes before being stored at -8℃. The level of IL-1β in saliva was examined and tested using Enzyme linked immunosorbent assay (ELISA). This study showed statistically insignificant results in the control group and the study group, no changes occurred in salivary IL-1β levels in the control group after the use of normal saline and black cumin oil. The results can be seen in Table 5. and Table 6 (Hassan et al., n.d.).

Another study was conducted by Hassan et al. in 2020 with 40 subjects who experienced chronic periodontitis with an average age of 36 years consisting of 22 male subjects and 18 female subjects. The

subjects were divided into 2 groups, namely the control group and the study group. The control group consisted of 20 subjects who were given normal saline as a placebo, and the study group consisted of 20 subjects given black cumin oil *(Nigella Sativa L.).* Using the randomised controlled trial research method, both groups randomly received 80 ml each of normal saline (UNISOL-NS®, Pakistan) and black cumin oil (Kalonji oil-Marbaha®) mouth rinses in amber bottles. The mouth rinses were administered after *scaling* and *root planing* treatments before the start of the clinical trial. Saliva samples of all subjects were taken on day 0 and day 15 (week 2) to check the level of IL-1β. Saliva collection was done by collecting 5ml of unstimulated saliva in a sterile tube through passive drooling technique in the morning between 08:00-09:00. Participants were instructed not to eat and drink and were not allowed to perform oral hygiene measures for at least 1 hour before saliva collection. Subjects were asked to rinse their mouth with distilled drinking water for 1 minute, then debris was removed with sterile cotton pellets, and saliva was collected. The collected saliva samples were placed on ice in eppendorf tubes before being stored at -8℃. The level of IL-1β in saliva was examined and tested using *Enzyme linked immunosorbent assay* (ELISA). This study showed statistically insignificant results in both the control and study groups, no changes occurred in salivary IL-1β levels in the control group after the use of normal saline and black cumin oil. Results can be seen in Table 5. and Table 6 (Hassan et al., 2020).

Table 5. Difference in Salivary IL-1β Levels After Gargling Black Cumin Oil

	Baseline	**2 weeks**	***P-value***
Control group	5,46±2,06	5,17±2,76	0,786
Study group	4,47±2,34	5,81±3,37	0,093

Table 6. Comparison of Salivary IL-1β after Gargling Black Cumin Oil

	Control group	**Study group**	***P-value***
Baseline	5.46+2.06	4.47+2.34	1,68
2 weeks	5.17+2.76	5.80+3.37	0,665

Differences in results were found between the research of Alaeeldin et al. and Khalil et al. with the research of Hassan et al. Research conducted on the immune system in the oral cavity of patients suffering from periodontitis is influenced by several factors. Research conducted by Alaeeldin et al. and Khalil et al. stated that the administration of black cumin in the form of a gel in periodontitis patients can significantly reduce the level of IL-1β, while the research of Hassan et al. stated that the administration of black cumin in the form of a mouth rinse solution in periodontitis patients had no effect on changes in IL-1β levels. The Alaeeldin et al. and Khalil et al. studies both used black cumin with a *thymoquinone* gel preparation that has a concentration of 0.1% which is given *intrapocket*, while the Hassan et al. study used black cumin with a 5 ml black cumin oil mouth rinse solution preparation. Based on the statements of the three journals, there are factors of differences in the treatment methods in the administration of black cumin in periodontitis patients so that it affects the immune system cells in the oral cavity. *Intrapocket* administration of drugs is more effective for reducing IL-1β because periodontal disease is usually localised around the periodontal pockets. Periodontal pockets are moistened by gingival sulcus fluid or GCF. GCF is an inflammatory exudate found at the gingival margin or within the gingival crevice. GCF becomes a natural medium to aid the distribution of

medications applied in the area throughout the periodontal pockets. (Alaaedin et al., 2017; *British Society for Immunology. Immune Responses in the Oral Cavity Category: Organs and Tissues*, 2022; Khalil & Alaeeldin, 2019)

Another factor that causes differences in results in Alaeeldin et al., Khalil et al. and Hassan et al. research is the periodontal disease biomarker used, although the three studies used IL-1β as a biomarker of periodontal disease, there were differences in how IL-1β was sampled. Alaeeldin et al. and Khalil et al. both took IL-1β samples directly from gingival sulcus fluid or GCF, while in the study of Hassan et al. IL-1β sampling came from saliva. Direct sampling of IL-1β in gingival sulcus fluid or GCF is more accurate than sampling IL-1β through saliva. Gingival sulcus fluid and saliva are widely used as diagnostic substrates to find biomarkers. Biomarkers are substances that are objectively measured and evaluated as indicators of normal biological processes, pathological processes, or pharmacological responses to therapeutic interventions (Jaedicke et al., 2016). IL-1β is a cytokine in the pathogenesis of periodontal disease, IL-1β is produced by many immune cells and mediates the inflammatory response. Patients with periodontal disease have higher levels of IL-1β in oral fluid. High concentrations of IL-1β were found in GCF in patients with periodontitis. Recent data shows that IL-1β, *macrophage inflammatory protein-1 alpha* (MIP-1α), IL-6 and *matrix metalloproteinase-8* (MMP-8) are identified as diagnostically acceptable biomarkers for periodontal disease. Research conducted by Tales et al. cited by Konova et al. in 2020 stated that average salivary IL-1β levels cannot be an accurate indicator to determine periodontal tissue health

A comparison of IL-1β levels in GCF and saliva was described in a study conducted by Konova et al. in 2020, which compared the level of IL-1β in GCF and the level of IL-1β in saliva in patients with gingivitis and periodontitis. The results showed that the level of IL-1β in GCF in the group of healthy individuals was significantly lower than the concentration of IL-1β in GCF in the group of patients with periodontitis with a value of $p < 0.0001$ while the concentration of IL-1β in saliva in the group of healthy individuals was significantly lower than the concentration of IL-1 in saliva in patients with periodontitis with a value of $p = 0.025$. This study shows that the level of IL-1β in GCF has a higher accuracy when compared to IL-1β in saliva (Konova, 2020).

The difference in results in the research of Alaeeldin et al., Khalil et al. with the research of Hassan et al. is also due to the duration factor of the study. Alaeeldin et al. and Khalil et al. research on periodontitis patients given 0.1% *thymoquinone* gel was observed for 12 weeks and significant results were seen in week 4, while the research conducted by Hassan et al. only had a duration of 15 days (2 weeks), causing Hassan et al.'s research on the effects of black cumin to be insignificant.

The effect of black cumin which has the active component *thymoquinone* on the immune system for oral health was also studied by Elamrousy W. in 2018 which states that the administration of 0.2% thymoquinone gel intra-pocket after SRP *scaling* and *root planing* treatment in periodontitis patients aged 24-37 years shows a significant decrease in *probing pocket depth* (PPD) and MMP-8 levels in gingival sulcus GCF. Similar to IL-1β, MMP-8 (*Matrix metalloproteinase-8*) is also an immune system response in the form of pro-inflammatory *cytokines* that can act as biomarkers of periodontal pathological conditions (Elamrousy, 2018).

The research conducted by Kapil et al. in 2018 is almost the same as Elamrousy W.'s research in 2018 using 0.2% *thymoquinone* gel. Kapil et al. conducted for 6 weeks with periodontitis patients aged 23-61 years who were given 0.2% *thymoquinone* gel showed a significant decrease in GI, PPD, PI, and a very significant decrease in *Gingival Crevicular Fluid-Alkaline*

phosphatase (GCF-ALP). Similar to IL-1β, MMP-8 in GCF, ALP contained in GCF is also a biomarker in periodontal tissue inflammation. ALP is a glycoprotein produced by many cells such as *polymorphonuclear leukocytes* (PMNL), osteoblasts, macrophages and fibroblasts within the periodontium and gingival crevice, ALP contained in saliva and GCF usually indicates periodontal tissue inflammation or damage (Harsh et al, 2018).

Research by Elamrousy W. and Kapil et al. showed significant results in increasing immune system cells by administering *thymoquinone* 0.2% gel applied *intrapocket*, although they used different periodontitis biomarkers. Research on the effect of black cumin was also conducted on experimental animals, such as research conducted by Kurnia et al. in 2021 in vivo with the subject of male wistar rats induced by *P. gingivalis* bacteria, namely the bacteria that cause periodontitis, given 0.5 ml of 3% black cumin extract twice a day for 21 days topically stated that topical administration of black cumin extract on gingiva exposed to *P. gingivalis* toxin bacteria showed significant results in significantly reducing MMP-8 levels (Kurnia et al., 2021). The same research was conducted by Setiawatie et al. in 2022 in vivo with male Wistar rat subjects who were given 1 mg of black cumin toothpaste twice a day, it was found that periodontitis rats given black cumin toothpaste showed anti-inflammatory effects by reducing the number of neutrophils, macrophages and lymphocytes in rat tissue, and reducing inflammatory cell activity by reducing IL-1β and PGE2 levels, and showing anti-destructive effects on periodontal extracellular matrix by reducing MMP1 and MMP1 levels. This study shows that black cumin toothpaste has the potential to improve the immune system in the oral cavity, namely as a healing agent for periodontitis (Setiawatie, 2022).

Black cumin application to patients with oral health disorders has a good effect on immune system cells in the oral cavity, especially in periodontitis patients. Periodontitis is one of the oral health disorders associated with the immune system, besides periodontitis, another disorder that occurs in the oral cavity is dental caries. Giving black cumin can potentially prevent the risk of caries. Research on the administration of black cumin to subjects experiencing dental caries was conducted by Al-Wafi et al. in 2014, examining the potential inhibitory role of *thymoquinone* on gingival inflammation and plaque formation in rat subjects and found that thymoquinone effectively reduces caries-causing bacteria and plaque formation in gingivitis rats (Al-Wafi, 2014).

DISCUSSION

The WHO defines oral health as a state free from oral pain, facial pain, infections and sores of the oral cavity, and oral diseases. The oral cavity is part of the immune system and plays an important role in primary health because the oral cavity can be an entry point for pathogenic microorganisms. The immune system has the ability to protect the body by containing or eliminating foreign bodies (disease-causing microorganisms such as bacteria or viruses) or abnormal cells (cancer cells) that are potentially harmful to the body, eliminating old cells and tissues damaged by trauma or disease, facilitating the process of wound healing and tissue repair, and can identify and destroy abnormal cancer cells originating from within the body. The immune system consists of leucocytes (white blood cells) and their derivatives, the thymus, lymph nodes, and lymph vessels (Sherwood, 2016).

Factors that affect the immune system include genetics, environment, diet, age and medication consumption. Immune system disorders at birth are often inherited from both parents, therefore the function of the immune system is linked to inherited genes. Genetically influenced immune system components are responsible for the immune response when pathogens first enter the body. Foods rich in fat and sugar as well as fast food tend to cause the immune

system to malfunction and can initiate a disease. Such a diet will make the body susceptible to degenerative or metabolic diseases such as heart disease, cholesterol and diabetes. Ageing causes the immune system to decline. Immune cells are generally at their peak activity when an individual is an adult, after which as they get older their activity decreases including in producing proteins that fight infection. Certain classes of drugs are known to reduce the immune system's ability to defend itself, one of which is a class of corticosteroids such as cortisone and hydrocortisone. The use of these drugs over a long period of time may decrease the immune system (Mälzer et al., 2016; Simon et al., 2015).

The soft and hard tissues of the oral cavity are protected by an immune system that includes specific (adaptive) and nonspecific (innate) immune systems. The innate immune system is the body's non-specific immune response that will immediately act on threatening substances. This non-specific response is an innate defence mechanism that non-selectively defends the body from any foreign or abnormal hazards. Components of the innate immune response consist of cytokines, interferons, natural killer cells, and the complement system. The Adaptive (Specific) Immune Response works by relying on the specific immune response and selectively attacks certain foreign substances that have been exposed to the body. The adaptive immune response is regulated by cells and organs in the body such as the spleen, thymus, bone marrow and lymph nodes. The adaptive immune response works when a foreign substance enters the body, these cells and organs will make antibodies and cause a multiplication of specific cells. The body's immune system will then adapt to remember the foreign substance (Figure 3). The adaptive immune response has two classes, B *lymphocytes* (IgM, IgG, Ig E, IgA and IgD) and T lymphocytes (*cytotoxic* T cells;killer cells, helper T cells, regulatory T cells). The innate and adaptive immune systems work together harmoniously to contain, and then eliminate substances that harm the body can be seen in Figure 2 (Sherwood, 2016; Silverthorn, 2013).

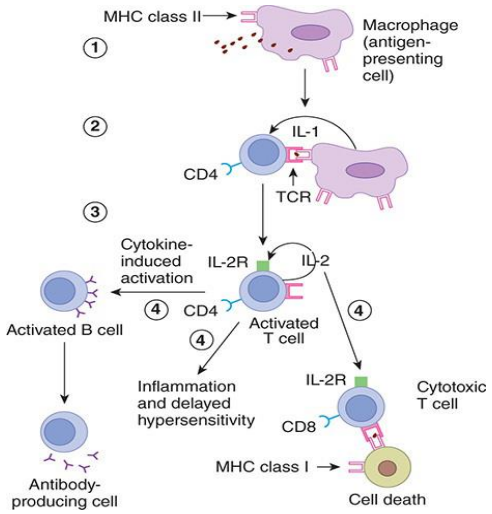

Figure 3. Black Cumin Plant (Sherwood, 2016)

The main function of the immune system in the oral cavity is to limit microbial colonisation of oral mucosal surfaces, tooth surfaces, and prevent harmful penetration through oral tissue surfaces. The oral immune system is present in saliva, periodontal tissues in *Gingival Crevicular Fluid* (GCF) and tonsils. Saliva is an important component of defence against infection in the oral cavity. Saliva contains molecular elements that limit microbial growth consisting of lysozyme, which breaks

down the bacterial cell wall, lactoferrin, which is a nutrient for the normal flora in the oral cavity, and antimicrobial peptides such as histatin, which inhibits the growth of *Candida albicans* and *Streptococcus mutans.* Saliva forms an immune system produced by salivary glands containing secretory IgA (sIgA). IgA in saliva serves to prevent bacterial colonisation in the oral cavity, thus preventing the formation of dental plaque and neutralising toxins. Salivary gland production stimulates the formation of IgA to release B lymphocytes, which then differentiate into plasma cells (*British Society for Immunology. Immune Responses in the Oral Cavity Category: Organs and Tissues*, 2022; Gomes, 2016).

Periodontal tissue is a component of the systemic immune system that has many defence elements including the gingival epithelium that prevents bacterial adhesion by continuously releasing keratinocytes into the oral cavity and protects the oral cavity from invasion by pathogenic microorganisms. Periodontal tissues are prone to acute and chronic inflammation caused by plaque bacteria that accumulate in the space between the teeth and gums (gingival sulcus). The gingival sulcus is moistened with a serum exudate called GCF, this fluid contains antibodies IgG, IgA, IgM, monocytes, neutrophils, T and B lymphocytes, and fibroblasts needed to prevent bacterial invasion of subgingival plaque and tonsils are part of the lymphoid organs of the immune system located at the back of the mouth. Tonsils consist of palatine tonsils, adenoid tonsils, lingual tonsils, and tubal tonsils. The tonsil tissue forms a ring of lymphoid tissue known as *Waldeyer's* ring that serves to protect the pharynx from invasion by pathogenic microorganisms (*British Society for Immunology. Immune Responses in the Oral Cavity Category: Organs and Tissues*, 2022).

People seek many ways to maintain and improve the immune system so that the body avoids disease starting from living a healthy lifestyle, to consuming additional nutrients (Ahmad et al., 2013; *British Society for Immunology. Immune Responses in the Oral Cavity Category: Organs and Tissues*, 2022; Simon et al., 2015). Nutrients to maintain the immune system can be fulfilled from exogenous sources and endogenous sources. One of the exogenous sources that can maintain and improve the immune system is the consumption of herbal ingredients. The World Health Organisation (WHO) states that around 80% of the world's population uses herbal medicines to boost immunity and maintain primary health. Micronutrients and components in herbal ingredients have very specific roles in promoting effective immune system maintenance.

Black cumin is one of the herbal medicines that is rich in benefits because it produces an active component, *thymoquinone*. The active component thymoquinone has many pharmacological properties such as antimicrobial, antibacterial, antifungal, and antiviral, anti-inflammatory, analgesic, antihypertensive, hypoglycaemic, anti-cancer, antioxidant, and immunomodulatory. Black cumin is believed to provide benefits to the health of the body including to maintain the oral immune system (Ijaz et al., 2017; Simon et al., 2015; Yazdi et al., 2018).

Black cumin is useful for mucosal inflammation therapy, one of which is *oral mucositis* which is often found in patients with cancer. *Oral mucositis* is an acute inflammation caused by necrosis of the basal layer of the oral mucosa, *oral mucositis* is a side effect that often occurs in head and neck cancer patients who are treated with radiotherapy or chemotherapy. The use of black cumin oil as a mouthwash for 6-7 weeks is 10 ml given every 6 hours. The mouthwash was given starting from the first week after initiation of radiotherapy or radiochemotherapy. Results showed significant healing of oral mucositis and reduction in pain levels. Black cumin when consumed will have a systemic effect in enhancing the immune system, namely a significant increase in CD3+ *lymphocytes* and T-helper cells (CD4+). These cells play a role

in immune destruction of incoming pathogens and can modulate the activity of other immune (Ameen et al., 2019; Salem et al., 2021).

Based on the research that has been described and analyzed in this literature review, it shows that the effects of black cumin given both locally and systemically can significantly increase immune system cells. The effect of thymoquinone in black cumin has been shown to be effective for enhancing the immune system in the oral cavity. Thymoquinone is the main active component in black cumin which can function as an immunomudulator and anti-inflammatory so that it can improve the work of the immune system, besides that thymoquinone has antibacterial properties that are effective for reducing and inhibiting disease-causing bacteria and accelerating the healing process of diseases in the oral cavity such as periodontitis, gingivitis, dental caries, and even mucositis due to cancer. Oral health conditions in Indonesia and around the world are still a serious problem. According to the Global Burden of Disease Study, around 3.5 billion people worldwide suffer from oral health problems. Between 2013 and 2018, oral health problems in the Indonesian population increased from 25.9% to 57.6%. For this reason, many efforts are made by the community to maintain oral health, starting from maintaining endurance (Kusparmanto et al., 2024).

CONCLUSION

Black cumin (*Nigella Sativa L.)* is an herbal plant that has a main active component, *thymoquinone*. *Thymoquinone* has immunomodulatory effects, analgesic, anti-inflammatory, antioxidant, and antibacterial properties. The use of black cumin can be used locally or systemically. The anti-inflammatory properties possessed by *thymoquinone* have an effect on increasing immune system cells which are characterised by reduced pro-inflammatory *cytokines* in periodontal disease, antibacterial properties of *thymoquinone* can reduce caries-causing bacteria and inhibit plaque formation, besides the analgesic properties of *thymoquinone* can reduce pain and help the healing process in mucosal inflammation, this shows that black cumin can affect the increase in immune system cells in the oral cavity. The use of black cumin containing *thymoquinone* is effective for increasing the immune system in the oral cavity if used at a concentration of 0.1%-0.2% and applied directly to the area experiencing inflammation, therefore it can be concluded that black cumin has an effect on increasing the immune system in that oral cavity.

REFERENCE

Ahmad, A., Asif, H., Mohd, M., Khan, S. A., Najmi, A. K., & Siddique, N. A. (2013). A review on therapeutic potential of Nigella sativa: A miracle herb. *Asian Pac J Trop Biomed*, *3*(5), 337–352.

Al-Wafi, H. A. (2014). *Benefits of Thymoquinone, a Nigella Sativa Extract in Preventing Dental Caries Initiation and Improving Gingival Health*.

Alaaedin, E., Gomaa, M. D., Eltewacy, N. K., Ali, A., & Khalil, A. (2017). Formulation and Characterization of Thymoquinone Bioadhesive Gel for Treatment of Chronic Gum Inflammation. *International Journal of Sciences: Basic and Applied Research (IJSBAR*, *31*(2), 321–330.

Ameen, H. A., Mohammed, M., Ali, R. H., Ahmed, K., & Hussain, S. (2019). Nigella Sativa Oil for Oral Mucositis. *Al Mustansiriyah Journal of Pharmaceutical Sciences*, *19*(4).

Assi, M. A., Noor, M. H., Bachek, N. F., Ahmad, H., Haron, A. W., Yusoff, M. S., & Rajion, M. A. (2016). The Various Effects of Nigella Sativa on Multiple Body Systems in Human and Animals. *PJSRR*, *2*(3), 3–10.

Baser, U., Gamsiz-Isik, H., Cifcibasi, E., Ademoglu, E., & Yalcin, F. (2015). Plasma and salivary total antioxidant capacity in healthy controls compared with aggressive and chronic

periodontitis patients. *Saudi Med. J*, *36*, 856–861.

British Society for Immunology. Immune Responses in the Oral Cavity Category: Organs and Tissues. (2022). https://www.immunology.org/public-information/bitesized-immunology/organs-and-tissues/immunity-in-the-oral-cavity

Elamrousy, W. (2018). Effect of locally delivered 0.2% Thymoquinone gel in subjects with Grade C Periodontitis: Clinical, Immunological and Microbiological Assessment. *European Journal of Molecular & Clinical Medicine*, *5*(1), 81–95.

Gomes. (2016). Inflammatory Cytokines Interleukin-1β and Tumour Necrosis Factor-α - Novel Biomarkers for the Detection of Periodontal Diseases. *A Literature Review. J Oral Maxillofac Res*, *7*(2), 2.

Harsh, K. K., DK, Suresh., Shalu C.B., & Karandeep S. A. (2018). Assessment of clinical efficacy of locally delivered 0.2% Thymoquinone gel in the treatment of periodontitis. *Saudi Dental Journal*, *30*, 348–354.

Hassan, G., Ghafoor, S., Chaudhry, S., & Khan, Z. A. (2020). Salivary Interleukin-1 Levels in Chronic Periodontitis Patients after use of Nigella Sativa (Kalonji) Oil. *JPDA*, *29*(04), 205–8.

Herlina, A. S. A., A, K., & DN, F. (2017). Growth and Production of Habbatusauda (Nigella Sativa L.) at Three Altitudes in Indonesia. *J. Agron. Indonesia*, *45*(3), 323–330.

Ijaz, H., Tulain, U. R., Qureshi, J., Danish, Z., Musayab, S., & Akhtar, M. F. (2017). Nigella sativa (Prophetic Medicine): A Review. *Pak. J. Pharm. Sci*, *30*(1), 229–234.

Jaedicke, K. M., Preshaw, P. M., & Taylor, J. J. (2016). Salivary cytokines as biomarkers of periodontal diseases. *Periodontol*, *70*(1), 164–83.

Khalil, A. A., & Alaeeldin, E. (2019). Clinical and Biochemical Evaluation of Thymoquinone Gel in the Treatment of Chronic Periodontitis. *Int. J. Adv. Res*, *7*(4), 83–93.

Konova, T. B. (2020). Concentrations of Interleukin-1ß in Gingival Crevicular Fluid and Saliva – a Potential Diagnostic Biomarker of Periodontal Diseases. *Folia Medica*, *62*(4), 825–30.

Kurnia, S., Steven, J., & Laksono, V. (2021). Immune Response Mechanism of the Gingival Epithelium in the Tissue Repair Exposed to Porphyromonasgingivalis Toxin on Topical Administration of Nigella sativa Extract. *European Journal of Molecular & Clinical Medicine*, *8*(3), 886–894.

Kusparmanto, F. S., Pakpahan, E. (2024). Study in the Potential of Chemical Compounds of Rosella Flower (Hibiscus Sabdariffa Linn) Extract As a Prevention of Relapse After Orthodontic Treatment. Moestopo International Review on Societies, Humanities, and Sciences.*Review on Social.* Vol. 4, No. 1 (2024) pp.78-87. https://doi.org/10.32509/mirshus.v4i1.71

Malzer, J. N., Schulz, A. R., & Andreas Thiel, A. (2016). Environmental Influences on the Immune System: The Aging Immune System. In E. C. Dalam (Ed.), *Environmental Influences on the Immune System*. Springer.

Newman, G. M., Takei, H. H., Klokkevold, P. R., & Carranza, F. A. (2018). *Newman and carranza's clinical periodontology* (13th ed.). Elsevier.

Salem, A., Bamosa, A., Alam, M., Alshuraim, S., Alyalak, H., & Alagga, A. (2021). Effect of Nigella sativa on general health and immune system in young healthy volunteers; a randomized, placebo-controlled, double-blinded clinical trial. *F1000Research*, *10*(1199).

Setiawatie. (2022). Nigella sativa toothpaste promotes anti-inflammatory and anti-destructive effects in a rat model of periodontitis. *Elsevier: Archives of Oral Biology*, 137.

Sherwood, L. (2016). *Human Physiology from Cell to Systems* (9th ed.). Cengage

Learning.
Silverthorn, D. U. (2013). *Human Physiology an Intergrated Approach* (6th ed.). Pearson.
Simon, A. K., Hollander, G. A., & McMichael, A. (2015). Evolution of the immune system in humans from infancy to old age. *Proc. R. Soc. B*, *282*, 2–7.
Suciyati, N. A., Nurcahyani, N., Sutyarso, R., & E. (2020). The Effect of Black Jintan Extract (Nigella sativa) Towards The Fetus Bone Structure from Mencit (Mus musculus L. *Jurnal Ilmiah Biologi Eksperimen Dan Keanekaragaman Hayati*, *7*(1).
Sulistiawati, F., & Radji, M. (2014). Potential Utilisation of Nigella Sativa L. as Immunomodulator and Anti-inflammatory (Mini Review).Fakultas Farmasi Universitas Indonesia. *Pharm Sci Res ISSN*, *2*(1), 2407–2354.
Tutuncu, S. (2020). Black Seed (Nigella Sativa) and Immunomodulatory Effect (Review Article. *International Journal of Veterinary and Animal Research*, *3*(1), 6–9.
Yazdi, H. S., Noorbakhsh, M. F., Hayati, F., Samarghandian, S., & Farkhondeh, T. (2018). Immunomodulatory and Anti-inflammatory Effects of Thymoquinone. Bentham Science Publishers. *Cardiovascular & Haematological Disorders-Drug Targets*, *18*, 52–60.