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Study Effectiveness and Stability Formulation Nanoemulsion of Black Cumin Seed (*Nigella sativa* L.) Essential Oil: A Review

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Abstract:
Background*: Black cumin (Nigella sativa L.) is one of the herbal plants from the Ranunculaceae family and has many properties to treat various chronic diseases. Black cumin seed essential oil is known to have pharmacological activities such as antimicrobial, antifungal, antiviral, anticancer, anti-inflammatory, immunomodulatory, anthelmintic, antidiabetic, antidepressant, antifertility, antioxidant, anti-aging, analgesic, hepatoprotector, cardioprotector, neuroprotector and others. In this review article, reviews of the effectiveness and stability of the nanoemulsion formulation of black cumin seed (Nigella sativa L.) essential oil will be discussed from several research journals. The purpose of this review article is to obtain information about the effectiveness and stability of several formulations of essential oil nanoemulsion preparations from black cumin seeds (Nigella sativa L.).*
Methods*: The literature used is obtained from several scientific journals that have been published at the international and national level through search engines in the form of Scopus, ScienceDirect, Google Scholar, DOAJ, Elsivier, Garuda Portal and Pubmed.*
Results*: Nano-delivery system in the formulation of the black cumin seed (Nigella sativa L.) essential oil nanoemulsion as a whole shows that there is an increase in the stability of the preparation and the effectiveness of the active substance. This increased stability was initiated by the addition of the nanoemulsion carrier and the surfactant used.*
Conclusion: *Nanoemulsions containing black cumin seed essential oil have been shown to increase drug solubility, increase drug bioavailability, stability and effectiveness of drug preparations.*
Key Word*: Essential oil, Nigella sativa, Nanoemulsion.*

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I. Introduction

Currently, herbal products are an alternative that has been widely used by the community. Around 60% of the population in the world depend on traditional medicine whereas in developing countries almost 80% depend on traditional medical practices, especially herbal medicine for their primary health care [1]. The use of herbal medicines from plants is increasingly attracting the attention of the world community, so medicines derived from plants are used in various kinds of treatment because they are considered to have low toxicity and fewer side effects compared to modern medicines. Black cumin seeds or in other languages are often called Black Seed (Nigella sativa L.) is an herbal plant that has many benefits and is often used in the treatment of diseases [2]. The amount of public interest in these herbal products makes black cumin (Nigella sativa L.) as a combined ingredientinto the several medicinal products, cosmetics and household health supplies (PKRT).

Black cumin (Nigella sativa L.) is an herbal plant that is mostly found in the Middle East, Central Europe, and West Asia [3]. Black cumin (Nigella sativa L.) or more familiarly called habbatussauda, black seed or black cumin is a plant that comes from the botanical family Ranunculaceae [2]. In several studies it was stated that black cumin seeds have pharmacological activities such as antimicrobial, antifungal, antiviral, antiparasitic, anticancer, anti-inflammatory, anthelmintic, antidiabetic, antidepressant, antifertility, antioxidant, analgesic, and can provide a protective effect on the heart. In addition, black cumin seeds also have properties to improve the immune system, treat dermatological problems, improve the hepatobiliary system, provide protection to the nervous system, improve the function of the gastrointestinal system, improve the function of the urinary system and others [4]. The seeds and essential oils in black cumin are used to cure several diseases [1]. Black cumin essential oil is obtained from black cumin seeds. This essential oil is also a component that plays an effective role in treating diseases [5].

Black cumin seed essential oil has the main active constituents namely thymoquinone (Tq), thymol, and carvacrol [6] it exhibits a protective effect against many diseases which is largely due to the high antioxidant activity of black cumin seed essential oil [7].

Apart from the many benefits and advantages of black cumin seed essential oil, it turns out that it also has poor physical properties in the development of its formulation such as its hydrophobic, unstable and volatile nature[8]. This black cumin seed essential oil showsactivity poor in-vivo due to low solubility in thewater. This causes a lack of bioavailability and absorption function of the various active components contained in these medicinal plants, so that their use needs to be consumed repeatedly and given in large doses to get optimal function. Judging from its solubility properties, this black cumin seed essential oil is made in the form of an emulsion to increase the stability of the preparation [9].

In further research, this black cumin seed essential oil emulsion was further developed into a nanoemulsion. Nanoemulsion preparations have the advantage of being faster in the penetration process. By modifying the shape and reducing the size to 100 nm, it is expected to increase the effectiveness and efficacy of black cumin seed essential oil for various applications [10].

Several drug carrier systems including nanoemulsions, microemulsions, liposomes, solid lipid nanoparticles, microspheres, and self-microemulsifying drug delivery systems have been studied to enhance the therapeutic efficacy of hydrophobic drugs or nutraceuticals by enhancing their bioavailability and tissue targeting capabilities. Among various new drug delivery systems, nanocarrier systems have emerged as the best and most appropriate alternative. In nanoemulsion preparations, the most stable nanocarrier systems have combined the advantages of other innovative carrier systems with the highest kinetic and thermodynamic stability, excellent acceptability and minimal inter-subject variability [11].

The use of nanoemulsions consisting of oil and water work together to achieve effective drug delivery targets. The active substances contained in this black cumin seed essential oil can be dissolved in the oil phase and then homogeneously dispersed in the water phase, so that the amount of dissolved active substances sent to the target area will increase. In addition, the release properties and treatment efficiency can also be improved. This allows for the simultaneous delivery of hydrophilic and lipophilic drugs [12].

Nanoemulsions can be produced using a variety of methods, including high energy emulsification methods such as high pressure homogenization and ultrasonication. Low energy methods can also be used, such as phase inversion composition, phase inversion temperature and solvent transfer methods. The purpose of making the preparation of black cumin seed essential oil nanoemulsion, so that the efficacy of the existing active substancesin the The black cumin seed essential oil can work effectively to achieve the expected effect in thebody. In addition, the reason for developing a formulation containing black cumin seed essential oil was to protect the substance from evaporation and degradation, and to achieve controlled release of the substance [12]. The purpose of this review article is to obtain information about the effectiveness and stability of several formulations of essential oil nanoemulsion preparations from black cumin seeds (Nigella sativa L.).

II. Material And Methods

Literature review of articles is carried out by tracing several journal articles obtained from published scientific journals at level international and national through search engines in the form of Scopus, ScienceDirect, Google Scholar, DOAJ, Elsevier, Garuda Portal and Pubmed. Screening of journals or articles based on content, title, abstract, and keywords in the form of Nigella sativa formulation, essential oil, black cumin, Black Seed, black seed, black cumin in nanoemulsion form. The inclusion criteria in this review regarding the effectiveness and stability of the formulation of essential oil nanoemulsion preparations from black cumin seeds (Nigella sativa L.) published starting from 2010 to 2020. Articles that meet the criteria will be used as a source for further review.

III. Result

Essential oils are a research material that is quite a lot developed by researchers today. Several researchers have documented the characteristics, uses and pharmacological effects of various types of essential oils. Some examples of essential oils used in the formulation of nanoemulsions are provided in Table 1. Essential oils are a large group of volatile vegetable oils, wherein they contain a large number of components of the main efficacious substances. The use of essential oils has been carried out in several research journals, for example, the use of essential oils derived from sea fennel, cumin, black cumin, nutmeg, peanuts, ginger and others.

Table 1: Examples of Essential Oils in Nanoemulsion Formulations.

No	Natural ingredients	Title	Writer (Year)
1.	Cumin (Cuminum cyminum) Essential Oil	*Ultrasonic Nanoemulsification of Cuminum cyminum Essential Oil and Its Applications in Medicine.*[13]	Nirmala, Durai, Rao, & Nagarajan, (2020)
2.	Sea Fennel Essential Oil (Crithmum maritimeum)	*Encapsulation of sea fennel (Crithmum maritimeum) essential oil in nanoemulsion and SiO2 nanoparticles for treatment of the crop pest Spodoptera litura and the dengue vector Aedes aegypti.*[14]	Suresh et al., (2020)
3.	Essential Oil Basil Leaves (Ocimum basilicum L.)	Formulation and Activity Test of Essential Oil Nanoemulsion of Basil Leaves (Ocimum basilicum L.) Against Salmonella typhii.[15]	Kristiani et al., (2019)
4.	Peanut Essential Oil (Arachis hypogaea)	*The Arachis hypogaea essential oil nanoemulsion as an efficient safe apoptosis inducer in human lung cancer cells (A549).*[16]	Fazelifar et al., (2020)
5.	Ginger (Zingiber officinale) Leaf Essential Oil	*Antibacterial activity of ginger (Zingiber officinale) leaves essential oil nanoemulsion against the cariogenic Streptococcus mutans.*[17]	Mostafa, (2018)
6.	Black Cumin Seed Essential Oil (Black cumin)	*Formulation, characterization and antimicrobial properties of black cumin essential oil nanoemulsions stabilized by OSA starch.*[18]	Sharif et al., (2017)

Essential oils in nanoemulsion formulations can be prepared by various methods, either high or low energy methods [17]. High energy methods involve the application of high pressure, homogenization or microfluidization [17] as in the manufacture of nanoemulsion formulations containing essential oil of cumin seeds (Cuminum cyminum)[13]. Peanut (Arachis hypogaea) essential oil [16], the nanoemulsion preparations were made using the ultrasonication method [19]. In addition, the manufacture of nanoemulsions with black cumin seed essential oil (Nigella sativa .L) also uses the high pressure homogenization method [18]. Whereas the low energy method involves continuous stirring of a mixture of oil, water, and surfactant, without drastic conditions or expensive equipment(Salam et al., 2016) such as in the nanoemulsion formulation of sea fennel essential oil (Crithmum maritimeum) using the Phase Inversion Temperature (PIT) method [14]. In the manufacture of essential oil nanoemulsions of basil (Ocimum basilicum L.) and ginger leaves [17] using the spontaneous emulsification method [15]. Of the various essential oils used in nanoemulsion formulations, black cumin seed essential oil (Nigella sativa .L) or black cumin is one of the ingredients that has beneficial potential when combinedinto thesome products or preparations. Besides being formulated into nanoemulsion form, this black cumin seed essential oil can be formulated into other dosage forms as shown in Table 2.

Table 2 : Formulation of Preparations Containing Black Cumin Seed Essential Oil.

No	Preparation Formula	Title	Writer (Year)
1.	Hydrogel	*The effect of a hydrogel made by Nigella sativa L. on acne vulgaris: A randomized double-blind clinical trial.*[20]	Soleymani et al., (2020)
2.	Hydrogel microemulsion	*Formulation evaluation of ketoconazole microemulsion- loaded hydrogel with nigella oil as a penetration enhancer.*[21]	Amra & Momin, (2019)

3.	Microemulsion	Microemulsion Formulation Contains Black Cumin Seed Oil (Nigella Sativa L.) and Olive Oil (Olea Europaea L.).[22]	Azzahra, Priani, & Gadri, (2018)
4.	Emulsion	*Caseinate-stabilized emulsions of black cumin and Tamanu oils: Preparation, characterization and antibacterial activity.*[23]	Urbánková et al., (2019)
5.	Nanoemulsion	*Development and optimization of self-nanoemulsifying drug delivery systems (SNEDDS) for curcumin transdermal delivery: an anti-inflammatory exposure.*[24]	Altamimi et al., (2019)
6.	Nanoemulsion	*Bioactive Self-Nanoemulsifying Drug Delivery Systems (Bio-SNEDDS) for Combined Oral Delivery of Curcumin and Piperine.*[25]	Kazi et al., (2020)

Of the various forms of formulations that use black cumin seed essential oil, preparations with a nanoemulsion delivery system have a good level of stability and effectiveness when formulated [26]. Black cumin seed essential oil in the form of nanoemulsion can provide good effectiveness because the drug is delivered in a very small size (nano) so that it can enter the body properly to treat a target disease [27]. In addition, the shape of this nanoemulsion tends to be stable [28]. The table below provides a summary of the results of the stability (Table 3) and effectiveness (Table 5) of various formulations of black cumin seed essential oil nanoemulsion that have been carried out.

Table 3 : Stability of Black Cumin Seed Essential Oil Nanoemulsion Preparation**.**

No	Ingredients	Stability	Title	Writer (Year)
1.	Black cumin seed oil, Tween 80 (non-ionic surfactant), Propylene glycol and 96% ethanol (cosurfactant).	The higher the concentration of oil used, the larger the average globule size (71.67 nm - 832.7 nm). Physical stability test showed that the nanoemulsion gel was stable at room temperature (25℃+2℃) and low temperature (4℃+2℃) for 8 weeks. Instability occurs at higher temperatures (40℃+2℃)	*Physical stability and antibacterial activity of black cumin oil (Nigella sativa L.) nanoemulsion gel.*[26]	Jufri & Natalia, (2014)
2.	Black cumin seed oil, Triton X-100 (non-ionic surfactant), Span-80 (non-ionic surfactant).	The surfactant concentration with an HLB value of 11.6 showed a smaller diameter with the lowest zeta potential, and without any phase separation.	*Synthesis, Stability and Selection Study of Oil-in-Water Nanoemulsions Containing Nigella Sativa L. Essential Oil.*[12]	Usta et al., (2017)
3.	Black cumin seed essential oil, Tween 80 (non-ionic surfactant), Ethanol (cosurfactant).	The average particle size of 37.47 nm indicates a minimum viscosity of 0.547 cps. The preparation is quite stable at cold temperatures compared to room temperature. Results showed no creaming or phase separation was observed in the formulation ($p<0.05$)	*Evaluation of the anticancer activity of sprout extract-loaded nanoemulsion of N. sativa against hepatocellular carcinoma.*[29]	Tabassum & Ahmad, (2018)
4.	Black cumin oil, cremophor RH 40, Tween 80 (surfactant), PEG 400, Transcutol, propylene glycol (cosurfactant).	The preparation met the requirements for percent transmittance (97.27 ± 0.06%), dispersibility test (grade A), stable in robustness and thermodynamic tests. The SNEDDS preparation was able to spontaneously form nanoemulsions with an average globule size of 99 nm with spherical globules.	Formulation and Characterization of SNEDDS (Self Nanoemulsifying Drug Delivery System) Containing Black Cumin Oil and Olive Oil.[30]	Priani et al., (2020)

5.	Black Seed Oil, Tween 20, Tween 80, Cremophor RH 40 (surfactant), PEG 400 (cosurfactant)	The preparation has a globule diameter of 57.6 ± 13.04 nm, a polydispersity index of 0.288 ± 0.033, and a zeta potential of 0.243 ± 0.136 mV. The results of the stability test on the centrifugation test showed that it was physically stable, although in the third cycle of freeze thaw it showed significant difference with the previous cycle in the polydispersity index and zeta potential.	Development, Evaluation, and Test of Acute Anti-Inflammatory Activity of Black Cumin Oil Spontaneous Nanoemulsion Preparation.[31]	Olii, Sofi, Mudhakir & Iwo, (2014)

IV. Discussion

Preparation Stability Study

The stability of nanoemulsion preparations in a study conducted by Jufri and Natalia, (2014) showed that the results of stability tests on the formulation of black cumin seed oil nanoemulsion gel used in high quantities made it difficult to form nanoemulsion gel due to instability in the system. In addition, the evaluation results show that the higher the concentration of black cumin oil, the lower the pH and viscosity of the preparation. The results of the physical stability test on the nanoemulsion in the form of a gel showed that the emulsion was stable at room temperature (25°C ± 2°C) (Figure 2) and low temperature (4°C ± 2°C) for 8 weeks (Figure 1). The acidity (pH) of all nanoemulsion gels during storage did not show a statistically significant difference ($P > 0.05$). Stability indicates that the selection of surfactant and cosurfactant concentrations is appropriate. Black cumin seed essential oil in this formula acts as an active substance and can be efficacious as antibacterial, antioxidant and antifungal, so it can reduce contamination by microorganisms and oxidation by air with or without light. After more than 8 weeks, storage at high temperature (40°C ± 2°C) became unstable (Figure 3). The acidity (pH) of all nanoemulsion gels showed a significant difference ($P < 0.05$). This can be caused by exposing the temperature to more than the normal temperature (room temperature) so that it can reduce stability. In addition, Tween 80 and carbomer are sensitive to oxidation, so the addition of a gel base can actually reduce the stability of the nanoemulsion preparation. Black cumin seed essential oil in this formula acts as an active substance and can be efficacious as antibacterial, antioxidant and antifungal, so it can reduce contamination by microorganisms and oxidation by air with or without light. After more than 8 weeks, storage at high temperature (40°C ± 2°C) became unstable (Figure 3). The acidity (pH) of all nanoemulsion gels showed a significant difference ($P < 0.05$). This could be caused by exposing the temperature to more than the normal temperature (room temperature) so as to reduce stability. In addition, Tween 80 and carbomer are sensitive to oxidation, so the addition of a gel base can actually reduce the stability of the nanoemulsion preparation. Black cumin seed essential oil in this formula acts as an active substance and can be efficacious as antibacterial, antioxidant and antifungal, so it can reduce contamination by microorganisms and oxidation by air with or without light. After more than 8 weeks, storage at high temperature (40°C ± 2°C) became unstable (Figure 3). The acidity (pH) of all nanoemulsion gels showed a significant difference ($P < 0.05$). This can be caused by exposing the temperature to more than the normal temperature (room temperature) so that it can reduce stability. In addition, Tween 80 and carbomer are sensitive to oxidation, so the addition of a gel base can actually reduce the stability of the nanoemulsion preparation. thereby reducing contamination by microorganisms and oxidation by air with or without light. After more than 8 weeks, storage at high temperature (40°C ± 2°C) became unstable (Figure 3). The acidity (pH) of all nanoemulsion gels showed a significant difference ($P < 0.05$). This can be caused by exposing the temperature to more than the normal temperature (room temperature) so that it can reduce stability. In addition, Tween 80 and carbomer are sensitive to oxidation, so the addition of a gel base can actually reduce the stability of the nanoemulsion preparation. thereby reducing contamination by microorganisms and oxidation by air with or without light. After more than 8 weeks, storage at high temperature (40°C ± 2°C) became unstable (Figure 3). The acidity (pH) of all nanoemulsion gels showed a significant difference ($P < 0.05$). This can be caused by exposing the temperature to more than the normal temperature (room temperature) so that it can reduce stability. In addition, Tween 80 and carbomer are sensitive to oxidation, so the addition of a gel base can actually reduce the stability of the nanoemulsion preparation. The acidity (pH) of all nanoemulsion gels showed a significant difference ($P < 0.05$). This can be caused by exposing the temperature to more than the normal temperature (room temperature) so that it can reduce stability. In addition, Tween 80 and carbomer are sensitive to oxidation, so the addition of a gel base can actually reduce the stability of the nanoemulsion preparation. The acidity (pH) of all nanoemulsion gels showed a significant difference ($P < 0.05$). This can be caused by exposing the temperature to more than normal temperature (room temperature) so that it can reduce stability. In addition, Tween 80 and carbomer are sensitive to oxidation, so the addition of a gel base can actually reduce the stability of the nanoemulsion preparation [26].

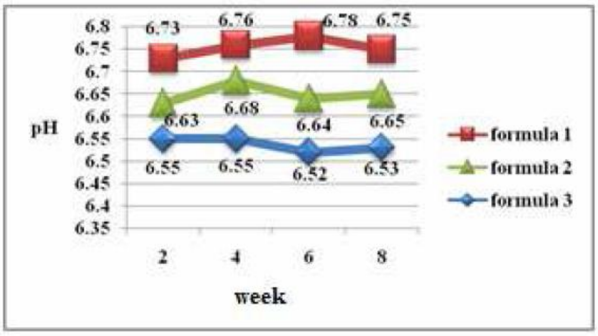

Figure 1 : Graph of changes in pH during storage (8 weeks) at low temperatures (4°C ± 2°C).[26]

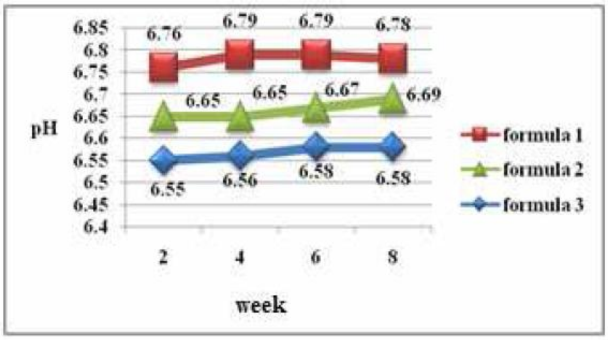

Figure 2 : Graph of changes in pH during storage (8 weeks) at room temperature (25°C ± 2°C).[26]

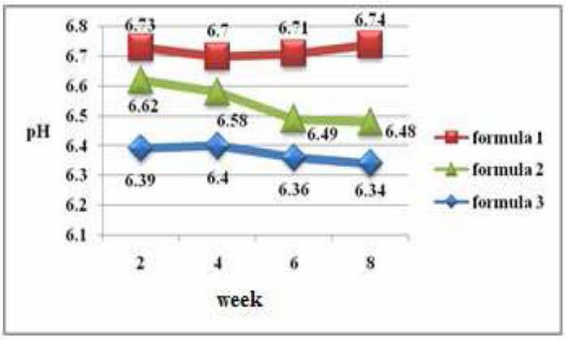

Figure 3 : Graph of changes in pH during storage (8 weeks) at high temperatures (40°C ± 2°C). [26]

Subsequent research conducted by Usta et al., (2017) showed that the average diameter of the globules could increase with the increase in the percentage of oil, so a high percentage of surfactant could produce the smallest diameter in nanoemulsion preparations. In this study, the surfactants used were Triton X-100 and Span 80 where the structure of Triton X-100 with a BM of 250.38 g/mol [32] smaller in size than the Span 80 with a BM of 428.6 g/mol[33]. The combination of the two surfactants was carried out to form the structure of the nanoemulsion preparation (figure 4). Overall, black cumin seed oil nanoemulsion preparations can be the best candidates for drug delivery applications [12].

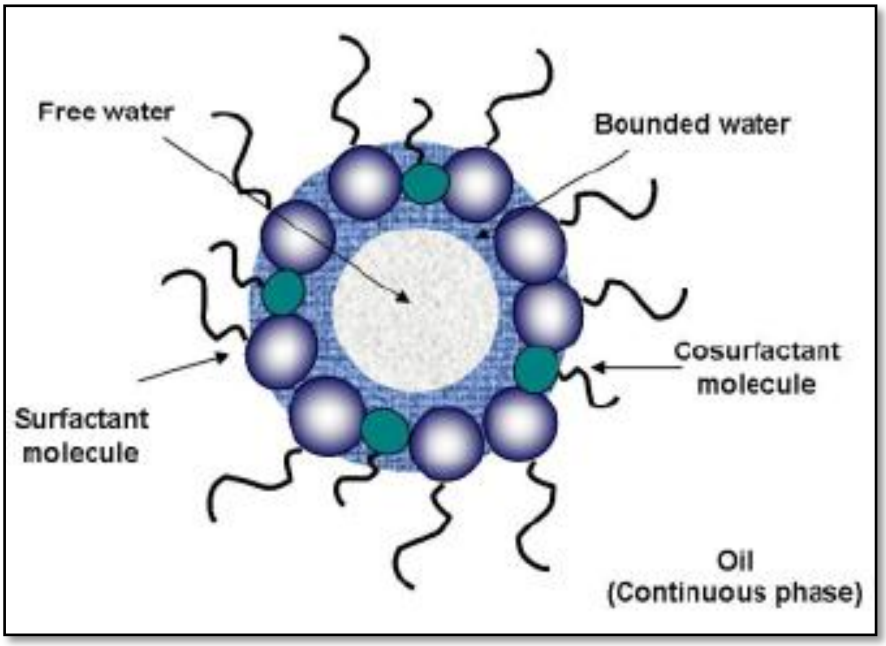

Figure 4 : Nanoemulsion Structure [34]

The next study, the optimized formulation of 5d S-NSNE nanoemulsion resulted in high stability in storage for 6 months and showed no creaming or phase separation in the observed preparations [29]. To determine the stability of the nanoemulsion formulation, the preparations were stored for a period of 6 months. Measurement of particle size, consistency and efficiency of nanoemulsion adsorption was carried out at time intervals (0, 30, 60, 120 and 180) days. As a result, no significant changes were found in the particle size, consistency and adsorption efficiency of the nanoemulsions during the given period (Table 4).

Table 4 : Stability of 5d S-NSNE [29]

Formulation Parameters	**Day**				
	0	**30**	**60**	**120**	**180**
Color	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
Consistency	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
Particle size	18.73±0.298*	20.02±9.1	25.32±11.2	28.00±17.3	32.22±11.9
Adsorption Efficiency (%)	83±1.15	82±2.86	80±2.57	79±3.46	77±2.79

All data were expressed as mean ± SD (n = 3).
* P < 0.05 was considered significant, when compared with (0-180) days.

Furthermore, the research conducted by Priani explained that the addition of surfactants and cosurfactants that are able to mix with the oil phase will increase the effectiveness of the formation of the nanoemulsion system. It is known that the SNEDDS preparation is able to form nanoemulsions spontaneously with the addition of water and produce globules with an average size of 99 nm with a standard deviation value according to the PSA results of 46 nm. This meets the SNEDDS criteria, which must be able to form a nanoemulsion system with a globule size of less than 100 nm. This provides an adequate reduction in free energy which can counteract thermodynamic instability [30].

Table 5 : Effectiveness of Preparation of Black Cumin Seed Essential Oil Nanoemulsion

No	Ingredients	Effectiveness	Title	Writer (Year)
1.	Black cumin seed oil, Tween 80 (surfactant), Propylene glycol and 96% ethanol (cosurfactant).	Black cumin seed oil in the form of nanoemulsion gel has an average inhibition zone in the range of 9-20 mm, while black cumin seed oil has an average inhibition zone of about 15-34 mm.	*Physical stability and antibacterial activity of black cumin oil (Nigella sativa L.) nanoemulsion gel.*[26]	Jufri & Natalia, (2014)
2.	Black cumin seed oil, Triton X-100 (non-ionic surfactant), Span-80 (non-ionic surfactant).	The preparation of black cumin seed oil nanoemulsion showed good preparation stability so that it was able to prove that black cumin seed oil in the form of nanoemulsion could be used as a candidate for drug delivery applications.	*Synthesis, Stability and Selection Study of Oil-in-Water Nanoemulsions Containing Nigella Sativa L. Essential Oil.*[12]	Usta et al., (2017)
3.	Black cumin seed essential oil (Nigella Sativa Essential Oil), Tween 80 (surfactant), Ethanol (cosurfactant)	The 5d S-NSNE nanoemulsion showed reduced cell viability and reduced colony formation with an IC50 value of 27,375 g/mL in 24 hours and an IC50 value of 54.75 g/mL in 48 hours.	*Evaluation of the anticancer activity of sprout extract-loaded nanoemulsion of N. sativa against hepatocellular carcinoma.*[29]	Tabassum & Ahmad, (2018)
4.	Cumin seed oil (Nigella Oil), Cremophore EL (surfactant), Tween 80 (cosurfactant)	The data prove that there is a high in vitro and significant ex vivo nasal mucosal flux. There was an increase in the concentration of the drug in the brain which indicated the efficiency of targeting the formulation through the in route. The resulting AUC values were 2048263.8 ± 23876.90 (ng. min/ml) (in the brain) and 1399579.6 ± 25896.62 (ng. min/ml) (in blood), and with a value of DTE% 420.35 ± 89.69 DTP% 85.43 ± 6.42.	*Chitosan coated synergistically engineered nanoemulsion of Ropinirole and nigella oil in the management of Parkinson's disease: Formulation perspective and In vitro and In vivo assessment.*[35]	Nehal et al., (2020)

Effectiveness Study

Jufri and Natalia (2014) showed that the nanoemulsion gel of black cumin seed oil has an average inhibition zone that is smaller than that of black cumin seed oil. This shows that the antibacterial activity of black cumin oil is better than in the nanoemulsion gel dosage form. There was a significant difference ($P < 0.01$) between the inhibition zone of black cumin seed essential oil and its nanoemulsion gel (Figure 5). This can occur due to the dissolution of black cumin seed oil in the gel base so that its antibacterial activity is reduced. Another factor that can cause the antibacterial activity of the nanoemulsion gel to be lower than that of the black cumin seed oil is due to the inhomogeneous effect of the black cumin oil concentration and ultimately lower the antibacterial effect in the inhibition zone. Formulas that do not add preservatives, such as parabens, and antioxidants such as BHT, can also be the reason why the antibacterial activity of the nanoemulsion gel activity is reduced from black cumin oil [26].

A research study conducted by Usta et al., (2017) stated that thymoquinone was the most active compound found in black cumin seed oil (Nigella sativa L.). Nigella sativa L. oil combined with oxidative agents showed significant anticancer activity in MCF-7 breast cancer cells. To increase the potential for effective drug targeting, nanoemulsions were chosen as the best candidates in drug delivery applications because they are considered to have good stability so as to increase the amount of dissolved drug to be delivered to the treatment target area [12]. Overall, several research results prove that the black cumin seed essential oil nanoemulsion preparation has good effectiveness so that it can be chosen as the best candidate in drug delivery applications [8].

Subsequent research conducted by Tabbasum and Ahmad (2018), showed that the optimized nanoemulsion (5d S-NSNE) also showed a reduction in the viability of cancer cells and their colony formation, as well as increased the intensity of ROS (Reactive Oxygen Species) and chromatin condensation on the cells. liver cancer without destroying normal cells. This study supports the use of target cell-based 5d S-NSNE nanoemulsion as a therapeutic application for liver cancer [29].

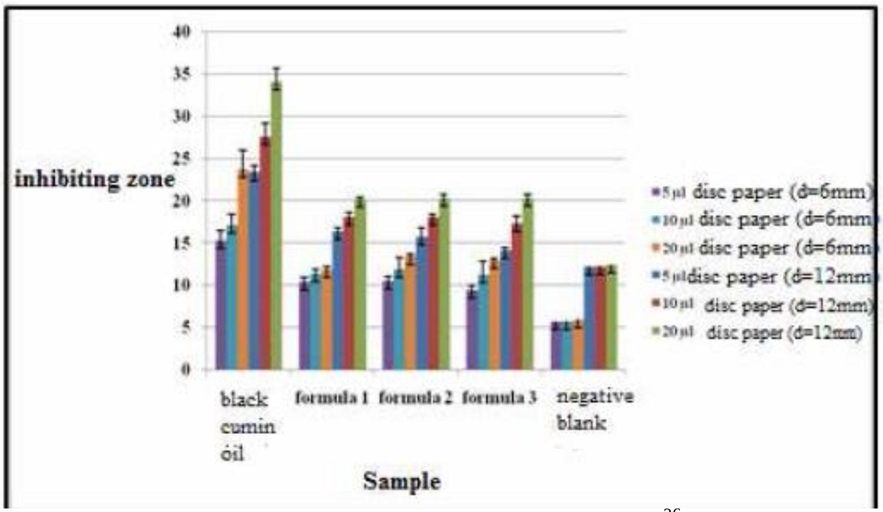

Figure 5 : Graph of Average Inhibition Zone [26]

The data were obtained through experiments conducted by Nehal et al., (2020) proved that there was a high in vitro yield and a significant ex vivo nasal flux on the mucosa. There was also an increase in the concentration of the drug in the brain indicating the efficiency of targeting the formulation via the intranasal route. Parkinson-like symptoms in 6-OHDA-induced mice can be treated with drugs containing black cumin seed oil nanoemulsion combined with ropinirole and described through behavioral studies, biochemical estimation, histopathological assays, and immunohistochemical assays. The results of pharmacokinetic testing showed that the Cmax value of RHCl nanoemulsion preparations combined with black cumin seed oil by the intra-nasal route was 36,180.99 ± 4,582.14 ng/mL (brain) and 18,722.07 ± 2,487.67 36,180.99 ± 4,582.14 ng/mL (blood). The AUC value for the minute 0 to 480 is 2,048,263.8 ± 23,876.90 ng. min/ml (brain) and 1,399,579.6 ± 25,896.62 ng. min/ml (blood), and with a value of drug targeting efficiency (DTE%) of 420.35 ± 89.69 and a value of direct transport percentage (DTP%) of 85.43 ± 6.42. Thus, nanoemulsion preparations administered via the intranasal route can avoid hepatic metabolism, protect against metabolic enzymes, increase drug bioavailability and increase drug absorption into the brain [35].

V. Conclusion

Based on the literature study, it can be concluded that the nano-delivery system in the formulation of the black cumin seed (Nigella sativa L.) essential oil nanoemulsion as a whole shows that there is an increase in the stability of the preparation and the effectiveness of the active substance. This increased stability was initiated by the addition of the nanoemulsion carrier and the surfactant used. In addition, several methods of making nanoemulsions can also affect the stability of the preparation. The effectiveness of nanoemulsion preparations can increase because the particle size of the active substance in the black cumin seed essential oil is smaller, making it easier for the distribution and permeation of the drug into the targeted cells so that it is more efficient in the application of the drug delivery.

The results of the study suggest that further toxicity tests should be carried out because the administration of drugs in nanoemulsion carriers can also cause toxicity at certain concentrations.

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