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Phytochemical and Anti-Inflammatory Activity of *Nigella sativa*: A Review

Nailatul Fhadillah[1], Ifora Ifora[*1], Sri Oktavia[1]
[1] *Department of Pharmacology and Clinical Pharmacy, School of Pharmaceutical Science Padang (STIFARM Padang), West Sumatra, Indonesia, 25147*
Corresponding Author : Nailatul Fhadillah
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Abstract: *Inflammation acts as the body's physiological response to infection and injury and maintains tissue homeostasis in various hazardous conditions. Therefore, this article was designed to provide up-to-date information on the phytochemical and anti-inflammatory activities of Nigella sativa. This review presents the literature evidence from 2011 to 2021. As a source of literature review, three bibliographic databases were used (Pubmed, ScienceDirect, Google Scholar). A total of 18 studies were used in this paper based on the eligibility criteria, and this review includes ten articles on phytochemicals and eight articles on an anti-inflammatory. Phytochemical compounds contained in Nigella sativa are alkaloids, flavonoids, steroids, phenolics, saponins, terpenoids, and resins. Pharmacological investigations reported the anti-inflammatory activities of Nigella sativa by inhibiting edema formation, decreasing the development of granulomatous tissue, reducing arthritis, reducing leukocyte count, increasing IL-10 and TGF-β gene expression, and inhibiting NO production decreasing IL-6 and TNF expression.*

Keywords: *Phytochemical; Pharmacology; Anti-inflammatory; Nigella*

I. INTRODUCTION

Inflammation is a protective strategy that develops in higher organisms in response to adverse disturbances such as microbial infection, tissue injury, and other harmful conditions [1], [2]. Inflammation is characterized by swelling (tumor), redness (rubor), pain (dolor), heat (color), and loss of function in response to infection or injury which ultimately leads to restoration of cellular homeostasis and tissue structure and function [3]. The uncontrolled tissue recovery process can lead to diseases such as vasomotor rhinorrhoea, rheumatoid arthritis, and atherosclerosis[4].

The most common drugs used to reduce inflammation are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)[5]. NSAID drugs have analgesic, antipyretic, and anti-inflammatory effects. Most NSAIDs are acidic compounds with relatively high bioavailability, they are also highly bound to plasma proteins and are metabolized in the liver [6]. Long-term use of NSAIDs can usually cause luminal ulceration, intestinal mucosal bleeding, renal and cardiovascular toxicity [7], [8]. Therefore, medicinal plants are indispensable as an alternative treatment for inflammation because of their relatively more minor side effects [9], [10].

Medicinal plants have been the primary source of medicine worldwide since ancient times [11], [12]. Previous research has discovered that different plants have varied therapeutic properties, such as anti-inflammatory properties [13], [15]. Medicinal plants can alter physiological and pathological processes and prevent or treat disease. In recent years, the use of medicinal plants as treatment has increased due to several factors such as easy access, lower costs, and fewer side effects[16]. *Nigella sativa* is one of the medicinal plants in the family Ranunculaceae, commonly known as Black Seed. *N. sativa* comes from Southern Europe, North Africa, Southwest Asia and is cultivated in many countries in the world such as the Mediterranean region of the Middle East, Southern Europe, India, Pakistan, Syria, Turkey, Saudi Arabia [17].

Previous pharmacological studies found that *N.sativa* has anti-bacterial [18], antifungal [19], anti-microbial[20], anticancer [12], antidiabetic[21], antioxidant [22] and anthelmintic activities[23]. However, little testing has been done regarding the phytochemical content and its use as an anti-inflammatory. Therefore, this study aims to provide up-to-date information on the phytochemical and anti-inflammatory activity of *Nigella sativa*.

II. METHODS

In preparing this article, the researchers verified the plant names using www.theplantlits.org. The most recent information on *N.sativa* is collected from accepted scientific journals worldwide via PubMed, ScienceDirect, and Google Scholar electronic searches. The literature search was conducted to provide evidence on phytochemical information and in-vivo and in-vitro anti-inflammatory activity of *N.sativa* collected from 2011 to 2021. In this study, the search was conducted using online media with the keywords as follows: "Phytochemicals," "Phytochemistry," "Anti-inflammatory," "Bioactive compounds," and "*Nigella sativa*." In this study, the articles reviewed are original or research articles published in English and Indonesian. Review articles, systematic reviews, meta-analysis, short communication, newsletters, editorials, case reports, and expert opinions are not used in this study. Complete articles were collected, examined, summarized, and concluded. The most relevant articles were selected for screening and included in this review.

III. RESULT AND DISCUSSION

The study regarding the phytochemical and anti-inflammatory *N.sativa* used as many as 18 studies. There are ten studies on the phytochemical *N.sativa* and eight literature studies on an anti-inflammatory.

3.1 Phytochemical

A phytochemical test is a method to determine the various chemical compounds formed and contained in plants ranging from chemical structure, biosynthesis, changes, metabolism, and bioactivity. The phytochemical content in *N.sativa* has been proven in several studies, and the results of these studies will be summarized in Table 1 below.

Table 1: Summary of Bioactive compounds of *Nigella sativa*

Parts	Compounds	Country	References
Seeds	Alkaloids, tannins, flavonoids, and sterols	Pakistan	[24]
Seeds	• Methanol and ethanol extract (steroids, tannins, flavonoids, coumarins, cardiac glycosides, saponins, and diterpenes) • Chloroform extract (steroids, terpenoids, flavonoids, coumarins, and cardiac glycosides)	Pakistan	[25]
Seeds	Thymol, α-phellandrene, camphor, borneol, carvacrol, α-thujene, α-pinene, sabinene, β-pinene, p-cymene, α-terpinene, α-terpinolene, unidentified, linalool, O-cymene, thymoquinone, β-caryophyllene, and α-eudesmol	India	[26]
Seeds	Flavonoids, tannins, sterols, phenols, saponins, and terpenoids	India	[27]
Seeds	Alkaloids, anthraquinone, tannins, saponins, flavonoids, steroids, terpenoids, thymoquinone, thymol, longifolene, supraene, campesterol, stigmasterol and β-sitosterol	India	[28]
Seeds	β-Pinene, O-Cymene, Trans-4-methoxy thujone, Terpinene-4-ol, Thymoquinone, 2-Isopropylidene-5-methylhex-4-enal, Limonen-6-ol, Longifolene, ß-bisabolene, and Stigmasterol.	Iraq	[29]
Seeds	β-pinene, thymoquinone, thymol, phenolics, tannins, and flavonoids	Arabic	[30]
Seeds	• Petroleum ether extract (Alkaloids, coumarins, phenols, resins, saponins, flavonoids, quinines, tannins) • Methanol extract (alkaloids, coumarins, phenols, resins, saponins, flavonoids, steroids, tannins) • Distilled water extract (alkaloids, coumarins, phenol, resins, saponins, flavonoids, steroids, quinines)	Arabic	[31]
Seeds	Steroids, triterpenoids, flavonoids, tannins, phenols, alkaloids, methyl salicylate	India	[32]

Seeds	• Hexane extract (steroids, terpenes, alkaloids, tannins, and saponins) • Acetone extract (steroids, terpenes, alkaloids, tannins, polyphenols, and flavonoids)	Africa	[33]

Phytochemical tests of *N.sativa* and *Trachyspermum ammi* plants were carried out by Javed *et al*. the test results showed the presence of alkaloids, tannins, flavonoids, and sterols in *N.sativa* and *T.ammi* plants. The content of tannins and sterols in *N.sativa* was found in quite large amounts (>75%), while flavonoids and alkaloids were found (50%) and (25%) respectively [24].

Based on research by Ishtiaq *et al.*, the extraction of *N.sativa* using methanol, ethanol, and chloroform as solvents showed effective antibacterial activity against gram-positive and gram-negative bacteria. Phytochemical screening for secondary metabolites showed that steroids, tannins, flavonoids, coumarins, cardiac glycosides, saponins, and diterpenes were present in the methanol extract and ethanol extract. Meanwhile, the chloroform extract showed steroids, terpenoids, flavonoids, coumarins, and cardiac glycosides [25].

The study conducted by Raj and Chandrasekaran reported the extraction of *N.sativa* using the hydrodistillation method. Hydrodistillation of *N.sativa* produced 0.03% (v/w) essential oil with a pale yellow-green color. Overall the compounds identified by GC-MS (Gas Chromatography and Mass Spectrometer) represent 100% essential oils. The chemical compounds contained in the essential oil are thymol (19.13 %), α-phellandrene (14.9 %), camphor (12.14 %), borneol (11.31 %), carvacrol (8.65 %), α-thujene (0.16 %), α-pinene (0.33 %), sabinene (0.16% %), β-pinene (0.12 %), p-cymene (3.32 %), α-terpinene (0.33 %), α-terpinolene (7.48 %), unidentified (0.49 %), linalool (1.33 %), O-cymene (0.83 %), thymoquinone (5.99 %), β-caryophyllene (7.98%) and α-eudesmol (5.82%) [26].

The existence of various phytochemical compounds in *N.sativa* using ethyl acetate extract and n-butanol extract as solvent was revealed by Amutha and Godavari. The ethyl acetate extract showed the presence of flavonoids, tannins, sterols, saponins, and terpenoids. Meanwhile, the n-butanol extract showed the presence of flavonoids, tannins, sterols, and saponins. Any of these secondary metabolites may be responsible for the anti-diabetic activity of the plant [27].

Phytochemical analysis of seeds of *N.sativa* was reported by Nivitha and Prasanna. The results of the analysis showed the presence of alkaloids, anthraquinones, tannins, saponins, flavonoids, steroids, and terpenoids. Researchers also conducted an analysis by GC-MS which showed the contents in *N.sativa* including thymoquinone (0.03%), thymol (0.06%) longifolene (0.03%), supraene (0.08%), campesterol (0.13%), stigmasterol (0.14%) and -sitosterol (0.40%) [28].

The identification of phytochemical compounds *N. sativa* was carried out by Hadi *et al* using GC-MS analysis using methanol as a solvent. The results of the GC-MS analysis showed that the main compounds were β-Pinene, O-Cymene, Trans-4-methoxy thuja, Terpinene-4-ol, Thymoquinone, 2-Isopropylidene-5-methylhex-4-enal, Limonen-6-ol, Longifolene, β-bisabolene, and Stiqmasterol [29].

A study conducted by Shaleh *et al.* reported the results of phytochemical analysis using the GC-MS method. The *N.sativa* oil capsule shows the presence of a compound in it, namely Beta-Pinene (10%), Thymoquinone (8.6%), and Thymol (10.3%). Researchers also analyzed the Folin Ciocalteu method to determine the total phenolic, tannin, and flavonoid content. Total phenolic compounds in oil And capsules of *N.sativa* was 248 mg/ml, in the aqueous extract was 21 mg/ml, and in the methanol extract was 39 mg/ml. The content of flavonoids in the oil and capsules was 19.8 mg/ml, in the aqueous extract was 0.11 mg/ml, and in the methanol extract was 2.98 mg/ml. While the tannin content in the oil was 3.4 mg/ml), in the capsules was 8.3 mg/ml, in the water extract was 0.49 mg/ml, and in the methanol extract was 1.5 mg/ml. The results showed that *N.sativa* is a potential source of natural phenolic compounds [30].

Reddy et al. conducted a phytochemical screening on *N.sativa* and leaves of *Cassia Angustifolia.* The solvents used were petroleum ether, methanol, and distilled water to find chemical compounds in it. The petroleum ether extract contains alkaloids, coumarins, phenols, resins, saponins, flavonoids, quinine, steroids, and tannins. The methanol extract contains alkaloids, coumarins, phenols, resins, saponins, flavonoids, steroids, and tannins. In contrast, the distilled water extract contains alkaloids, coumarins, phenols, resins, saponins, flavonoids, steroids, and quinine. Alkaloids are present in high amounts in petroleum ether, methanol, and distilled water. Flavonoids are also high quantities in petroleum ether solvents and distilled water. Meanwhile, phenols, resins, saponins, and steroids were also found in high amounts in all solvent extracts [31].

GCMS analysis was performed by Selvaraju *et al* on the ethanolic extract of *N.sativa.* The analysis results were found to contain various components, namely steroids, triterpenoids, flavonoids, tannins, phenols, alkaloids, and methyl salicylate [32].

Furthermore, Tiji *et al.* also carried out phytochemical tests of hexane extract and *N.sativa* to find chemical components. In the hexane extract, steroids, terpenes, alkaloids, tannins, and saponins were found. While in the acetone extract, steroids, terpenes, alkaloids, tannins, polyphenols, and flavonoids were found [33].

3.2 Anti-inflammatory activity

N. sativa plants have various kinds of pharmacological activities so they are very beneficial for the body, one of which is anti-inflammatory activity. The anti-inflammatory activity of *N.sativa* has been proven by in-vivo and in-vitro studies. A total of 8 research studies have been conducted and the results of these studies are summarized in Table 2 below.

Table 2. Summary of Anti-Inflammatory Properties of *Nigella sativa* (In-vivo and In-vitro studies)

Type of extract/ Formulation	Plant part	Dose/ Concentration	Experimental Model	Animal/ Cell/ specimen	Reported activity	Region	References
In-vivo							
Ethanol extract	Seeds	250, 500 mg/kg BW	Carrageenan induced rat paw edema model	Long Evans Norway Rats	Ethanol extract of *N.sativa* showed anti-inflammatory activity by inhibiting edema formation	Bangladesh	[34]
Methanol extract	Seeds	1 mg/kg BW	Kaolin induction	Male Wistar rats	Methanolic extract of *N.sativa* showed significant anti-inflammatory activity by inhibiting edema formation in	Indian	[35]
Ethanol extract	Seeds	50 mg/Kg BW	Formalin induction	Male albino rats	Seeds exerts of *N.sativa* showed an anti-inflammatory effect characterized by reduction of edema at all time intervals	Pakistan	[36]
Fixed oil	Seeds	10 ml/kg BW	Carrageenin-induced hind paw edema, cotton pellet granuloma, formaldehyde induced arthritis method	Albino Wistar rats	Fixed oil showed anti-inflammatory activity characterized by decreased edema, decreased granulomatous tissue formation, and reduced arthritis.	India	[37]
Oil	Seeds	5%, 7, 5% and 10%	Carrageenan-induced paw edema and granuloma pouch on rats.	Wistar rats	Balsam sticks can overcome acute and sub-acute inflammation as indicated by high edema inhibition, lowering the number of leukocytes and significantly lowering TNF- levels	Indonesia	[38]
Oil	Seeds	0.91 and 1.82 mL/ kg	Complete Freund's Adjuvant (CFA) Induced arthritis method	Female Wistar rat	*N.sativa* oil can significantly attenuate adjuvant-arthritis in Italian rats	Italy	[39]
Oil	Seeds	1, 2, and 4 mL/kg BW	Carrageenan-induced paw edema	Wistar-Bratislava	*N.sativa* oil showed significant anti-inflammatory activity characterized by reducing paw edema	Romania	[40]
In-vitro							
Ethanol Extract	Seeds	1µg/mL	LPS induction	RAW cells 264.7	Ethanol extract of *N.sativa* showed anti-inflammatory activity by significantly increasing the expression of the IL-10 gene and decreasing the expression of IL-6 and TNF-α in RAW cells 264.7. The combination of *N.sativa* and *Silybum marianum* methanol extract significantly increased the	Arab	[41]

					expression of IL-10 and TGF-β, decreased the expression of IL-6, TNF-α, and inhibited NO production in RAW 264.7 cells and peritoneal macrophages.		

3.2.1. In-vivo study

Parveen *et al* tested the effect of anti-inflammatory activity of the ethanolic extract of *N.sativa* on Long Evans Nowregia rats. The ethanolic extract of *N.sativa* given at doses of 250 and 500 mg/kg BW orally showed an anti-inflammatory effect. Inhibition of edema formation showed 28.75% and 43.79%, respectively, comparable to standard aspirin 40.52 % and hydrocortisone 47.71%. So the results of this test found that a significant anti-inflammatory effect was shown in the administration of 500 mg/kg BW ethanol extract with 43.79% inhibition [34].

The study conducted by Islam *et al* reported the results of testing the anti-inflammatory activity of *N.sativa* at various stages of germination (days 5, 7, and 11) by dividing the rats into 6 test groups, namely one control group, one standard group, and four test groups. An increase in paw volume was observed after 1, 3, 6, and 18 hours and compared with the volume measured after kaolin injection. The germination extract on day 5 was inhibited by 72.5%, while the indomethacin group was 51.25% and the seed extract was 46.25% at the same time (18 hours). The inhibition of edema growth in hind paws of rats was higher in the germination extract on day 5 followed by day 7 and indomethacin which was used as the standard group. The values obtained showed a significant decrease in the growth of rat hind paw edema [35].

Testing of the anti-inflammatory activity of the ethanolic extract of *N.sativa* was carried out by Bashir *et al*. Rats were randomly divided into 3 groups, each group was given a different dose. In the treatment group A (10 ml/Kg BW of ordinary salt), Group B (ethanol extract of *N. sativa* 50 mg/kg BW), and group C (diclofenac sodium 25 mg/kg BW). Increased edema was measured at 1, 3, 10, and 25 hours after formalin injection. At all time intervals, the reduction in edema caused by diclofenac sodium was greater than that of *N.sativa* except at 25 hours when *N.sativa* caused a 26.66% reduction in inflammation compared to 23.33% of diclofenac sodium. *N.sativa* extract has a longer duration of anti-inflammatory activity than diclofenac sodium [36].

The anti-inflammatory activity effect of *N.sativa* was proven by Pise and Padwal using 3 methods, namely carrageenin-induced hind paw edema, cotton pellet granuloma, and formaldehyde induced arthritis method. The model of acute inflammation is carrageenin-induced paw edema in rats. *N.sativa* showed statistically significant anti-inflammatory activity compared to controls ($P < 0.001$) but was lower than aspirin. In the cotton pellet-induced glaucoma method, *N.sativa* significantly reduced granulomatous tissue formation, compared to the control ($P < 0.001$). Whereas in the chronic inflammation model using formaldehyde-induced arthritis, *N.sativa* showed significant anti-inflammatory activity comparable to aspirin ($P > 0.05$) [37].

The results of the test on the anti-inflammatory activity of *N.sativa* on balsam sticks were reported by Dwita *et al* . This test used two methods, namely carrageenan induction to test for acute inflammation and granuloma pouches for sub-acute inflammation. The test was carried out by applying the test substance topically to the rat's paw according to the group. The positive control group was smeared with control cream, the negative control group was smeared with hydrocortisone 2.5%, and the NB group (balsam stick *N.sativa*) was smeared with balsam containing *N. sativa* 5%, 7.5%, 10%. From the results of this test, it can be concluded that the balsam sticks containing 10% *N.sativa* are effective against acute and sub-acute inflammation characterized by high edema inhibition, namely 60.64%, reducing the number of leukocytes (43.55%) and the concentration of Tumor Necrosis Factor-α (TNF-α) which is significant [38].

The effect of the anti-inflammatory activity of *N.sativa* was tested by Nasuti *et al* using the arthritis method by inducing Complete Freund's Adjuvant (CFA). CFA-induced rats were divided into 4 groups, the first group received 0.91 mL/kg *N. sativa*, the second group received 1.82 mL/kg *N.sativa*, the third group received 1.82 mL/kg saline, and the fourth group received 3 mg/kg Indomethacin. *N.sativa* oil significantly attenuated adjuvant arthritis in rats and at high doses (1.82 mL/kg) prevented the development of arthritis with 56% inhibition [39].

Similar to previous studies, Pop *et al* reported the results of their tests regarding the anti-inflammatory activity of *N.sativa* with 3 concentrations, namely 1, 2, and 4 mL/kg. Measurements were taken at the beginning of 24 hours before and at 90, 120, 180, and 360 minutes after carrageenan induction. In acute inflammation, administration of 4 mL/kg of *N.sativa* showed the highest inhibitory effect, namely 23.41% after 6 hours. And the inhibitory effect of *N.sativa* at the three doses given (1, 2, and 4 mL/kg) was more significant than the control group, but at low doses, the effect only lasted 3 hours. while the sub-acute administration of *N.sativa* did not provide an anti-inflammatory effect [40].

3.2.1 In-vitro study

Tests of anti-inflammatory activity were carried out by Bahrami *et al* on the ethanol extract of *N.sativa* (NEE) and the methanol extract of *Silybum marianum* (SME) using the lipopolysaccharide induction method (RAW 264.7). SME, NEE, and their mixtures (SME and NEE) can significantly reduce Nitric Oxide (NO) levels in RAW 264.7 and murine peritoneal macrophages. NEE can also significantly increase the expression of the gene Interleukin-10 (IL-10) and significantly decrease the expression of Interleukin-6 (IL-6) and TNF-α in 264.7 RAW cells. In mixed-treated peritoneal macrophages, the expression of IL-10 and Transforming Growth Factor (TGF-β) significantly increased, while IL-6 and TNF-α decreased. So this test proves that the mixture of SME and NEE has anti-inflammatory and immunomodulatory activities that are beneficial in the treatment of diseases of immunopathological origin [41].

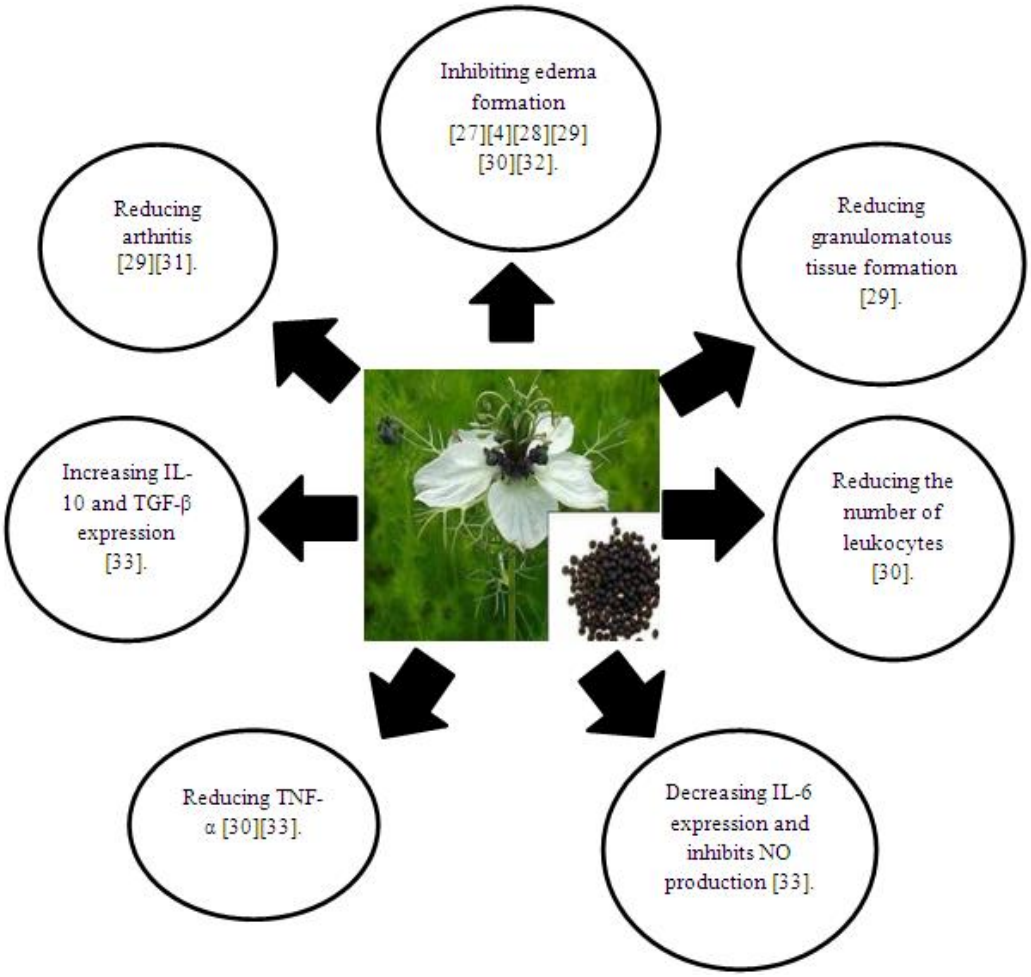

Fig 1: Mechanism of Action of *Nigella sativa* as an Anti-inflammatory

The main ingredient in *N. sativa* which acts as an anti-inflammatory is thymoquinone. The mechanism of thymoquinone as an anti-inflammatory is by reducing the levels of TNF-α and IL-1β in a rats model with arthritis [42] and suppression of NO production by rats macrophages [43]. The content of alkaloids plays a role in the metabolism of arachidonic acid, namely inhibiting the biosynthesis of prostaglandins, thromboxanes, and leukotrienes by inhibiting COX and LOX enzymes [44]. Flavonoids can also decrease the release of prostaglandins from mast cells by inhibiting the production of pro-inflammatory cytokines, neutrophils, and other immune cells [45], [46].

IV. CONCLUSIONS

N. sativa plants have various properties as medicinal plants because the plants contain many phytochemicals that can be used by people in their daily lives. Phytochemical compounds contained in *N. sativa* are alkaloids, flavonoids, phenolics, steroids, saponins, terpenoids, and resins. This study shows the importance of the *N. sativa* plant as a natural anti-inflammatory as evidenced by in-vivo and in-vitro studies. Several pharmacological studies have reported the anti-inflammatory activity of *N. sativa,* namely by inhibiting the formation of edema, reducing the formation of granulomatous tissue, reducing arthritis, reducing the number of leukocytes, increasing the expression of IL-10 and TGF-β genes, inhibiting NO production, and decreasing the expression of IL-6 and TNF-α. However, further research needs to be done to ascertain the anti-inflammatory activity of *N. sativa* so that it can be used as a treatment in the future by understanding metabolism in the body and receptor interactions associated with inflammation.

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Abbreviations

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; *N.sativa*: *Nigella sativa*; *T.ammi: Trachyspermum ammi*; GC-MS: Gas Chromatography and Mass Spectrometer; *C.Angustifolia*: *Cassia Angustifolia*; TNF-α: Tumor Necrosis Factor-α; CFA: Complete Freund's Adjuvant; NB group: balsam stick *N.sativa*; NEE: extract of *N.sativa*; SME: methanol extract of *Silybum marianum*; IL-6: Interleukin-6; IL-10: Interleukin-10; TGF-β: Transforming Growth Factor; NO: Nitric Oxide.

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