**REVIEW ARTICLE**

# The in Vivo and in Vitro Effects of Nigella Sativa on Infection Causing Bacteria: A Systematic Review

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## ABSTRACT

Aim: To examine the in-vitro and in-vivo antibacterial activity of Nigella sativa against infection-causing bacteria.

Methods: A systematic review was conducted, and the PubMed, Scopus, Web of Science and Cochrane databases were searched. The targeted papers had to be primary research investigating the antibacterial activity of N. sativa and had to be published from 2010 to 2020. 14 articles were identified.

Results: Majority of the examined bacteria were susceptible to different concentrations of N. sativa whole extract, its essential oils or the thymoquinone component. They included common bacteria such as B. cereus, B. subtilis, S. aureus and E. coli. Infection-causing bacteria such as MRSA, coagulase-negative S. aureus, S. pneumoniae, S. epidermidis, S. mutans, S. salivarius, M. luteus, H. influenzae, M. catarrhalis, V. paraheamolyticus, H. pylori, Proteus spp. and Porphyromonas spp. were sensitive. However, some strains of S. aureus, L. monocytogenes, P. aeruginosa, Campylobacter spp. and S. typhimurium exhibited varying proportions of antimicrobial resistance towards N. sativa.

Conclusion: N. sativa extract can be used as an adjunct to antibiotics when treating bacterial infections. It is used in clinical and agricultural application should also be controlled to minimize the development of antimicrobial resistance.

**Keywords:** Bacterial infection, Antibiotic resistance, Nigella sativa, Black cumin, Antibacterial activity

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## INTRODUCTION

### Background

The benefits of antibiotics declined in the 1960s when multidrug-resistant (MDR) bacteria were detected (1,2). Overuse and misuse of antibiotics, slow place of drug development and increased international travel were implicated in their emergence and persistence (2,3). Other factors include excessive use of antibiotics in food animals, poor sanitation and release of non-metabolized antibiotics into the environment through manure/faeces (1,4). Various infection-causing bacteria such as Mycobacterium tuberculosis, Escherichia coli, Salmonella enterica, Pseudomonas aeruginosa, Staphylococcus aureus, Listeria monocytogenes and Klebsiella spp. have displayed multi-drug resistance (1). Methicillin-resistant S. aureus (MRSA) and resistant Streptococcus pneumoniae have also been widely encountered in the hospital environment in recent years (1,2). MDR micro-organisms are making it challenging to prescribe anti-microbial drugs. As such, finding new anti-microbial agents to treat resistant species has become an urgent matter. Alternative strategies have to be adopted to fight MDR bacteria and promote their elimination from the environment (3,5).

Natural products, particularly medicinal plants should be explored to provide new molecular entities and mechanisms of action for fighting microbes (4–6). For instance, the black cumin plant (Nigella sativa) is a good candidate. Nigella sativa (*N sativa*) is a small flowering annual herb that produces the black seeds. It occurs in Southern Europe, North Africa and most Asian countries and contains Thymoquinone (TQ) as the main and most abundant active ingredient (27.8– 57%). Besides TQ, the essential oil (EO) contains fixed and volatile oils in the proportion of 32-40% and 0.45% respectively (5,6,7). Phenolic compounds such as nigellone, thymohydroquinone, thymol, carvacrol, α- and β-pinene, d-limonene, d-citronellol, and p-cymene are also present in the EO. Other components include flavonoids, alkaloids, saponins, steroids, terpenes, monoterpenes, essential amino acids, vitamins, and carbohydrates. These components confer *N sativa* with antimicrobial (antibacterial, antifungal, and antiviral), antioxidant, anti-inflammatory, anti-ulcer and anti-cancer properties (5,7). Thus, *N sativa* forms a viable natural substance whose antibacterial activity should be tested and ascertained before being used in antibiotic production.

### Aim and Objectives

The research intends to examine the effects of N sativa on infection-causing bacteria. The specific objectives are:

- To investigate the in-vitro antibacterial activity of N sativa
- To evaluate the *in-vivo (*humans and animals*)* effects of *N sativa* on bacterial infections
- To determine the role of (extent/proportion) thymoquinone in the antibacterial action of N sativa

### Study Justification and Significance

*N sativa* was chosen based on religious and cultural acceptance. The Islamic religion acknowledges it as 'an effective remedy for all diseases except death' as captured in the prophetic statements (Haddith) of Prophet Muhammad (5, pp 2). The Bible and other religions also recommend its medicinal use (8). Additionally, *N sativa* has contributed to the treatment of skin diseases,

dyspepsia, diabetes, influenza, asthma, cancer, gastrointestinal disease, heart, kidney and liver problems. It also has potential to help in dysmenorrhea and infertility (5,6,8). Besides, *N sativa* has proved through scientific studies to have in-vitro and in-vivo antibacterial effects against bacteria such as S. aureus and E. coli (6,7,9). Therefore, consolidation of evidence on the antibacterial activity of *N sativa* will be the first step towards reducing the burden associated with antibiotic resistance and improving the management of bacterial infections. According to ECDC (European Centre for Disease Prevention and Control), approximately 25000 people die from MDR bacterial infections annually. These infections escalate healthcare services and mediate productivity losses in 1.5 billion euros in Europe and 35 billion dollars in USA annually (3,5).

## METHODOLOGY

The study adopted the systematic review (SR) approach. SRs enable extensive coverage of published literature to provide sufficient evidence and identify research gaps. SRs provide accurate, up-to-date information and the precise methodology minimises biased evidence assessment. They also save time when sourcing for evidence to guide for evidence based practice EBP (10). The steps below were followed:

### Formulation of Research Question

Formulating the research question (RQ) was the first step and the PEO format was employed. The problem of interest (P) was infection-causing bacteria, exposure (E) was treatment with N. sativa extracts while in-vivo and in-vitro antibacterial effects were the targeted outcomes (O). Consolidation of the PEO elements yielded the following RQ was formulated as:

What is the in-vitro and in-vivo antibacterial impact (O) of *N. sativa* (E) on infection-causing bacteria (P)?

### Search Strategy

Keywords were specified to aid in developing an effective search. The PEO elements and their synonyms were used as search terms. The MeSH thesaurus in PubMed was also utilised in expanding the vocabulary associated with these terms. Eventually, the keywords used were "*Nigella sativa*" OR "thymoquinone" OR "Black seed oil" OR "black cumin" AND "anti-microbial" OR "antibacterial" AND "in vivo" AND "topical" AND NOT "cancer" AND NOT "diabetes". The Boolean operators optimised the search process where 'OR' widened the search by capturing papers with any of the mentioned keywords. 'AND' narrowed the results by returning articles that have all the identified words. 'NOT' was used to exclude specified phrases from the search results (10,11).

### Databases

Several databases including PubMed, Scopus (Science Direct), Web of Science and Cochrane Library were searched since one database cannot be exhaustive. These electronic databases allow replication of the search process and retrieval of journal articles (11). More papers were found through reading the reference list (hand-searching) of the identified studies and other systematic reviews on the anti-microbial effects of *N. sativa* (hand-searching) Table 1 below shows the search outcomes.

**Table 1: Search Outcomes**

| Database | Search Outcomes |
|---|---|
| PubMed | 20 |
| Science Direct | 30 |
| Web of Science | 1 |
| Cochrane | 2 |
| Hand-searching | 7 |
| Total | 60 |

### Eligibility criteria and article selection

A screen review from the PBS Research Ethics committee was used to assess whether ethical approval was needed. After conducting the review, it was determined that ethical approval was not required, approval ID: 787100.

Inclusion and exclusion criteria were used to eliminate literature that was unrelated to the selected topic. Results were filtered to papers published under the subject of pharmacology in the last ten years. They also had to be experimental studies preferably randomised controlled trials examining the in-vitro or in-vivo antimicrobial effects of *N. sativa* and had to be written in English. Many papers were excluded due to insufficient information on the selected topic, researching *N. sativa*'s abilities in areas other than "anti-microbial effects" or being out-dated. The PRISMA chart in figure 1 below depicts the sequential elimination based on eligibility criteria.

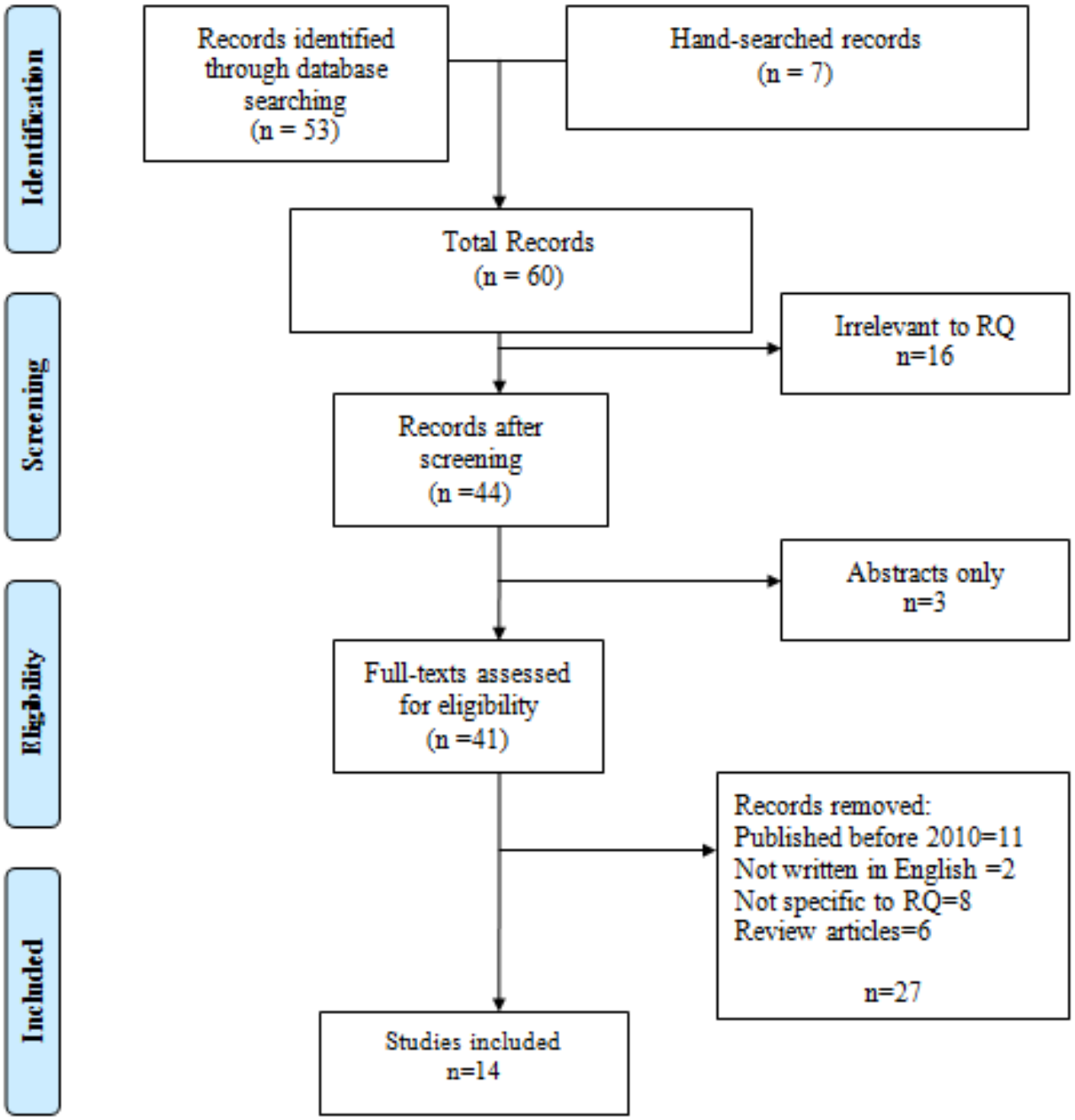


**Figure 1:** PRISMA chart illustrating article selection process

## KEY FINDINGS

Our results regarding the characteristics of the studies included (total 14 studies) are shown in Table 2.

**Table :2 Characteristics of the included studies**

| Authors | Origin | Aim | Research methods | Sample | Findings | Strengths | Limitations |
|---|---|---|---|---|---|---|---|
| Mouwakeh et al. 2018 (12) | Budapest Hungary | To investigate the antimicrobial and resistance modifying activity of N. sativa against Listeria monocytogenes | Broth microdilution method<br><br>Ms Excel (2016). | 9 strains of Listeria monocytogenes | N. sativa EO, TQ and carvacrol were active against L. monocytogenes | 1. Testing against several strains of L. monocytogenes<br>2.Novel study of N. sativa on antibiotic resistance | 1.Antibacterial activity of N. sativa was not compared with standard antibiotics |

| Authors | Origin | Aim | Research methods | Sample | Findings | Strengths | Limitations |
|---|---|---|---|---|---|---|---|
| Mouwakeh et al. 2019 (13) | Budapest Hungary | To evaluate the antimicrobial efficacy of N. sativa EO, TQ, carvacrol, and p-cymene against S. aureus strains | Broth microdilution | MRSA Ofloxacin-resistant S. aureus<br><br>Other S. aureus strains | EO, TQ, carvacrol, and p-cymene exhibited antibacterial action against MRSA and methicillin-susceptible S. aureus | 1.Comparison of resistant and sensitive S. aureus strains | 1.Antimicribial action was not compared with a standard antibiotic |
| Kouidhi et al. 2011 (17) | Monastir, Tunisia | To determine the in-vitro inhibitory and resistance-modifying properties of TQ, tetracycline and BC | Broth microdilution method | 11 laboratory reference and 16 oral bacterial strains | 7/16 species of oral bacteria and 4/11 reference bacteria were sensitive to TQ. | 1.Comparison of TQ with benzalkonium chloride and tetracycline<br>2. Testing against several bacteria | |
| Boka et al. 2014 (21) | Isfahan, Iran | To investigate impacts of varying concentrations of black cumin seeds on intestinal E. coli count and jejunal epithelial cells in laying hens | Experimental diets containing N. sativa | 100 Leghorn hens (49-weeks old) | Black cumin significantly decreased E. coli in the ileum | 1.Suitable duration for intestinal colonization<br>2. Adequate sample size | 1. Other intestinal bacteria in hens were not examined |
| Petrujki´ et al. 2018 (22) | Texas, USA | To determine the effects of N. sativa extract on wild-type E. coli, Campylobacter spp. and S. typhimurium in pigs | Animal feed supplementation | 72 Yorkshire American Landrace crossbreed piglets 3-weeks-old) | E. coli in the jejunum and rectum significantly decreased but Campylobacter and S. typhimurium were unaffected | 1.Adequate sample size | 1. Short study duration |
| Emeka et al. 2014 (23) | Nsukka, Southeast Nigeria | To investigate the susceptibility of MDR S. aureus to Nigella sativa | Well diffusion susceptibility method of microbial cultures from diabetic wounds | 34 diabetic patients | Undiluted NS oil was active against 42% of microbial isolates but 58% were resistant to various oil concentrations | 1.Examination of clinically significant microbes<br>2. Comparison of N. sativa oil with antibiotics | 1. Small sample size of patient and microbial isolates) |
| Kocoglu et al. 2019 (19) | İstanbul, Turkey | To determine the in-vitro antibacterial activity of N. sativa against bacteria affecting the middle and inner ear | Broth dilution technique. | Clinical isolates of M. catarrhalis, H. influenzae, S.pneumoniae and P. aeruginosa | N. sativa showed bactericidal activity against S. pneumoniae, H. influenzae, and M. catarrhalis, but had no effect on P. aeruginosa | 1. Examination of clinically significant bacteria<br>2. Comparison with standard antibiotics | 1. Small number of bacterial strains |
| Zohra et al. 2018 (18) | Mascara, Algeria | To determine in vitro antimicrobial activity of EO and methanol extract from Algerian N. sativa seeds against microbes isolated from the oral cavities of patients with periodontitis | Broth microdilution method | 12 Gram-positive bacteria<br><br>11 Gram-negative bacteria | N. sativa EO and methanolic extract had excellent and moderate bactericidal activity respectively. Bacterial regrowth occurred after 18 hours in both test substances | 1. Multiple bacterial strains<br>2.Use of different bioactive compounds of N. sativa separately | |
| Gawron et al. 2019 (15) | Gdansk, Poland | To examine the activity of N. sativa extract against MRSA and cytotoxicity against dermal fibroblasts | Well-plate diffusion assay | 5 isolates of MRSA | NS extract exhibited strong antibacterial activity against MRSA even at low concentrations (4–16 µg/ml) | 1.Comparison with other antimicrobial agents | 1.Low diversity of bacterial species and small sample size |

| Authors | Origin | Aim | Research methods | Sample | Findings | Strengths | Limitations |
|---|---|---|---|---|---|---|---|
| haaban et al. 2015 (20) | Cairo, Egypt | To assess the antibacterial activity of N sativa EO produced in a microemulsion system | Agar well diffusion method | B. cereus<br>E. coli<br>S. aureus,<br>S.typhimurium<br>L.monocytogenes<br>P.aeruginosa | N. sativa EO was strongly potent against S. aureus, B. cereus and S. typhimurium but L. monocytogenes and P. aeruginosa were resistant. NS was also more effective than Ceftriaxone and Eugenol | 1.Comparison of efficacy with other antimicrobials<br>2. Several bacterial species | . |
| Salem et al. 2010 (24) | Al-Khobar, Saudi Arabia, | To determine the efficacy of N. sativa in clearing H. pylori infections in non-ulcer dyspeptic patients. | Randomized controlled trial<br>Histopathologic examination<br>Rapid urease test | 88 adults with H. Pylori infections | 1, 2 and 3g of N sativa eradicated H. pylori by 47.6, 66.7 and 47.8%. Triple therapy of antibiotics was more effective (82.6%) | 1.Adequate sample size<br>2. Randomized design and comparison with antibiotics | |
| Rafati et al. 2014 (25) | Tehran, Iran | To investigate the anti-microbial activity of NS seeds extract on skin pustules infection | Randomised controlled trial | S. aureus<br>S. epidermis | Neonates treated with mupirocin recovered faster (69.4 hrs ) than those receiving NS extract (75.1 hrs) | 1.Antimicrobial activity of NS was compared with mupirocin<br>1.No adverse reactions in the newborn | 1. Small sample size |
| Goel et al. 2018 (16) | Pune, India | To evaluate the antibacterial potential of TQ and its mechanism of action | Broth microtiter dilution method | P. aeruginosa<br>E. coli<br>S. aureus,<br>B. subtilis | TQ inhibited bacterial growth and biofilm formation in all the four bacteria tested | 1.Both in-vitro and in-vivo (cell-line) investigations<br>2. Examination of several bacteria species | 1.Use of commercial bacterial strains rather than clinical isolates |
| Ugur et al. 2016 (14) | Konya, Turkey | To examine the in-vitro antibacterial activity and cytotoxicity effect of N. sativa oil | Broth microdilution method | E. coli<br>Enterococcus faecalis<br>P. aeruginosa<br>MRSA<br>MR coagulase-negative Staphylococci | MRSA and MR coagulase-negative Staphylococci were susceptible to NS essential oil without in-vitro cytotoxicity. It is thus a suitable antimicrobial source. | 1.Testing N. sativa against numerous clinically significant bacteria | 1. Not compared against standard antibiotics |

## In-vitro antibacterial activity

Essential oil derived from *N. sativa*, p-cymene carvacrol and TQ were effective against strains of *L. monocytogenes* and *S. aureus* (12–14). Both *MRSA* and methicillin-sensitive *S. aureus* were inhibited by all the four test substances (13). Clinical isolates of *Staphylococci* including *MRSA and* methicillin-resistant coagulase negative *S. aureus* had the greatest susceptibility to *NS* essential oil and the minimum inhibitory concentration (MIC) of TQ ranged from <0.25 µg/mL to 1 µg/Ml (14). Similarly, *S. aureus* and *E. faecalis* had lower MICs of 0.5 µg/mL, and 2 µg/mL respectively while *E. coli* and *P. aeruginosa* were slightly resistant and were both inhibited by a higher MIC of NS (64 µg/mL) (14). The MIC of TQ against MRSA in the research done by Gawron et al. (15) was slightly higher, at 4–16 µg/ml and even more was needed for *L. monocytogenes* where an MIC of 40 µg/ml was recorded (12). The MIC of NS essential oil ranged from 116 to 466 µg/ml while that of carvacrol was 150 µg/ml. P-cymene did not inhibit the growth of *Listeria* (12). When tested against common gram positive (*B. subtilis and S. aureus*) and gram negative bacteria (*E. coli and P. aeruginosa*), TQ inhibited bacterial growth and biofilm formation at MIC range of 1.56 to 100 µg/ml (16).

*N. sativa* was also potent against bacteria associated with oral infections and hygiene. Oral bacteria including *S. aureus* strains, *Streptococcus mutans*, *Streptococcus salivarius*, *Staphylococcus epidermidis*, *Porphyromonas sp.* among others were susceptible to *N. sativa* (17,18). EO had MBC (minimum bactericidal concentration) value of 16,500 µg/ml against the most sensitive bacteria (*S. epidermidis* and *Porphyromonas sp*.) However, the antibacterial activity did not reach the significance threshold in other bacteria. Methanolic extract had moderate antibacterial activity with an MBC of 125,000 µg/ml) against all the tested microbes tested. *Porphyromonas sp.* and *Proteus sp.* were the most sensitive bacteria while *S. aureus* was the most resistant ($p<0.05$). Interestingly, regrowth of some bacteria was also observed with methanolic extract and EO after 18 hours (18).

TQ had a lower MIC ranging between 8 to 64 µg/ml for *S. aureus*, *S. mutans*, *S. salivarius* and 4/11 reference strains (*S. epidermidis*, *S. aureus*, *Micrococcus luteus* and *Bacillus cereus*. The remaining microbes were more resistant with higher MIC (128-512 µg/ml) and *P. aeruginosa* was the most resistant with an MIC value >512 µg/ml (17) . Its resistance was replicated in the research by Kocoglu et al. (19). Other bacteria affecting the ear including *Moraxella catarrhalis, Haemophilus influenza* and *S. pneumoniae* were susceptible to different concentrations of black cumin (19). Shaaban et al. (20) presented more evidence supporting the antibacterial activity of NS. EO showed high effectiveness against *B. cereus, S. aureus*, and *S. typhimurium at* an MIC of 100 µg/well and its activity against the last two bacteria was superior to Ceftriaxone. However, the essential oil did not affect *L. monocytogenes* and *P. aeruginosa* not affected but the latter was sensitive to Eugenol although it was efficient against other bacteria compared to EO (20).

### In-vivo antibacterial activity

Research conducted by Boka et al. (21) involving 100 egg-laying Leghorn hens showed that *NS* significantly reduced ($p < 0.05$) the population of intestinal E. coli over ten weeks. Chicken fed with diets containing concentrations of 0, 1%, 2% and 3% black cumin had 4.93, 3.87, 4.18 and 4.11 $\log_{10}$ cfu/g respectively of E. coli in the ileum (21) . A similar study examining weanling pigs showed that black cumin seeds significant decreased the rectal and jejunal wild-type E. coli but they had no effect on Campylobacter and Salmonella typhimurium (22).

The antibacterial activity of black cumin against human pathogens was also confirmed in-vivo. 42% (8/19) MDR microbial isolates from diabetic patients were susceptible to undiluted NS oil but only 4/8 isolates were inhibited by 200, 400 and 800 mg/ml dilutions. However, the remaining isolates (11/19) were resistant to both the diluted and undiluted *N. sativa* oil (23). Salem et al. (24) and Rafati et al. (25) contradicted other studies as their research showed that antibiotics were more effective than NS extract. The antibiotics given as a triple therapy of amoxicillin, clarithromycin, and omeprazole reduced *H. pylori* by 82.6% compared to 47.6%, 66.7% and 47.8% achieved by 1g, 2g and 3g of *NS* respectively. The effect of the triple therapy was significantly different except for the 2g NS and its superior bactericidal action might have been due to the synergistic effects of the three drugs (24). Rafati et al. assessed antibacterial active through recovery time which was shorter with muciporin (69.4 hours) while neonates given NS took 75.1 hours to heal. However, the recovery times were not significantly different ($p=0.69$) (25).

### Reduced antibiotic resistance

*N. sativa* minimised antibiotic resistance against standard antimicrobials when half MIC (different in each study) was added in-vitro. EO was associated with the greatest reduction in antibiotic resistance in 7/10 strains of *L. monocytogenes* and *MRSA* when combined with antibiotics in the experiments done by Mouwakeh et al. (12) and Mouwakeh et al. (13) respectively. TQ caused a four-fold reduction in the MIC of erythromycin against seven strains of *L. monocytogenes,* carvacrol had a two-fold decrease in all the strains while the two-fold reduction of p-cymene supplementation was observed in six strains (12). Compared to other components in the essential oil, thymoquinone had pronounced effects. It reduced the MIC (x16) for tetracycline and x8 for ciprofloxacin against MRSA. The effect on *S. aureus ATCC 25923* was mild at two- and four-fold reduction for tetracycline and ciprofloxacin respectively (13). Similarly, the MIC of tetracycline and benzalkonium chloride (BC) against all reference and oral bacteria was lowered by thymoquinone. The greatest decline (eight-fold) was observed in *Vibrio parahaemolyticus* and 2/8 strains of *S. aureus* (17).

Three studies also examined the influence of NS extract on efflux pumps used by bacteria to counteract the action of antibiotics. Ethidium bromide was used as the efflux pump substrate in (12,13) while Kouidhi et al. (17) utilised DAPI (4,6-diamidino-2-phenylindole). Uptake of these substrates, denoted by fluorescence, reduced the efficiency of efflux pumps thereby reducing antibiotic resistance. *N. sativa* EO, thymoquinone and carvacrol significantly ($p<0.0001$) increased the accumulation of ethidium bromide in the cells of *L. monocytogenes*, MRSA and *S. aureus.* However, compound p-cymene was devoid of such effect on *S. aureus* (12,13). Similarly, TQ supplementation inhibited the DAPI efflux pump as shown by the DAPI accumulation assay (17). These substrates also disrupted the bacterial cell membrane increasing its permeability and subsequently permitting the influx of tetracycline and ciprofloxacin (12,13).

## DISCUSSION

## INTERPRETATION OF FINDINGS

This current systematic review aimed at investigating the antibacterial effects of *NS* extract on disease-causing bacteria. Five studies (15,21,22,24,25) examined the extract in its entirety while seven investigated individual components. (12,13,18–20,23) focused on the essential oil and bioactive compounds therein, Kouidhi et al. (17) was specific to thymoquinone while Zohra et al. (18) also assessed the methanolic portion. As previously mentioned in (6,7), TQ was found to be the dominant component in the essential oil and the resultant antibacterial effect was attributed to it. Mouwakeh et al. (12) and Mouwakeh et al. (13) further acknowledged the inhibitory activity of carvacrol and p-cymene also found in the oil.

The examined in-vitro studies confirmed that *N. sativa* was efficient in killing various bacteria and inhibiting their growth. Their findings correlate with previous research (6,8,9) where *S. aureus*, *E. coli* and MRSA recurred as the most tested and sensitive species. *L. monocytogenes, P. aeruginosa* and *S. typhimurium* portrayed mixed reactions to NS across different studies while *Campylobacter* remained resistant (19, (12,20) 22). MDR bacteria gain antibiotic resistance through numerous mechanisms including mutations that modify specific drug receptors and enzymatic pathways responsible for antimicrobial susceptibility. They also produce hydrolytic enzymes that inactivate antibiotics or use efflux pumps to reduce drug concentration in the bacterial cell (3,12). TQ and other components of NS essential oil reduced antibiotic resistance by inhibiting the efflux pumps and disrupting membrane integrity (12,13,17).

In vivo experiments in hens (21), pigs (22) and humans (23–25) confirmed that *Nigella sativa* was selective against bacteria and did not harm animal and human cells. The IC50 (concentration for 50% host cell viability) of NS against human fibroblasts was 0.2 mg/ml, which was 2x higher than the MIC and MBC against bacteria (15,16). These findings coincide with other studies (7,8) which focused on the efficacy of NS at the clinical level with animal models and humans.

### Strengths and Limitations

This systematic review has several strengths and limitations. On the positive side, it shows the distribution of MDR bacteria and the antibacterial efficacy of *Nigella sativa* from a global perspective since the studies originate from different countries (see Appendix 3). The quantitative nature of the included studies and comparison with standard antibiotics also aid in gauging the antibacterial efficacy of *N. sativa.* Furthermore, the review has captured clinically significant microbes that are responsible for human diseases and hospital-acquired infections. However, a major limitation is the lack of exhaustive literature coverage as some pertinent research may be missing from the current review. There is also a shortage of in-vivo papers and only four such studies were captured here.

### Clinical Implications and further research

Bacterial infections and antibiotic resistance are major public health concern on a global level. Thus, the findings of the current review on the antimicrobial activity of *N. sativa* and its modulating effect on antibiotic resistant have practical implications. First, NS extract and its bioactive compounds available commercially should be used as adjunct therapy in bacterial infections rather than an alternative to the standard antibiotics. Use should also be on prescription basis to prevent the development of resistance. Second, its use as a feed supplement agricultural sector to boost the health of farm animals should also controlled to lower the risk of resistance.

Further research on the antimicrobial activity of *N. sativa* should be done especially in developing countries. Emeka et al. (23)

highlight that the lack of resources for proper treatment in Nigeria and other similar countries puts millions of lives at risk of MDR microbes. These studies should focus on disease-causing bacteria rather than the common microbes (*S. aureus* and *E. coli*) which are relatively harmless. The in-vitro activity should be ascertained in in-vivo studies to ensure that the effects are replicated in animals and human beings and also rule out adverse reactions.

## CONCLUSION

For centuries, *Nigella sativa* has been used a medicinal plant in the treatment of various diseases. The current review demonstrated that its extracts inhibit the growth of clinically - important and non-lethal Gram-positive and Gram-negative bacteria in in-vitro and in-vivo settings. Thymoquinone is the main active ingredient but phenolic compounds occurring NS essential oil also exhibited antibacterial activity. The susceptibility of MDR pathogenic bacteria to *N. sativa* suggest that it could be used in the treatment of bacterial infections. However, the evidence of resistance demonstrates that black cumin seed extract cannot be used as an alternative drug. Instead, it could be beneficial as an adjunct/ add-on treatment to the standard antibiotics.

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