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Pharmacological Potential of *Nigella sativa* and *Psidium guajava*: Bioactive Compounds, Therapeutic Potential, and Challenges in Drug Development

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Abstract

Antimicrobial resistance (AMR) is a growing global health crisis exacerbated by the slow pace of new drug development. This study systematically evaluated the pharmacological and antimicrobial properties of Nigella sativa and Psidium guajava, focusing on their bioactive constituents, clinical relevance, and therapeutic potential. A comprehensive search of nine databases covering the period 2015-2024 yielded 1,057 records, of which 111 full-text articles met the inclusion criteria. Ultimately, 24 studies were included in the qualitative synthesis, and 12 provided quantitative MIC data suitable for meta-analysis. Using a random-effects model, the pooled MIC estimate for thymoquinone was 6.83 µg/mL (95% CI: 4.85-8.82), indicating consistent broad-spectrum antimicrobial activity. Heatmaps and Venn diagrams highlighted compound-pathogen interactions and revealed overlapping and unique antibacterial spectra among thymoquinone, carvacrol, and quercetin-glycosides. The ROBINS-I tool revealed a low to moderate risk of bias in most domains, although the confounding and outcome measurement domains showed a serious risk in a few studies. Notably, publication bias was evident due to selective reporting of favorable MIC values. N. sativa and P. guajava exhibited significant antimicrobial, anti-inflammatory, and antitumor activities, mediated by compounds such as thymoquinone, carvacrol, tannins, and quercetin. These findings emphasize the potential of these plants as adjuncts or alternatives in antimicrobial therapy. However, challenges including standardization, bioavailability, and regulatory frameworks must be addressed through multidisciplinary research and sustainable bioproduction approaches.

Keywords: Nigella sativa, Psidium guajava, antimicrobial resistance, phytochemicals, Bioactive compounds, pharmacological synergy, MIC meta-analysis

INTRODUCTION

Medicinal plants have been an essential component of African traditional medicine frameworks and local health systems across sub-Saharan Africa (Thomford *et al.*, 2015). Plant-derived natural products have played a crucial role in contributing to modern medicine and providing a rich source of bioactive compounds for new drug development (Chaachouay and Zidane, 2024). The renewed interest in this area stems from unmet therapeutic needs, advancements in detection techniques, and improved production methods (Aware *et al.*, 2022).

According to the WHO, 80% of the developing world relies on traditional plant-based medicine (Khan and Ahmed, 2019). Out of an estimated 374,000 plant species, approximately 28,187 have been discovered to possess medicinal properties (Chassagne et al., 2021; Iduh et al., 2024). More than 1,340 of these species exhibit antimicrobial characteristics, and over 30,000 antimicrobial compounds have been isolated (Iduh *et al.*, 2024). Another study estimated that 14-28% of higher plant species are medicinal, and 74% of bioactive plant compounds were discovered through traditional use (Mustafa *et al.*, 2017).

Nigella sativa (black seeds or black cumin) is an annual flowering plant in the Family Ranunculaceae that is native to the Mediterranean region but is also cultivated in Saudi Arabia, northern Africa, and parts of Asia (Al Dhaheri *et al.*, 2022). A great number of investigations and studies were conducted in the past few years, targeting not only the use of these plants but also the testing of their ingredients and active components, which could elucidate or explain these pharmacological actions on both experimental and clinical pharmacology grounds (Shetty *et al.*, 2018; Alobaedi *et al.*, 2017; Memar *et al.*, 2017).

Native to tropical America, *Psidium guajava*, of the family Myrtaceae, is currently grown worldwide in suitable tropical climates (Proença *et al.*, 2022). This plant has been reported to exhibit excellent antimicrobial activity against several tested strains, which is attributed to its full array of bioactive compounds (Bashir *et al.*, 2021). Recent studies have shown that the bioactive compounds of *Psidium guajava* possess remarkable antibacterial activity against a wide variety of bacterial pathogens (Bano et al., 2023; Huynh et al., 2025; Díaz-de-Cerio et al., 2017; Bashir *et al.*, 2021). *P. guajava* contains more than 20 compounds distributed in leaves, stems, bark and roots (Kumar *et al.*, 2021). Guava leaves contain an essential oil rich in cineol, tannins, triterpenes, flavanoids, resin, eugenol, malic acid, fat, cellulose, chlorophyll, mineral salts, and several other fixed substances (Kumar et al., 2021).

Nigella sativa contains various bioactive compounds, of which thymoquinone (TQ) has been the most extensively studied (Mahomoodally *et al.*, 2022). Thymoquinone is a volatile bioactive component recognized for its strong antioxidant, anti-inflammatory, and antimicrobial characteristics (Abbas *et al.*, 2024). It has been demonstrated that it is capable of producing powerful anticancer effects, inducing apoptosis as well as inhibiting tumor growth in several cancer cell lines (Majdalawieh & Fayyad, 2016). Additional compounds of significance include nigellidine, nigellicine, and alpha-hederin, which play a vital role in the immunomodulatory and hepatoprotective abilities of the herb (Fayed, 2022). Besides, other studies have reported the antimicrobial effects of TQ against multidrug-resistant pathogens; hence, TQ is considered a promising target for developing new drugs to overcome antibiotic resistance (Yu *et al.*, 2024). Among these compounds, quercetin was identified as one of the major bioactive phytochemicals in Psidium guajava (Naseer *et al.*, 2018). Quercetin is a well-known flavonoid with potent antioxidant and anti-inflammatory activities and has been linked to cardiovascular protection as well as cancer prevention (Kumar *et al.*, 2021). Moreover, it exhibits antimicrobial effects, especially against resistant bacterial strains (Nguyen and Bhattacharya, 2022).

Although numerous medicinal plants have been explored for their antimicrobial potential, *Nigella sativa* and *Psidium guajava* were strategically prioritized in this study due to their extensive ethnopharmacological use (Ugbogu *et al.*, 2022), broad-spectrum antimicrobial activity (Shafodino *et al.*, 2022), and the growing body of scientific evidence supporting their efficacy against clinically relevant drug-resistant pathogens. *N. sativa*, known for its active compound thymoquinone, and *P. guajava*, rich in quercetin and tannins, exhibit mechanisms such as membrane disruption, efflux pump inhibition, and reactive oxygen species generation, which are critical in overcoming bacterial resistance (Tiotsop *et al.*, 2023). Unlike many other medicinal plants that lack consistent bioactive profiles, these two species offer reproducible antimicrobial effects and are widely accessible in low- and middle-income countries (Ullah *et al.*, 2020), aligning with WHO's traditional medicine frameworks. Despite their widespread use, previous studies on *N. sativa* and *P. guajava* remain fragmented often limited to crude extract evaluations without comparative synthesis or standardized potency assessments (Bylappa *et al.*, 2024; Odieka *et al.*, 2022; Bashir *et al.*, 2021). Moreover, there is a lack of integration between their phytochemical evidence base and the global agenda on antimicrobial resistance (AMR). To address these gaps, this study conducts a systematic review and meta-analysis of minimum inhibitory concentration (MIC) data, applies a rigorous risk-of-bias (ROBINS-I) assessment to the included studies, and contextualizes the findings against WHO-priority bacterial pathogens. By doing so, it provides a consolidated pharmacological profile and a strategic framework for guiding future drug development and policy considerations.

STUDY DESIGN

A modified version of the method described by Chouni and Paul (2018) were adopted where a systematic literature search was conducted using Boolean operators of "*Nigella sativa*" AND "antimicrobial activity" OR "resistance" OR "MIC", "*Psidium guajava*" AND "antibacterial" OR "bioactive compound" OR "efflux inhibition", "phytochemical synergy" AND ("plant extract" OR "natural compound") AND "antibiotic". The search was applied to PubMed, Google Scholar, and ScienceDirect, Web of Science, Citationsy, ResearchGate, and LiveDNA and Filters were applied to restrict results to peer-reviewed articles published in English between 2015 and 2024 yielding **1,057 records.** After removing **213 duplicates** and **42 automatically excluded entries** (non-English and non-peer-reviewed), 802 records were screened based on title and abstract. Based on inclusion criteria (reporting

MIC or antibacterial outcomes of *Nigella sativa* or *Psidium guajava* compounds), **111 full-text articles** were evaluated. Of these, **87 studies were excluded** for reasons including lack of quantitative MIC data (n = 31), absence of specific plant compounds (n = 21), general pharmacological reviews (n = 10), or studies not involving plant-based antimicrobials (n = 25). The remaining **24 studies** met all eligibility criteria and were included in the qualitative synthesis. Among these, **12 studies** reported comparable and extractable MIC values suitable for meta-analysis and ROBINS-I risk of bias assessment. The complete selection process is depicted in Figure 1 **(PRISMA 2020 Flow Diagram).**

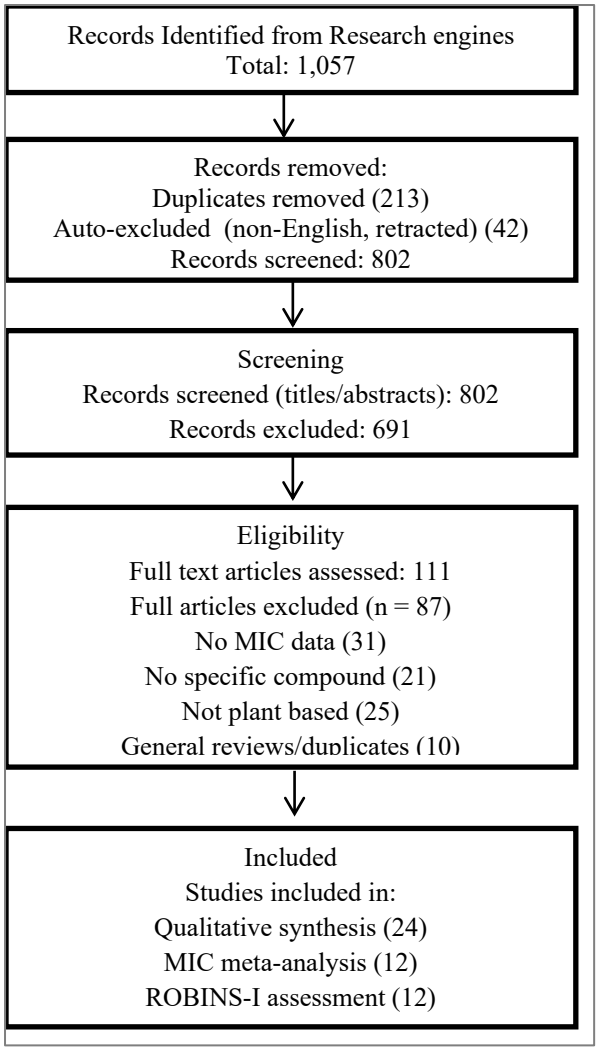

Figure 1: PRISMA Flow diagram

A meta-analysis was performed using a random-effects model due to the expected heterogeneity in study designs, bacterial strains, and extract types. The primary endpoint was the pooled MIC for each plant compound against clinically relevant bacterial pathogens. MIC data were log-transformed before analysis, and summary statistics were calculated. Studies included in the meta-analysis were limited to those reporting comparable experimental designs and identified test organisms. Heatmaps were generated to visualize pooled antimicrobial effectiveness across compounds and pathogens. Also, a heatmap was constructed to depict the relative sensitivity of key pathogens to various bioactive compounds extracted from *Nigella sativa* and *Psidium guajava*. MIC values were color-coded (green indicating high sensitivity and red indicating low sensitivity) and organized by bacterial species and plant compound. This enabled the visualization of compound-specific trends in antimicrobial efficacy and facilitated the identification of high-potential candidates for clinical development.

RESULT

Chemical Composition of the *Nigella sativa* Seeds and *Psidium guajava*

Their multipurpose preventive and relieving effects have been attributed to prominent constituents such as nigellicine, nigellidine, thymoquinone (TQ), dithymoquinone, thymol, and carvacrol (Ahmad *et al.*, 2014). Many other active compounds have also been isolated and identified in different *N. sativa* varieties. The essential oil of the plant contains various pharmacologically active constituents, such as TQ (30–48%), thymol, thymohydroquinone, dithymoquinone, p-cymene (7–15%), carvacrol (6–12%), sesquiterpene longifolene (1–8%), 4-terpineol (2–7%), t-anethol (1–4%), and α -pinene (Ahmad *et al.*, 2014). The seeds of the plant also contain many nonoily and non-caloric components in trace amounts, including pyrazole alkaloids, isoquinoline alkaloids (nigellicimine and nigellicimine-N-oxide), alpha-hederin (a water-soluble pentacyclic triterpene), saponin (a potential anticancer agent), vitamins (riboflavin, thiamin, niacin, pyridoxine, folic acid, and vitamin E), and minerals (potassium, sodium, calcium, phosphorus, magnesium, copper, and iron) (Gholamnezhad *et al.*, 2016).

On the other hand, guava contains sesquiterpene compounds, including beta-caryophyllene, tans-nerolidol, gloobulol, and D-limonene, with variations among varieties due to genetic variability and other factors (Hassan *et al.*, 2020).

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Table 1: Antimicrobial Activity of *Nigella sativa* Chemical Components

Compound	Extract Type	Plant Part Used	Effect	Study type	Reference
Thymoquinone (TQ)	Crude Methanolic Extract		Antibacterial activity against *Staphylococcusaureus* (MIC: 2-8 µg/ml); limited activity against gram-negative bacilli and Enterococcus faecalis.	Bacteria wound infection study	Babu *et al.*(2023)
	Essential Oil	Seeds	Antifungal activity with MIC values of 7.0 ppm against *P. digitatum* and 8.5 ppm against *C. gloeosporoides*	Antifungal activity study	Akansha *et al.*, 2023
	Crude Methanolic Extract	Seeds	Inhibits SARS-CoV-2 main protease with 63.21% inhibition; high cytotoxicity	*In vitro* assessment of viral enzyme	Abdallah *et al.*, 2022
Carvacrol	Essential Oil	Seed	Antibacterial activity against multidrug-resistant *K. pneumoniae*; eradicates bacterial cells within 4 hours	*In vitro* and *in vivo* studies	de Souza *et al.*, 2021
	Essential Oil	Seed	Antifungal activity against *Candida krusei* (MIC: 6.00 ± 2.80 µg/mL to 8.00 ± 0.00 µg/mL) and decreased fungal load in kidneys	*In vitro* and *in vivo* studies	Feridoniy *et al.*, 2020
	Essential Oil	Seed	Antiviral activity against HSV-2 (EC50: 0.43, 0.19, 0.51 mmol/L for prevention, treatment, and direct inactivation, respectively)	*In vitro* HSV infection study	Wang *et al.*, 2020
Thymol	Essential Oil	Seed	Antibacterial activity against *Streptococcus iniae* (MIC: 128 µg/mL, MBC: 256 µg/mL)	*In vitro* antibacterial study	Yin *et al.*, 2022
	Essential Oil	Seed	Antifungal activity against *Candida albicans* (MIC: 39 µg/mL), *C. krusei* (MIC: 39 µg/mL), and increased MIC against *C. albicans* in the presence of ergosterol	*In vitro* antifungal and Mode of action study	De Castro *et al.*, 2015

Table 2: Antimicrobial Activity of *Psidium guajava* Chemical Components

Compound	Extract Type	Plant Part Used	Effect	Study type	Reference
Quercetin-glycosides	Flavonoid Extract	Leaves, Peel, Flesh	Antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* (MIC: 5.00 mg/mL; MBC: 0.625 mg/mL) and Induced changes in micro-morphology of bacteria	Antibacterial efficacy and mechanism of action studies	Zhang *et al.*, 2018
	Flavonoid Extract	Not Specified	Antifungal activity against *Candida albicans* (MIC: 128 µM); inhibited biofilm formation, adhesion, and invasion; reduced inflammatory cytokines in VVC model	*In vivo* and *in vitro* antifungal activity	Tan *et al.*, 2023
	Flavonoid Extract	Leaves, Flowers	Inhibits influenza A virus (IAV) replication; activates P53 and regulates IL-1ß and IL-8; competitive inhibition of IAV replication	Antiviral efficacy and mechanism of action	Khalil*et al.*, 2019
Tannins	Herbal Extract	Various (14 herbal drugs)	Anti-biofilm activity against multi-resistant E. coli (down to 10 µg/mL)	Antimicrobial and anti-biofilm activities	Neumann *et al.*, 2022
	Natural Polyphenol	Not Specified	Inhibited mycelial growth and spore germination of *Penicillium digitatum*	Antifungal activity and mechanism of action	Zhu *et al.*, 2019
	Natural Polyphenol	Not Specified	Improved clinical scores and reduced virus titers in HSV-2 infection; enhanced anti-HSV-2 immune response	*In vivo* antiviral efficacy and immune response studies	Hassan*et al.*, 2022
Carotenoids	Methanolic Extract	Ripe Fruits	Antibacterial activity; MIC: 0.50 µg/ml against *E. coli*, 0.39 µg/ml against *S. aureus* and significant antioxidant	Antioxidant activity and antibacterial efficacy	Bano *et al.*, 2023
Terpenoids		Various	Activates antiviral genes and boosts macrophage activity	Molecular interaction studies	Srivastava *et al.*, 2025

Anti-Inflammatory and Immunomodulatory Effect of *N. sativa*

Nigella sativa has demonstrated significant anti-inflammatory and immunomodulatory properties across various disease models, offering potential therapeutic benefits in diverse conditions. Mushtaq *et al.* (2024) found that *N. sativa* seed extract protected against liver injury in a Concanavalin A-induced liver damage model by reducing liver injury markers, such as Alanine Aminotransferase and Aspartate Aminotransferase, as well as oxidative stress levels. Moreover, it modulated pro-inflammatory cytokines and apoptotic pathways, highlighting its hepatoprotective effects. Similarly, Haitamy *et al.* (2024) demonstrated that *N. sativa* significantly reduced inflammatory markers, such as Cyclooxygenase-2 (COX-2), p50, and p65, in an *Aspergillus niger*-induced otitis externa model, showing its potential for treating microbial-induced inflammation. Bashir *et al.* (2023) highlighted the anti-adipogenic and anti-inflammatory effects of *N. sativa in vitro*, where the black cumin seed extract inhibited lipid accumulation and reduced the expression of inflammatory cytokines like Tumor Necrosis Factor-alpha(TNF-α) and Interleukin-6 (IL-6) by suppressing Nuclear Factor kappa B(NF-κB) and Mitogen-Activated Protein Kinase (MAPK) pathways. In the context of malaria, Ojueromi *et al.* (2022) found that *N. sativa supplementation in Plasmodium berghei-infected mice reduced parasitemia and modulated inflammatory cytokines, thereby* improving antioxidant status and immune function. A similar study by Ojueromi *et al.* (2024), which used N. sativa - fortified cookies, also revealed a reduction in parasitemia and inflammatory markers, further supporting its potential as a therapeutic agent for malaria-related immune and inflammatory dysfunction. Additionally, Wei *et al.* (2022) demonstrated that active ingredients from *N. sativa* activated the NF-κB and MAPK signaling pathways, regulating inflammation and immune responses.

Antitumor Effect of *N. sativa*

Nigella sativa L. (*N. sativa*), a plant traditionally used in Middle Eastern medicine, has gained attention for its potential anti-tumor properties, which are attributed to its antioxidant and antiangiogenic effects. Several studies have investigated its therapeutic potential, particularly in cancer treatment. A study by Bahramian *et al.* (2016) demonstrated that *N. sativa* crude oil significantly reduced tumor volumes, inhibited angiogenesis (via decreased vascular endothelial growth factor (VEGF) and increased endostatin), and enhanced antioxidant enzyme activities (superoxide dismutase and catalase) in breast tumor-bearing mice. Similarly, Rafati *et al.* (2019) reported that *N. sativa* gel alleviated acute radiation dermatitis (ARD) in breast cancer patients undergoing radiotherapy, reducing pain and delaying the onset of severe skin reactions. Moreover, Imaduddin *et al.* (2022) highlighted the antileukemic effect of *N. sativa* seed extract in benzene-induced leukemia in rats, showing improvements in blood parameters and demonstrating significant therapeutic efficacy, which is attributed to the presence of bioactive compounds such as alkaloids and flavonoids. Additionally, Aftab *et al.* (2023) explored the antineoplastic potential of the vegetative part of *N. sativa*, finding significant cytotoxic effects against the human epithelial cell line (Hep2) and human breast cancer cell lines (MCF7), particularly with n-butanol and chloroform extracts.

Antidiabetic, Antihyperlipidemic, and Hepatoprotective Effects of *N. sativa* on Metabolic Syndrome

A study by El Rabey *et al.* (2017) demonstrated that *N. sativa* methanol extract alleviated biochemical and histopathological alterations in streptozotocin-induced diabetic rats, with effects comparable to those of propolis, although propolis exhibited greater efficacy. Similarly, a pilot study by Pelegrin et al. (2019) found that N. sativa powder did not significantly affect insulin sensitivity or glucose regulation in healthy volunteers; however, it showed potential to lower lipid concentrations, particularly in hyperlipidemic subjects. Moreover, *N. sativa* has been shown to mitigate oxidative stress and lipid peroxidation in hyperlipidemic rats, improving antioxidant enzyme activities such as superoxide dismutase, catalase, and glutathione-S-transferase (Ahmad & Beg, 2016). Its hepatoprotective effects have also been established in diabetic rats, where it alleviated liver damage by reducing liver enzyme levels and improving histopathological findings (Das, 2016). Furthermore, *the effect of N. sativa* on vascular health has been highlighted in studies examining endothelial dysfunction in diabetes, where it improved endothelial nitric

oxide synthase expression and vasorelaxation in aortic rings, revealing beneficial effects on vascular inflammation (Abbasnezhad *et al.*, 2019). In addition to its antidiabetic, antihyperlipidemic, and hepatoprotective effects, *N. sativa* oil has been shown to possess genoprotective and free radical scavenging properties, particularly against liver toxicity induced by fungicides (Hashem *et al.*, 2018).

Effects of *N. sativa* on Neurological, Cardiovascular, and Respiratory Disorders and their Anti-Infertility Properties

A study by Seghatoleslam *et al.* (2016) showed that pre-treatment with NS hydro-alcoholic extract reduced seizure scores and improved memory and hippocampal histology in rats after pentylenetetrazole-induced seizures. Additionally,*Nigella sativa*(NS) has exhibited antimanic-like effects and modulated brain inflammatory mediators, with a marked reduction in interleukin-6, tumor necrosis factor-α, and other inflammatory markers (Uzzan *et al.*, 2024). In the context of neurotoxicity, NS oil alleviated aluminum chloride-induced cerebellar damage by reducing nitric oxide metabolites and reactive oxygen species (ROS), and preserving cerebellar histoarchitecture, demonstrating its neuroprotective effects (Imam *et al.*, 2022). Cardiovascularly, *N. sativa* oil improved vascular function by enhancing flow-mediated dilation and increasing plasma nitric oxide levels, though it had no significant effect on certain adhesion molecules (Emamat *et al.*, 2022). Additionally, NS supplementation improved cardiovascular risk factors in obese and overweight women, increasing high-density lipoprotein (HDL) cholesterol, reducing low-density lipoprotein (LDL) cholesterol, and lowering systolic blood pressure (Razmpoosh *et al.*, 2021). In respiratory health, the addition of NS to standard treatment has improved clinical outcomes in patients with uncomplicated respiratory infections, resulting in faster symptom resolution compared to those receiving standard treatment alone (Elango *et al.*, 2022). Furthermore, in the management of COVID-19, a combination of NS and vitamin D3 enhanced viral clearance and alleviated symptoms more effectively than standard treatment alone (Said *et al.*, 2022). In reproductive health, an ethanolic extract of NS seeds demonstrated hormone-like activities, increasing luteinizing hormone (LH), estrogen (E2), and progesterone levels, and improving fertility in female rats, suggesting its potential for treating female infertility (Nagy *et al.*, 2024).

Anti-Inflammatory and Immunomodulatory Effect of *Psidium guajava*

A study by Vasconcelos *et al.* (2017) demonstrated that lycopene-rich extracts (LEG) and purified lycopene (LPG) from red guava exhibited significant anti-inflammatory effects in Swiss mice, as evidenced by reduced paw edema induced by various inflammatory agents, decreased leukocyte migration, and lowered myeloperoxidase (MPO) levels. These effects were associated with the downregulation of inflammatory mediators and an increase in glutathione (GSH) levels. Similarly, Kariawasam *et al.* (2017) reported that the aqueous leaf extract of *Psidium guajava* exhibited dose-dependent anti-inflammatory activity, with significant inhibition of egg albumin and bovine serum albumin denaturation. This effect was comparable to the anti-inflammatory drug Diclofenac sodium, and in the egg albumin denaturation assay, guava extract showed nearly 30 times stronger activity. Moreover, studies on the immunomodulatory effects of guava leaves have demonstrated their ability to stimulate both humoral and cell-mediated immunity. Shabbir *et al.* (2016) found that the methanolic leaf extract of guava significantly increased white blood cell (WBC) count, hemoglobin levels, and platelet counts in mice, while also improving delayed-type hypersensitivity responses and preventing cyclophosphamide-induced myelosuppression. Furthermore, the extract boosted **anti-Sheep Red Blood Cell (anti-SRBC**) antibody titers and reduced the lethality rate in mice compared to cyclophosphamide treatment, indicating the potential of guava leaves as an immunostimulant.

Antitumor Effect of *Psidium guajava*

Ashraf *et al.* (2016) explored the antitumor effects of methanol, hexane, and chloroform extracts of *P. guajava* leaves on human carcinoma cell lines including **human chronic myelogenous leukemia**(KBM5), human squamous cell carcinoma(SCC4), and**human multiple myeloma cell line**(U266), revealing dose-dependent decreases in cell viability with IC50 values ranging from 22.73 to 89.55 µg/mL. The hexane extract notably inhibited TNF-α induced NF-κB activation in KBM5 cells, emphasizing its anti-inflammatory potential. Further research by Qin *et al.* (2017) identified meroterpenoids in guava fruit, specifically

psiguajavadial B, which exhibited high cytotoxicity against A549 human lung cancer cells, with an IC50 value of 150 nM. This compound also demonstrated inhibitory activity against topoisomerase I, a crucial enzyme for DNA replication in cancer cells. Meroterpenoids such as Psiguajavadial D and Guapsidial A were shown to exert cytotoxic effects across multiple cell lines, including HL-60 and MCF-7, with IC50 values ranging from 3.21 to 9.94 µmol/L (Kumar et al., 2021). In addition to these compounds, Zhu *et al.* (2019) isolated guavinoside E, benzophenone, and guavinoside B from *P. guajava* leaves. Compound 2 showed strong apoptotic activity in HCT116 colon cancer cells through the upregulation of p53 and cleaved caspases. Moreover, Polinati *et al.* (2022) investigated the effects of lycopene extracted from guava on MCF-7 breast cancer cells, demonstrating its role in inducing apoptosis and modulating the G2-M cell cycle checkpoint.

Antidiabetic, Antihyperlipidemic, and Hepatoprotective Effects of *Psidium guajava* on Metabolic Syndromes

Psidium guajava, specifically its leaf extracts, has shown promise in managing metabolic disorders, including type 2 diabetes mellitus (T2DM), dyslipidemia, and liver dysfunction. The aqueous extract of guava leaves has been found to improve glucose tolerance, insulin sensitivity, and hepatic glycogen accumulation in diabetic db/db mice, while also restoring gut microbiota composition and increasing GLUT2 expression in hepatocytes (Chu *et al.*, 2022). In streptozotocin-induced diabetic rats, guava leaf extract reduced hormone-sensitive lipase (HSL) activity, increased glycogen storage, and improved lipid profiles by lowering triglycerides, total cholesterol, and LDL cholesterol, while raising HDL cholesterol (Tella *et al.*, 2019). A lycopene-rich extract from red guava fruit has also demonstrated antihyperlipidemic effects by reducing plasma triglycerides, total cholesterol, and LDL cholesterol, along with improving oxidative stress markers in hypercholesterolemic hamsters (Brito *et al.*, 2019). Additionally, *Psidium guajava* leaf extract has exhibited hepatoprotective effects, mitigating ketoconazole-induced liver damage by reducing elevated alanine aminotransferase (ALT) levels in Wistar rats (Innih *et al.*, 2016).

Antibacterial Activity of Major Compounds in *Nigella Sativa* against Drug-Resistant Strains

Thymoquinone is a highly effective antibacterial and antibiofilm agent. Goel and Mishra (2018) reported its efficacy against both Gram-positive and Gram-negative bacteria, with MICs ranging from 1.56 to 100 µg/mL. Wang *et al.* (2022) via disruption of bacterial viability and biofilms while inducing oxidative stress and energy depletion. This compound also proves highly effective against drug-resistant strains, as indicated by Jankowski *et al.* (2023), who also describe the killing mechanism of *Mycobacterium tuberculosis* induced by TQ through sigma factor overexpression. Similarly, Dera *et al.* (2021) highlighted its synergistic effect with antibiotics against pathogens such as *Klebsiella pneumoniae* and *Staphylococcus aureus*, emphasizing its role in combination therapies.

Thymol is another notable chemical compound that exhibits strong antibacterial activity and a broader range of applications. Yin *et al. 2022* reported its efficacy against drug-resistant *Streptococcus iniae* and its protective effects in aquaculture. Its property of disturbing cell membranes and homeostasis makes it an effective agent in avoiding food contamination, according to Tian *et al.* (2021). Farhadi *et al.* (2024) examined its synergistic effects with antibiotics, such as tetracycline, and emphasized its ability to inhibit biofilms.

A broad-spectrum antibacterial agent, carvacrol synergizes with other components of Nigella sativa, including activity against methicillin-resistant and -susceptible *Staphylococcus aureus* (Mouwakeh *et al.*, 2019). Wijesundara *et al.* 2021 and 2022 demonstrated that it damages bacterial cell membranes, inducing increased permeability and a lower cell potential. Mir et al. (2019) Its noteworthiness is especially attributed to its rapid bactericidal activity; however, its modes of action in conjunction with antibiotics render conflicting results, which can only be addressed by careful consideration in terms of therapy.

Antibacterial Activity of Major Compounds in *Psidium guajava* against Multi-drug Resistant Strains

Psidium guajava has gained significant attention for its antimicrobial properties, particularly against multidrug-resistant (MDR) bacterial strains, including *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*. Studies have shown that ethanolic extracts of guava leaves exhibit notable antibacterial activity against carbapenem-resistant *K. pneumoniae*, with minimum inhibitory concentrations (MIC) and

minimum bactericidal concentrations (MBC) as low as 6.25 mg/ml with the antibacterial activity being attributed to the presence of bioactive compounds such as flavonoids and other antimicrobial phytochemicals (Hackman *et al.*, 2020). Furthermore, guava leaf extracts have demonstrated effectiveness against extended-spectrum beta-lactamase (ESBL)-producing *K. pneumoniae*, which are a major cause of urinary tract infections (Hackman *et al.*, 2020). In addition, guava extracts have been found to possess antibiotic-resistance reversal properties, particularly in *P. aeruginosa*, where guava bark and leaf extracts resensitize MDR strains overexpressing efflux pumps to commonly prescribed antibiotics, thereby enhancing the efficacy of conventional treatments (Tiotsop *et al.*, 2023). Studies also indicate that guava leaf extracts are effective against other MDR pathogens, including Staphylococcus aureus and Salmonella typhi, with notable antibacterial effects at higher concentrations (Buah *et al.*, 2023; Moses *et al.*, 2019).

Table 3: Sensitivity of Multidrug-Resistant Pathogens to *Nigella sativa*

Pathogen	Sensitivity to *Nigella sativa*	Extract type	Plant part used	Study Type	References
Acinetobacter baumannii	Sensitive (MIC: 2.5 mg/ml)	Ethanol Extract	Seeds	*In vitro* antibacterial activity studies	Dhanasekaran, 2019
Methicillin-resistant *Staphylococcus aureus*	Sensitive (42% to undiluted oil; 21% at 200, 400, 800 mg/ml)	Essential Oil	Seeds	*In vitro* antibacterial susceptibility study	Emeka *et al.*, 2015
Escherichia coli	Sensitive (MIC: 0.4 mg for 90% ethanol; Inhibition zone: 12 mm)	Ethanol Extract	Seeds	*In vitro* antibacterial susceptibility study	Khalid and Ahmad 2024
Pseudomonas aeruginosa	Sensitive (varied zones of inhibition with different dilutions)	Essential Oil	Seeds	*In vitro* antibacterial activity study	Maryam *et al.*, 2016
Proteus mirabilis	Sensitive (MIC: 1.5 mg/ml)	Ethanol Extract	Seeds	*In vitro* antibacterial activity study	Al Dosary, 2023
Klebsiella pneumonia (ESBL)	Sensitive (MIC: 2.5 mg/ml)	Ethanol Extract	Seeds	*In vitro* antibacterial activity study	Al Dosary, 2023
Staphylococcus aureus	Sensitive (Inhibition zone: 17 mm at 100 µg/mL)	Silver Nanoparticles	Seeds	*In vitro* antibacterial activity study	Ezeh *et al.*, 2022
MDR-TB	Sensitive (at 5% and 10% concentrations)	Methanol Extract	Seeds	*In vitro* susceptibility study	Masri *et al.*, 2021
Staphylococcus epidermidis	Sensitive (MIC: 1.04-8.3 µg/mL)	Thymoquinone	Seeds	*In vitro* susceptibility study	Dera *et al.*, 2021

Table 4: Sensitivity of Multidrug-Resistant Pathogens to *Psidium guajava*

Pathogen	Sensitivity to *Nigella sativa*	Extract type	Plant part used	Study Type	References
Pseudomonas aeruginosa	Sensitive (MIC: 64-2048 µg/mL; ≤512 µg/mL	Methanol Extract	Leaves and Bark	*In vitro* antibacterial activity study	Tiotsop *et al.*, 2023
Staphylococcus aureus	Sensitive (MIC: 6.8 mg/mL)	Aqueous Extract	Leaves	*In vitro* antibacterial activity study	Pereira *et al.*, 2023
Escherichia coli	Sensitive (MIC: 40.0 mg/mL)	Methanol Extract	Leaves	*In vitro* antibacterial activity study	Ilesanmi *et al.*, 2020
Staphylococcus epidermidis	Sensitive (MIC: 40.0 mg/mL)	Methanol Extract	Leaves	*In vitro* antibacterial activity study	Ilesanmi *et al.*, 2020
Proteus mirabilis	Sensitive (MIC: 40.0 mg/mL)	Methanol Extract	Leaves	*In vitro* antibacterial activity study	Ilesanmi *et al.*, 2020
Staphylococcus saprophyticus	Sensitive (MIC: 40.0 mg/mL)	Methanol Extract	Leaves	*In vitro* antibacterial activity study	Ilesanmi *et al.*, 2020
Bacillus cereus	Sensitive (MIC: 40.0 mg/mL)	Methanol Extract	Leaves	In vitro antibacterial activity study	Ilesanmi *et al.*, 2020

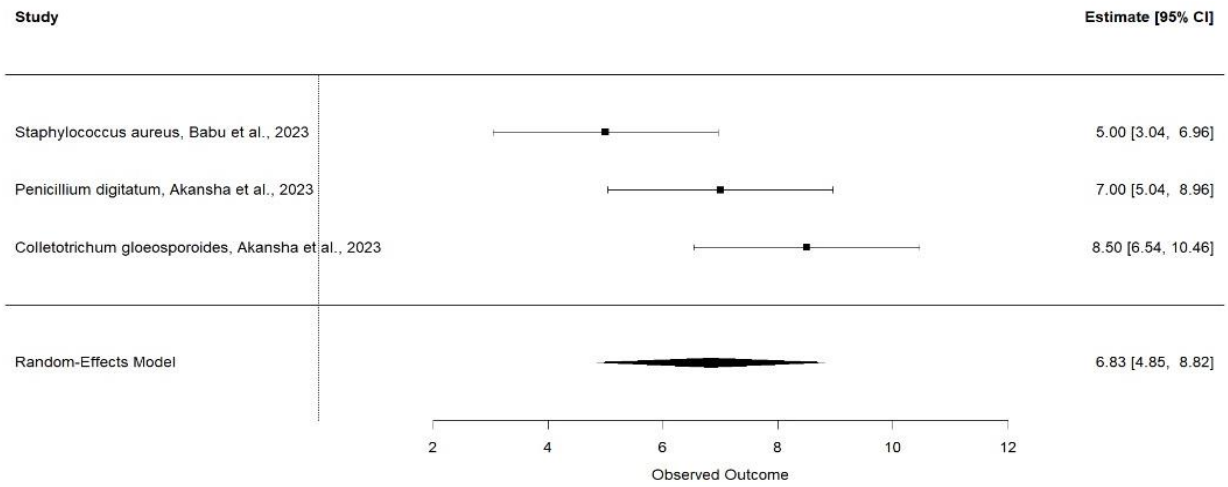

Figure 2: Meta-analysis on MIC values

A meta-analysis (Figures 2) was conducted on the minimum inhibitory concentration (MIC) values of thymoquinone against three pathogenic organisms reported in independent studies. The pooled MIC estimate using a random-effects model was 6.83 µg/mL with a 95% confidence interval of 4.85 to 8.82 µg/mL, indicating consistent antimicrobial activity across diverse microbial species. Specifically, thymoquinone demonstrated the greatest potency against *Staphylococcus aureus* (5.00 µg/mL), followed by *Penicillium digitatum* (7.00 µg/mL) and Colletotrichum gloeosporioides (8.50 µg/mL). The non-overlapping confidence intervals and tight distribution show moderate heterogeneity and robust antimicrobial efficacy. These findings support thymoquinone's broad-spectrum potential, particularly against Gram-

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positive and fungal pathogens, and emphasize its promise for further preclinical development. The clustered heatmap (Figure 3) depicted the relative antimicrobial potency of six phytocompounds against seven pathogens, based on MIC values (µg/mL).

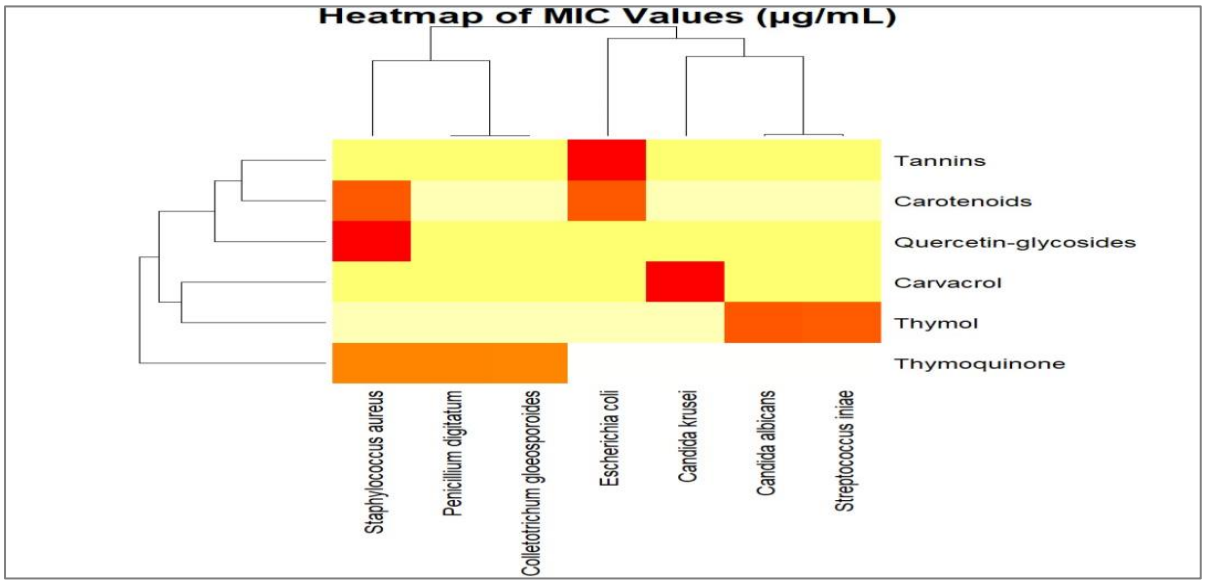

Figure 3: Heatmap of MIC values

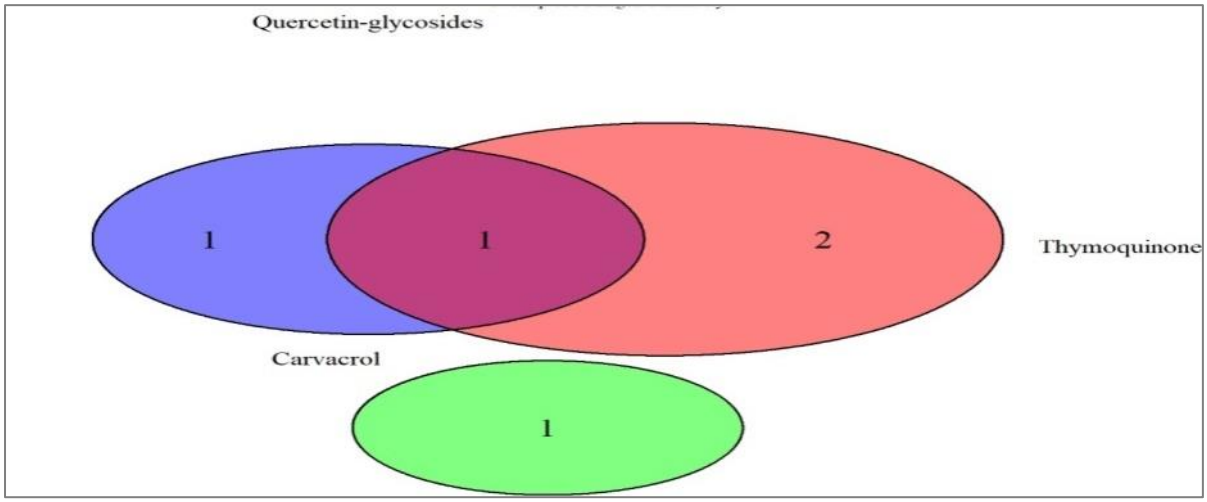

Figure 4: Overlap of pathogen sensitivity

Warmer colors (red and orange) indicate higher MICs (lower potency), while cooler shades (yellow to pale) denote lower MICs and greater efficacy. Notably, carotenoids and thymoquinone clustered together, both exhibiting potent activity across *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, showing a shared spectrum of efficacy. Thymol and quercetin glycosides showed selective activity, with quercetin demonstrating reduced potency against E. coli (high MIC), while carvacrol exhibited narrower, more targeted inhibition against *Candida krusei*. The dendrograms revealed a degree of overlap in the antimicrobial spectrum among certain phytochemicals, underscoring the potential utility of *N. sativa* and *P. guajava* compounds in targeting both Gram-positive bacteria and opportunistic fungi. These visual insights support the prioritization of compounds for future mechanistic studies and antimicrobial formulation development. The Venn diagram (Figure 4) highlighted the overlap in antimicrobial activity among thymoquinone, carvacrol, and quercetin-glycosides based on their target pathogens. Thymoquinone demonstrated the broadest spectrum, uniquely inhibiting two pathogens not shared by the other compounds. Quercetin glycosides and thymoquinone overlapped in their activity against a common pathogen, indicating partial redundancy. Carvacrol showed the narrowest

spectrum, targeting a single unique pathogen with no overlap, except for one shared target with quercetin glycosides. These findings showed that while there is some functional redundancy, each compound also contributes uniquely to the antimicrobial portfolio, reinforcing the rationale for multi-compound phytotherapeutic strategies to broaden pathogen coverage. The bar chart (Figure 5) displayed the average MIC values (µg/mL) of six bioactive compounds, highlighting substantial variability in antimicrobial efficacy.

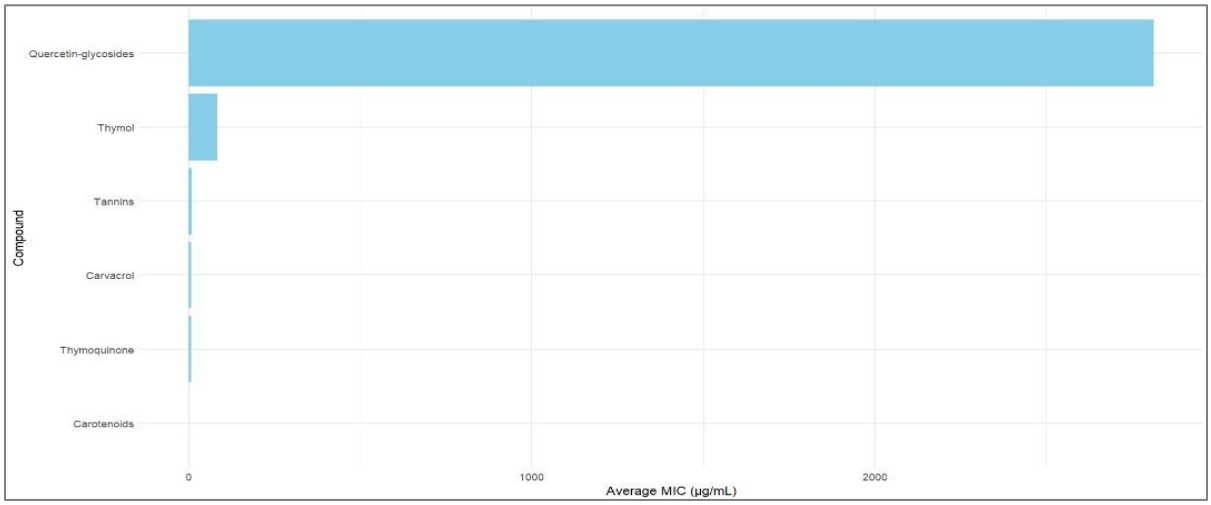

Figure 5: Average MIC by Compounds

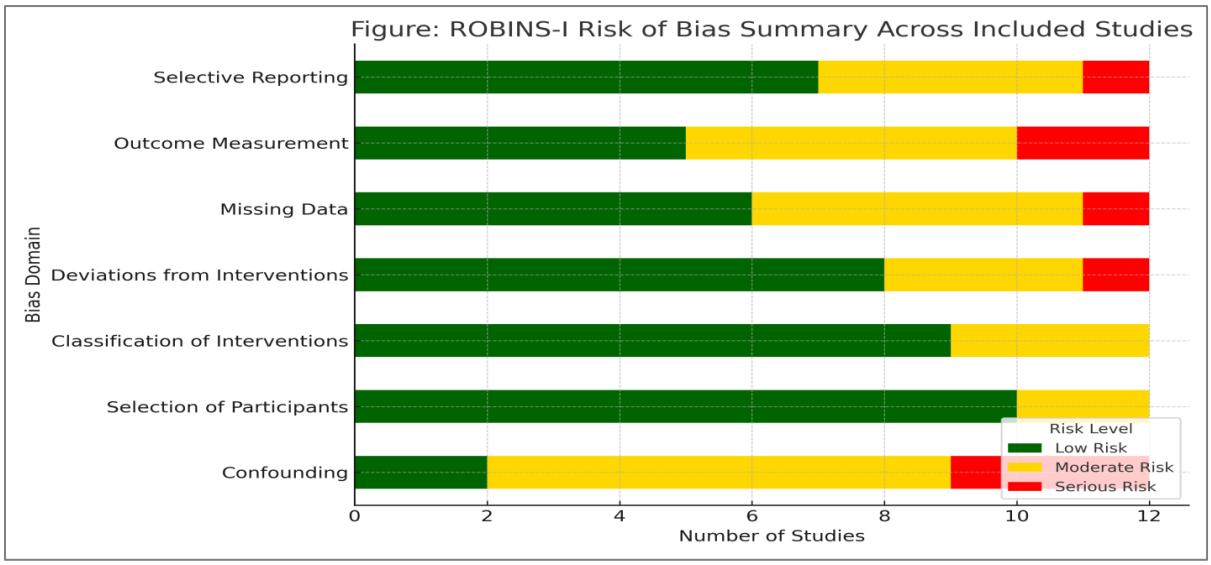

Figure 6: ROBINS-I Risk of Bias Summary Across Included Studies

Carotenoids and thymoquinone exhibited the lowest average MICs, indicating the highest potency across tested pathogens. Carvacrol and tannins followed with modestly low MIC values, reinforcing their intermediate efficacy profiles. In contrast, quercetin-glycosides showed markedly higher average MIC values, exceeding 2000 µg/mL, indicating comparatively weak antimicrobial activity in vitro. These findings provide quantitative support for the superior potency of compounds derived from *Nigella sativa* compared to those from *Psidium guajava*, underscoring their potential for prioritization in further preclinical evaluation and formulation.

As illustrated in Figure 6 (ROBINS-I Risk of Bias Summary Across Included Studies), the majority of included studies exhibited low to moderate risk of bias across key methodological domains, particularly in participant selection and intervention classification, indicating overall consistency in inclusion criteria and reporting standards. However, serious risk of bias was identified in critical areas such as confounding due to the absence of comparator groups or failure to control for experimental variables and outcome measurement, where unvalidated or poorly defined MIC reporting undermined reliability. The distribution of reported MIC

values shows potential publication bias, characterized by an overrepresentation of favorable outcomes and underreporting of null or weak antimicrobial effects.

DISCUSSION

Multiple mechanisms, including efflux pumps, target modification, and biofilm formation, drive the antimicrobial resistance (AMR) crisis. Phytochemicals present in *Nigella sativa* and *Psidium guajava* have shown potential to counteract these mechanisms (Arip *et al.*, 2022). Thymoquinone exhibits membrane-disruptive activity that destabilizes bacterial cell integrity (Wu et al., 2016), while flavonoids, such as quercetin glycosides, have been reported to inhibit efflux pumps (Alnour et al., 2022), thereby increasing the intracellular accumulation of antibiotics. Tannins in *P. guajava* also impair bacterial adhesion, limiting biofilm development, which is a major contributor to chronic and multidrug-resistant infections (Vermaak, 2020). These multifaceted actions demonstrate that plant-derived compounds not only kill pathogens but may also re-sensitize resistant strains to conventional antibiotics, offering an important strategy for reversing AMR.

The observed synergy between bioactive plant compounds and antibiotics has important therapeutic implications (Vaou *et al.*, 2022). Carvacrol from *N. sativa* has demonstrated synergy with cefixime and other ß-lactams, possibly by enhancing membrane permeability and inhibiting efflux-mediated resistance (Herman and Herman, 2023). This potentiation effect allows for reduced antibiotic dosing, which in turn can minimize side effects and slow the emergence of resistance. Similarly, guava-derived flavonoids have been shown to exhibit additive or synergistic effects in combination with aminoglycosides and tetracyclines (Qu *et al.*, 2019). Such interactions could enable the development of **combination therapies** that are both cost-effective and clinically viable, particularly in low-resource settings where access to next-generation antibiotics is limited (Chidzwondo and Mutapi, 2024). These findings support the integration of plant-based adjuvants in the design of future antimicrobial protocols.

Despite the promising results, several challenges hinder the clinical application of these plant-derived compounds. First, standardizing plant extracts remains challenging due to variability in phytochemical content across geographical and seasonal contexts (Liebelt *et al.*, 2019). Second, **limited bioavailability and stability** of compounds like thymoquinone may affect their efficacy in vivo (Hemananthan, 2020). Third, rigorous **clinical trials and toxicological assessments** are lacking, making regulatory approval difficult (Pognan *et al.*, 2023). Additionally, intellectual property and formulation barriers complicate the incorporation of phytochemicals into mainstream medicine. Addressing these issues requires coordinated efforts in pharmacokinetic modeling, nanocarrier development, and harmonization of herbal pharmacopoeias to enable safe and effective clinical translation (Krishnaswamy, 2024).

Challenges in the Therapeutics of *Nigella Sativa* and *Psidium Guajava*

The overharvesting of these plant species for their medicinal properties can lead to the depletion of natural resources and pose a threat to the survival of these plant species (Mir *et al.*, 2021). This unsustainable practice raises concerns about ecological balance and biodiversity. Unsustainable plant collection can degrade habitats, disrupt ecosystems, and threaten biodiversity (Kumari *et al.*, 2021). This highlighted the importance of sustainable sourcing methods and the preservation of medicinal plants to protect both ecosystems and the indigenous communities that rely on them. Ensuring consistent quality and effectiveness of plant-based chemicals is difficult because factors such as genetics, environmental conditions, and harvesting practices can alter their chemical composition (Alamgir *et al.*, 2017).

The standardization of plant extracts is significant for consistently replicating their medicinal effects (Govindaraghavan and Sucher, 2015). To ensure the safety and effectiveness of herbal products, it's important to implement stringent quality control measures, including thorough testing and precise quality standards (Heinrich *et al.*, 2022). Variations in bioactive compound concentrations and impurities can impact the reliability and safety of these remedies. The pharmacokinetics of plant-derived substances exhibit significant variability, influencing their bioavailability, distribution, metabolism, and elimination in the body (Chaachouay and Zidane 2022). The efficiency of pharmacological medicines may be influenced by their absorption rates, interactions with other compounds, and chemical stability. Understanding and optimizing the pharmacokinetic properties of

plant-derived chemicals is crucial for developing medications that exhibit predictable and consistent therapeutic effects (Stielow *et al.*, 2023).

The development of plant-derived medications involves complex regulatory frameworks that vary by region, requiring rigorous safety and efficacy testing, which can increase costs and timelines (Hossain *et al.*, 2022). Additionally, issues surrounding intellectual property and equitable compensation for indigenous peoples arise from the commercialization of traditional knowledge and plant resources (Bhaduri, 2023). The accessibility and affordability of certain botanical substances, often sourced from specific geographic areas, further complicate their use in clinical settings (Aware *et al.*, 2022). Limited access to plant-based medicines affects underserved communities (Efe *et al.*, 2024). A comprehensive strategy is needed, focusing on conservation, sustainable harvesting, quality control, regulatory alignment, and ethical practices to ensure equitable benefits (Selvakumar *et al.*, 2025). The use of plant-derived chemicals in drug discovery offers substantial potential for innovation in healthcare. However, it is essential to address associated challenges responsibly to maximize benefits while minimizing negative impacts on the environment and society. A balanced approach will ensure sustainable development in this field (Nasim *et al.*, 2022).

PROSPECTS FOR FUTURE RESEARCH

Plant-derived natural compounds remain significant for developing innovative medications and treatments due to their diverse chemical variations (Najmi *et al.*, 2022). This wide array of plant chemicals provides numerous potential applications in medicine, highlighting their ongoing significance in pharmacological research and therapeutic development (Aware *et al.*, 2022). Recent advancements in identifying bioactive substances from plants, combined with a deeper understanding of their mechanisms of action, underscore the feasibility of plant-based drug development (Dar *et al.*, 2023). This approach is increasingly vital as researchers pursue sustainable alternatives in pharmacotherapy (Streicher, 2021). The integration of genomics and metabolomics has played a crucial role in this progress, with the sequencing of plant genomes illuminating the genetic pathways involved in the synthesis of bioactive compounds, thereby enhancing the cultivation and utilization of these valuable resources (Wang *et al.*, 2024). Metabolomics provides a comprehensive analysis of small molecules in plant systems, enabling the precise identification of potential bioactive compounds. Advanced methodologies in this field facilitate functional predictions and genome manipulation to enhance the production of valuable metabolites. This systematic approach streamlines the discovery process, reduces extensive testing, and promotes the development of compounds tailored for targeted therapeutic applications (Zhang *et al.*, 2017).

Biotechnology and synthetic biology play an important role in optimizing the extraction and utilization of plant-derived compounds. Anticipated advancements in bioproduction, genetic engineering, and route optimization are expected to expand the variety of substances obtainable from plants. These innovations aim to enhance both the efficiency and sustainability of producing valuable natural compounds, thus facilitating diverse applications across medicine, agriculture, and industry (Wei *et al.*, 2024). Bioreactors present a sustainable and scalable solution for producing plant-derived molecules, effectively addressing ecological challenges. The incorporation of genetic modifications and pathway engineering allows for the customization of plant metabolites to meet specific pharmaceutical requirements. This approach enhances production efficiency while advancing the development of targeted therapeutics (Upadhyay and Singh, 2023). The future of precision medicine offers significant potential for incorporating plant-derived chemicals into personalized therapeutics. By utilizing genomic and metabolomic data, researchers aim to tailor therapies to match individuals' unique genetic profiles and health conditions. This strategy aims to enhance treatment efficacy and improve patient outcomes through personalized healthcare solutions (Chintada and Golla, 2025). This approach emphasizes the customization of plant-based substances to enhance treatment efficacy and reduce adverse effects. Growing research on the synergy between plant-derived chemicals and traditional medications reveals potential for improved therapeutic outcomes, reduced side effects, and addressing medication resistance in diverse medical conditions (Aware *et al.*, 2022). Future drug development from plant sources will prioritize the exploration of understudied species with medicinal potential. Untapped biological resources worldwide present opportunities for targeted research, potentially leading to the discovery of novel therapeutic compounds and expanding the

pharmacological repertoire from natural sources (Chaachouay and Zidane 2024).

CONCLUSION

N. sativa and *P. guajava* exhibit potent antimicrobial and antitumor activities, yet clinical translation requires standardized extracts, pharmacokinetic studies, and large-scale trials. Future research must prioritize synergistic formulations and sustainable bio-production to combat AMR

REFERENCES

Abbas, M., Gururani, M. A., Ali, A., Bajwa, S., Hassan, R., Batool, S. W., … Wei, D. (2024). Antimicrobial properties and therapeutic potential of bioactive compounds in *Nigella sativa*: A review. *Molecules, 29*(20), 4914. [Crossref]

Abbasnezhad, A., Niazmand, S., Mahmoudabady, M., Rezaee, S. A., Soukhtanloo, M., Mosallanejad, R., & Hayatdavoudi, P. (2019). *Nigella sativa* L. seed regulated eNOS, VCAM-1 and LOX-1 genes expression and improved vasoreactivity in aorta of diabetic rat. *Journal of Ethnopharmacology, 228*, 142–147. [Crossref]

Abdallah, H. M., El-Halawany, A. M., Darwish, K. M., Algandaby, M. M., Mohamed, G. A., Ibrahim, S. R., … Elfaky, M. A. (2022). Bio-guided isolation of SARS-CoV-2 main protease inhibitors from medicinal plants: In vitro assay and molecular dynamics. *Plants, 11*(15), 1914. [Crossref]

Aftab, A., Yousaf, Z., & Rashid, M. (2023). Vegetative part of *Nigella sativa* L. potential antineoplastic sources against Hep2 and MCF7 human cancer cell lines. *Journal of Taibah University for Science, 17*. [Crossref]

Ahmad, S., & Beg, Z. H. (2016). Evaluation of therapeutic effect of omega-6 linoleic acid and thymoquinone enriched extracts from *Nigella sativa* oil in the mitigation of lipidemic oxidative stress in rats. *Nutrition, 32*(6), 649–655. [Crossref]

Akansha, Kaushal, S., Arora, A., Heena, Sharma, P., & Jangra, R. (2023). Chemical composition and synergistic antifungal potential of *Nigella sativa* L. seeds and *Syzygium aromaticum* (L.) Merr. & L. M. Perry buds essential oils and their major compounds, and associated molecular docking studies. *Journal of Essential Oil Bearing Plants, 26*(3), 602–625. [Crossref]

Al Dhaheri, Y., Wali, A. F., Akbar, I., Rasool, S., Razmpoor, M., Jabnoun, S., & Rashid, S. (2022). *Nigella sativa*, a cure for every disease: Phytochemistry, biological activities, and clinical trials. In *Black Seeds (Nigella Sativa)* (pp. 63–90). Elsevier. [Crossref]

Al Dosary, R. A. A. Q. (2023). Antibacterial and alteration of drug resistance activities of black cumin seed (*Nigella sativa*) extracts against urinary pathogens. *Journal of Public Health Sciences, 2*(03), 148–158. [Crossref]

Alamgir, A. N. M., & Alamgir, A. N. M. (2017). Cultivation of herbal drugs, biotechnology, and in vitro production of secondary metabolites, high-value medicinal plants, herbal wealth, and herbal trade. In *Therapeutic Use of Medicinal Plants and Their Extracts: Volume 1: Pharmacognosy* (pp. 379–452). [Crossref]

Alnour, T. M., Ahmed-Abakur, E. H., Elssaig, E. H., Abuduhier, F. M., & Ullah, M. F. (2022). Antimicrobial synergistic effects of dietary flavonoids rutin and quercetin in combination with antibiotics gentamicin and ceftriaxone against *E. coli* (MDR) and *P. mirabilis* (XDR) strains isolated from human infections: Implications for food-medicine interactions. *Italian Journal of Food Science, 34*(2), 34–42. [Crossref]

Alobaedi, O. H., Talib, W. H., & Basheti, I. A. (2017). Antitumor effect of thymoquinone combined with resveratrol on mice transplanted with breast cancer. *Asian Pacific Journal of Tropical Medicine, 10*(4), 400–408. [Crossref]

Al-Rabia, M. W., Asfour, H. Z., Alhakamy, N. A., Abdulaal, W. H., Ibrahim, T. S., Abbas, H. A., … Nazeih, S. I. (2024). Thymoquinone is a natural antibiofilm and pathogenicity attenuating agent in *Pseudomonas aeruginosa*. *Frontiers in Cellular and Infection Microbiology, 14*, 1382289. [Crossref]

Arip, M., Selvaraja, M., Tan, L. F., Leong, M. Y., Tan, P. L., Yap, V. L., … Jubair, N. (2022). Review on plant-based management in combating antimicrobial resistance—Mechanistic perspective. *Frontiers in Pharmacology, 13*, 879495. [Crossref]

Ashraf, A., Sarfraz, R. A., Rashid, M. A., Mahmood, A., Shahid, M., & Noor, N. (2016). Chemical composition, antioxidant, antitumor, anticancer and cytotoxic effects of *Psidium guajava* leaf extracts. *Pharmaceutical Biology, 54*(10), 1971–1981. [Crossref]

Aware, C. B., Patil, D. N., Suryawanshi, S. S., Mali, P. R., Rane, M. R., Gurav, R. G., & Jadhav, J. P. (2022). Natural bioactive products as promising therapeutics: A review of natural product-based drug development. *South African Journal of Botany, 151*, 512–528. [Crossref]

Babu, B., Rao, P., Suman, E., & Udayalaxmi, J. (2023). A study of antibacterial effect of *Nigella sativa* seed extracts on bacterial isolates from cases of wound infection. *Infectious Disorders—Drug Targets, 23*(5), 41–45. [Crossref]

Bahramian, S., Bigdeli, M. R., Rasoulian, B., & Moridi, F. M. (2016). Antitumor and antiangiogenic effects of the crude oil of *Nigella sativa* L. in tumor tissues in BALB/c mice. *Zahra Journal of Research in Medical Sciences, 18*(1). [Crossref]

Balouiri, M., Sadiki, M., & Ibnsouda, S. K. (2016). Methods for in vitro evaluating antimicrobial activity: A review. *Journal of Pharmaceutical Analysis, 6*(2), 71–79. [Crossref]

Bano, A., Gupta, A., Rai, S., Sharma, S., Upadhyay, T. K., Al-Keridis, L. A., … Saeed, M. (2023). Bioactive compounds, antioxidant, and antibacterial activity against MDR and food-borne pathogenic bacteria of *Psidium guajava* L. fruit during ripening. *Molecular Biotechnology*. [Crossref]

Bashir, A., Ado, A., & Alli, A. I. (2022). Determination of antibacterial activity of *Psidium guajava* leaf extract against bacteria isolated from mobile phones of Umaru Musa Yar'adua University, Katsina community. *UMYU Journal of Microbiology Research, 6*(1), 219–226. [Crossref]

Bashir, K. M. I., Kim, J. K., Chun, Y. S., Choi, J. S., & Ku, S. K. (2023). In vitro assessment of anti-adipogenic and anti-inflammatory properties of black cumin (*Nigella sativa* L.) seeds extract on 3T3-L1 adipocytes and RAW264.7 macrophages. *Medicina, 59*(11), 2028. [Crossref]

Bhaduri, A. (2023). Communities as inventors: Rethinking positive protection of traditional knowledge through patents. *The Journal of World Intellectual Property, 26*(3), 414–435. [Crossref]

Brito, A. K. D. S., Lima, G. D. M., Farias, L. M. D., Rodrigues, L. A. R. L., Carvalho, V. B. L. D., Pereira, C. F. D. C., … Martins, M. D. C. D. C. E. (2019). Lycopene-rich extract from red guava (*Psidium guajava* L.) decreases plasma triglycerides and improves oxidative stress biomarkers on experimentally-induced dyslipidemia in hamsters. *Nutrients, 11*(2), 393. [Crossref]

Buah, J. D., Musa, D. D., & Eberemu, N. C. (2023). Antibacterial activities of guava (*Psidium guajava*) and orange (*Citrus sinensis*) leaves extracts on *Staphylococcus aureus* and *Escherichia coli*. *Sahel Journal of Life Sciences FUDMA, 1*(1), 130–136. [Crossref]

Bylappa, Y., Balasubramanian, B., Park, S., Joseph, K. S., Chacko, A. M., Sudheer, W. N., … Khaneghah, A. M. (2024). Three decades of advances in extraction and analytical techniques for guava (*Psidium guajava* L.): A review. *Results in Chemistry*, 101708. [Crossref]

Chaachouay, N., & Zidane, L. (2024). Plant-derived natural products: A source for drug discovery and development. *Drugs and Drug Candidates, 3*(1), 184–207. [Crossref]

Chassagne, F., Samarakoon, T., Porras, G., Lyles, J. T., Dettweiler, M., Marquez, L., ... & Quave, C. L. (2021). A systematic review of plants with antibacterial activities: A taxonomic and phylogenetic perspective. *Frontiers in Pharmacology, 11*, 586548. [Crossref]

Chidzwondo, F., & Mutapi, F. (2024). Challenge of diagnosing acute infections in poor resource settings in Africa. *AAS Open Research, 4*, 28. [Crossref]

Chintada, V., & Golla, N. (2025). Exploring the therapeutic potential of bioactive compounds from plant sources. In *Biotechnological Intervention in Production of Bioactive Compounds: Biosynthesis, Characterization and Applications* (pp. 229–247). Springer Nature Switzerland. [Crossref]

Chu, S., Zhang, F., Wang, H., Xie, L., Chen, Z., Zeng, W., & Hu, F. (2022). Aqueous extract of guava (*Psidium guajava* L.) leaf ameliorates hyperglycemia by promoting hepatic glycogen synthesis and modulating gut microbiota. *Frontiers in Pharmacology, 13*, 907702. [Crossref]

Dar, R. A., Shahnawaz, M., Ahanger, M. A., & Majid, I. U. (2023). Exploring the diverse bioactive compounds from medicinal plants: A review. *Journal of Phytopharmacology, 12*(3), 189–195. [Crossref]

Das, K. K. (2016). Hepatoprotective effect of *Nigella sativa* seed in streptozotocin-induced diabetic albino rats: Histological observations.

De Castro, R., De Souza, T., Bezerra, L., Ferreira, G., De Brito Costa, E., & Cavalcanti, A. (2015). Antifungal activity and mode of action of thymol and its synergism with nystatin against *Candida* species involved with infections in the oral cavity: An in vitro study. *BMC Complementary and Alternative Medicine, 15*. [Crossref]

De Souza, G. H. D. A., Dos Santos Radai, J. A., Mattos Vaz, M. S., Esther da Silva, K., Fraga, T. L., Barbosa, L. S., & Simionatto, S. (2021). In vitro and in vivo antibacterial activity assays of carvacrol: A candidate for development of innovative treatments against KPC-producing *Klebsiella pneumoniae*. *PLoS ONE, 16*(2), e0246003. [Crossref]

Dera, A. A., Ahmad, I., Rajagopalan, P., Al Shahrani, M., Saif, A., Alshahrani, M. Y., … Alfhili, M. A. (2021). Synergistic efficacies of thymoquinone and standard antibiotics against multi-drug resistant isolates. *Saudi Medical Journal, 42*(2), 196. [Crossref]

Dhanasekaran, S. (2019). Alteration of multi-drug resistance activities by ethanolic extracts of *Nigella sativa* against urinary pathogens. *International Journal of Pharmacology, 15*(8), 962–969. [Crossref]

Díaz-de-Cerio, E., Verardo, V., Gómez-Caravaca, A. M., Fernández-Gutiérrez, A., & Segura-Carretero, A. (2017). Health effects of *Psidium guajava* L. leaves: An overview of the last decade. *International Journal of Molecular Sciences, 18*(4), 897. [Crossref]

Efe, E. E., Agabi, K. J., & Ozock, D. (2024). Exploring the socio-economic impact of herbal medicine practices in Ondo State, Nigeria.

El Rabey, H. A., Al-Seeni, M. N., & Bakhashwain, A. S. (2017). The antidiabetic activity of *Nigella sativa* and propolis on streptozotocin-induced diabetes and diabetic nephropathy in male rats. *Evidence-Based Complementary and Alternative Medicine, 2017*(1), 5439645. [Crossref]

Elango, A., Rao, L. N., Sugumar, P., & Radhakrishnan, A. (2022). Evaluation of clinical efficacy and safety of *Nigella sativa* seed oil added to standard treatment in uncomplicated respiratory infection—A randomised, open labelled, and parallel arm study. *Journal of Communicable Diseases*, 91–97. [Crossref]

Emamat, H., Mousavi, S. H., Kargar Shouraki, J., Hazrati, E., Mirghazanfari, S. M., Samizadeh, E., & Hadi, S. (2022). The effect of *Nigella sativa* oil on vascular dysfunction assessed by flow-mediated dilation and vascular-related biomarkers in subjects with cardiovascular disease risk factors: A randomized controlled trial. *Phytotherapy Research, 36*(5), 2236–2245. [Crossref]

Emeka, L. B., Emeka, P. M., & Khan, T. M. (2015). Antimicrobial activity of *Nigella sativa* L. seed oil against multi-drug resistant *Staphylococcus aureus* isolated from diabetic wounds. *Pakistan Journal of Pharmaceutical Sciences, 28*(6).

Ezeh, C. K., Eze, C. N., Dibua, M. E. U., Emencheta, S. C., & Ezeh, C. C. (2022). Synthesis of silver nanoparticles using *Nigella sativa* seed extract and its efficacy against some multidrug-resistant uropathogens. *Biomedical and Biotechnology Research Journal (BBRJ), 6*(3), 400–409. [Crossref]

Ezeh, C. K., Eze, C. N., Dibua, M. E. U., Emencheta, S. C., & Ezeh, C. C. (2022). Synthesis of silver nanoparticles using *Nigella sativa* seed extract and its efficacy against some multidrug-resistant uropathogens. *Biomedical and Biotechnology Research Journal (BBRJ)*, *6*(3), 400–409. [Crossref]

Farhadi, K., Rajabi, E., Varpaei, H. A., Iranzadasl, M., Khodaparast, S., & Salehi, M. (2024). Thymol and carvacrol against *Klebsiella*: Antibacterial, anti-biofilm, and synergistic activities—a systematic review. *Frontiers in Pharmacology, 15*, 1487083. [Crossref]

Fayed, M. A. (2022). *Nigella sativa* L.: A golden remedy: Significance worldwide highlighting their possible use for COVID-19. *Universal Journal of Pharmaceutical Research, 7*(3). [Crossref]

Feridoniy, M., Alizadeh, F., Kokhdan, P., & Khodavandi, A. (2020). Study of the antifungal potential of carvacrol on growth inhibition of *Candida krusei* in a systemic candidiasis. *Advances in Traditional Medicine, 20*, 591–598. [Crossref]

Fermiano, T. H., Perez de Souza, J. V., Murase, L. S., Salvaterra Pasquini, J. P., de Lima Scodro, R. B., Zanetti Campanerut-Sá, P. A., … Cardoso, R. F. (2024). Antimicrobial activity of carvacrol and its derivatives on *Mycobacterium* spp.: Systematic review of preclinical studies. *Future Medicinal Chemistry, 16*(7), 679–688. [Crossref]

Gholamnezhad, Z., Havakhah, S., & Boskabady, M. H. (2016). Preclinical and clinical effects of *Nigella sativa* and its constituent, thymoquinone: A review. *Journal of Ethnopharmacology, 190*, 372–386. [Crossref]

Goel, S., & Mishra, P. (2018). Thymoquinone inhibits biofilm formation and has selective antibacterial activity due to ROS generation. *Applied Microbiology and Biotechnology, 102*(4), 1955–1967. [Crossref]

Govindaraghavan, S., & Sucher, N. J. (2015). Quality assessment of medicinal herbs and their extracts: Criteria and prerequisites for consistent safety and efficacy of herbal medicines. *Epilepsy & Behavior, 52*, 363–371. [Crossref]

Hackman, H. K., Annison, L., Arhin, R. E., Azumah, B. K., Boateng, D., Nwosu, B., & Appenteng, M. (2020). Antimicrobial activity of *Psidium guajava* (guava) leaves extract on extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* that cause multi-drug resistant urinary tract infections.

Hackman, H. K., Arhin, R. E., Azumah, B. K., Boateng, D., Nwosu, B., & Apenteng, M. (2020). *In vitro* antibacterial activity of *Psidium guajava* (guava) leaves extract on carbapenem-resistant *Klebsiella pneumoniae* causing multi-drug resistant systemic infections.

Haitamy, M. N., Kariosentono, H., Prayitno, A., Setiamika, M., Nurwati, I., Riswiyanto, R. C. A., & Brahmadi, A. (2024). Exploring the anti-inflammatory effects of *Nigella sativa* on cyclooxygenase-2 through the nuclear factor-kappa B pathway in an *Aspergillus niger*-induced otitis externa mouse model. *Journal of Advanced Pharmaceutical Technology & Research, 15*(4), 341–345. [Crossref]

Hashem, M. A., Mohamed, W. A., & Attia, E. S. (2018). Assessment of protective potential of *Nigella sativa* oil against carbendazim- and/or mancozeb-induced hematotoxicity, hepatotoxicity, and genotoxicity. *Environmental Science and Pollution Research, 25*, 1270–1282. [Crossref]

Hassan, E., Gendy, A., Abd-ElGawad, A., Elshamy, A., Farag, M., Alamery, S., & Omer, E. (2020). Comparative chemical profiles of the essential oils from different varieties of *Psidium guajava* L. *Molecules, 26*(1), 119. [Crossref]

Hassan, S. T., Šudomová, M., Mazurakova, A., & Kubatka, P. (2022). Insights into antiviral properties and molecular mechanisms of non-flavonoid polyphenols against human. *International Journal of Molecular Sciences, 23*(22), 13891. [Crossref]

Heinrich, M., Jalil, B., Abdel-Tawab, M., Echeverria, J., Kulić, Ž., McGaw, L. J., … Wang, J. B. (2022). Best practice in the chemical characterisation of extracts used in pharmacological and toxicological research—The ConPhyMP-guidelines. *Frontiers in Pharmacology, 13*, 953205. [Crossref]

Hemananthan, E. (2020). *In vitro* studies to analyze the stability and bioavailability of thymoquinone encapsulated in the developed nanocarrier. *Journal of Dispersion Science and Technology*.

Herman, A., & Herman, A. P. (2023). Herbal products and their active constituents used alone and in combination with antibiotics against multidrug-resistant bacteria. *Planta Medica, 89*(2), 168–182. [Crossref]

Hossain, C. M., Gera, M. E. E. T. A., & Ali, K. A. (2022). Current status and challenges of herbal drug development and regulatory aspect: A global perspective. *Asian Journal of Pharmaceutical and Clinical Research, 15*, 31–41. [Crossref]

Huynh, H. D., Nargotra, P., Wang, H. M. D., Shieh, C. J., Liu, Y. C., & Kuo, C. H. (2025). Bioactive compounds from guava leaves (*Psidium guajava* L.): Characterization, biological activity, synergistic effects, and technological applications. *Molecules, 30*(6), 1278. [Crossref]

Iduh, M. U., Imam, U. A., Muhammad, N. B., Enitan, S. S., & Hassan, Y. (2024).

Mechanism of antimicrobial activities of medicinal plants extracts, from traditional knowledge to scientific insights. *International Journal of Pathogen Research, 13*(4), 72–86. [Crossref]

Ilesanmi, F., Opeyemi, O., & Praise, O. (2020). Effect of different extraction solvents on the antimicrobial activity of *Psidium guajava* (guava) leaves against multi-drug resistant bacteria implicated in nosocomial infections. *International Journal of Biotechnology, 9*(1), 24–37. [Crossref]

Imaduddin, M., Saba, N., Eman, A., Saba, K., & Kashfiya, A. (2022). Phytochemical screening and *in vivo* antileukemic activity of methanolic extract of seeds of *Nigella sativa* L. on benzene-induced leukemia in Wistar rats. *Asian Pacific Journal of Health Sciences*. [Crossref]

Imam, A., Sulaimon, F. A., Sheu, M., Busari, M., Oyegbola, C., Okesina, A. A., … Ajao, M. S. (2022). *Nigella sativa* oil ingestion mitigates aluminum chloride induced cerebella oxidative, neurogenic damages and impaired motor functions in rats. *Anatomy Journal of Africa, 11*(1), 2109–2121. [Crossref]

Innih, S., Osirike, P., Ubhenin, A., Ehi-Omosun, M., & Imafidon, E. (2016). Hepatoprotective effect of aqueous leaf extract of *Psidium guajava* in ketoconazole-treated adult male Wistar rats. *Nigerian Journal of Life Sciences, 6*(1), 218–224. [Crossref]

Jankowski, G., Sawicki, R., Truszkiewicz, W., Wolan, N., Ziomek, M., Hryć, B., & Sieniawska, E. (2024). Molecular insight into thymoquinone mechanism of action against *Mycobacterium tuberculosis*. *Frontiers in Microbiology, 15*, 1353875. [Crossref]

Kariawasam, K. W. J. C., Pathirana, R. N., Ratnasooriya, W. D., Handunnetti, S., & Abeysekera, W. P. K. M. (2017). Phytochemical profile and in vitro anti-inflammatory activity of aqueous leaf extract of Sri Lankan variety of *Psidium guajava* L. *Journal of Pharmacognosy and Phytochemistry, 6*(4), 22–26.

Khalid, A., & Ahmad, S. S. (2024). Antibacterial activity of *Nigella sativa* against multi-drug resistant bacteria. *International Journal of Pathology, 22*(2), 45–95. [Crossref]

Khalil, H., Abd El Maksoud, A. I., Roshdey, T., & El-Masry, S. (2019). Guava flavonoid glycosides prevent influenza A virus infection via rescue of P53 activity. *Journal of Medical Virology, 91*(1), 45–55. [Crossref]

Khan, M. S. A., & Ahmad, I. (2019). Herbal medicine: Current trends and future prospects. In *New Look to Phytomedicine* (pp. 3–13). Academic Press. [Crossref]

Krishnaswamy, S. (2024). Phytopharmaceutical biotechnology: Integration of botany, pharmacology and plant biotechnology to deliver the best therapeutic potential of herbs. In *Concepts in pharmaceutical biotechnology and drug development* (pp. 437–464). *Springer Nature Singapore*. [Crossref]

Kumar, M., Tomar, M., Amarowicz, R., Saurabh, V., Nair, M. S., Maheshwari, C., ... & Satankar, V. (2021). Guava (*Psidium guajava* L.) leaves: Nutritional composition, phytochemical profile, and health-promoting bioactivities. *Foods, 10*(4), 752. [Crossref]

Kumari, R., Deepali, B., & Bhatnagar, S. (2021). Biodiversity loss: Threats and conservation strategies. *International Journal of Pharmaceutical Sciences Review and Research, 68*(1), 242–254. [Crossref]

Mahomoodally, M. F., Aumeeruddy, M. Z., Legoabe, L. J., Montesano, D., & Zengin, G. (2022). *Nigella sativa* L. and its active compound thymoquinone in the clinical management of diabetes: A systematic review. *International Journal of Molecular Sciences, 23*(20), 12111. [Crossref]

Majdalawieh, A. F., & Fayyad, M. W. (2016). Recent advances on the anti-cancer properties of *Nigella sativa*, a widely used food additive. *Journal of Ayurveda and Integrative Medicine, 7*(3), 173–180. [Crossref]

Maryam, A. J., Fatimah, A. A., Ebtesam, A. K., Abdulrahman, A. S., & Ineta, B. E. (2016). In-vitro studies on the effect of *Nigella sativa* Linn. seed oil extract on multidrug-resistant Gram-positive and Gram-negative bacteria. *Journal of Medicinal Plants, 4*(2), 195–199.

Masri, M., Muthiadin, C., Masita, M., Cahyanto, T., Lianah, L., Rusny, R., & Tridesianti, S. (2021). Black cumin (*Nigella sativa*) against *Mycobacterium tuberculosis* strain H37RV and MDR-TB. *Elkawnie: Journal of Islamic Science and Technology, 7*(1), 182–196. [Crossref]

Memar, M. Y., Raei, P., Alizadeh, N., Aghdam, M. A., & Kafil, H. S. (2017). Carvacrol and thymol: Strong antimicrobial agents against resistant isolates. *Reviews and Research in Medical Microbiology, 28*(2), 63–68. [Crossref]

Mir, T. A., Jan, M., Khare, R. K., & Bhat, M. H. (2021). Medicinal plant resources: Threat to its biodiversity and conservation strategies. In *Medicinal and aromatic plants: Healthcare and industrial applications* (pp. 717–739). *Springer*. [Crossref]

Moses, A. S., Singh, S. N., Pratap, D., & Salam, S. (2019). Determination and comparison of antimicrobial activity of *Psidium guajava* and *Emblica officinalis* against MDR bacteria. *Journal of Pharmacognosy and Phytochemistry, 8*(1), 2169–2172.

Mouwakeh, A., Kincses, A., Nové, M., Mosolygó, T., Mohácsi-Farkas, C., Kiskó, G., & Spengler, G. (2019). *Nigella sativa* essential oil and its bioactive compounds as resistance modifiers against *Staphylococcus aureus*. *Phytotherapy Research, 33*(4), 1010–1018. [Crossref]

Mouwakeh, A., Telbisz, A., Spengler, G., Mohacsi-Farkas, C., & Kiskó, G. (2018). Antibacterial and resistance modifying activities of *Nigella sativa* essential oil and its active compounds against *Listeria monocytogenes*. *In Vivo, 32*(4), 737–743. [Crossref]

Mushtaq, A., Aslam, B., Faisal, M. N., Hussain, A., Shamim, S., Kousar, S., ... & Umer, A. (2024). *Nigella sativa* L. attenuates oxidative stress, inflammation and apoptosis in Concanavalin A-induced acute immunological liver damage in mice. *Brazilian Archives of Biology and Technology, 67*, e24230554. [Crossref]

Mustafa, G., Arif, R., Atta, A., Sharif, S., & Jamil, A. (2017). Bioactive compounds from medicinal plants and their importance in drug discovery in Pakistan. *Matrix Science Pharma, 1*(1), 17–26. [Crossref]

Nagy, A. M., Abdelhameed, M. F., Elkarim, A. S. A., Sarker, T. C., Abd-ElGawad, A. M., Elshamy, A. I., & Hammam, A. M. (2024). Enhancement of female rat fertility via ethanolic extract from *Nigella sativa* L. (black cumin) seeds assessed via HPLC-ESI-MS/MS and molecular docking. *Molecules, 29*(3), 735. [Crossref]

Najmi, A., Javed, S. A., Al Bratty, M., & Alhazmi, H. A. (2022). Modern approaches in the discovery and development of plant-based natural products and their analogues as potential therapeutic agents. *Molecules, 27*(2), 349. [Crossref]

Naseer, S., Hussain, S., Naeem, N., Pervaiz, M., & Rahman, M. (2018). The phytochemistry and medicinal value of *Psidium guajava* (guava). *Clinical Phytoscience, 4*(1), 1–8. [Crossref]

Nasim, N., Sandeep, I. S., & Mohanty, S. (2022). Plant-derived natural products for drug discovery: Current approaches and prospects. *The Nucleus, 65*(3), 399–411. [Crossref]

Neumann, N., Honke, M., Povydysh, M., Günther, S., & Schulze, C. (2022). Evaluating tannins and flavonoids from traditionally used medicinal plants with biofilm inhibitory effects against MRGN E. coli. *Molecules, 27*(7), 2284. [Crossref]

Nguyen, T. L. A., & Bhattacharya, D. (2022). Antimicrobial activity of quercetin: An approach to its mechanistic principle. *Molecules, 27*(8), 2494. [Crossref]

Odieka, A. E., Obuzor, G. U., Oyedeji, O. O., Gondwe, M., Hosu, Y. S., & Oyedeji, A. O. (2022). The medicinal natural products of *Cannabis sativa* Linn.: A review. *Molecules, 27*(5), 1689. [Crossref]

Ojueromi, O. O., Oboh, G., & Ademosun, A. O. (2022). Effect of black seeds (*Nigella sativa*) on inflammatory and immunomodulatory markers in *Plasmodium berghei*-infected mice. *Journal of Food Biochemistry, 46*(11), e14300. [Crossref]

Ojueromi, O. O., Oboh, G., & Ademosun, A. O. (2024). *Nigella sativa*-fortified cookies ameliorate oxidative stress, inflammatory and immune dysfunction in *Plasmodium berghei*-infected murine model. *Journal of Medicinal Food, 27*(6), 552–562. [Crossref]

Patyra, A., Kołtun-Jasion, M., Jakubiak, O., & Kiss, A. K. (2022). Extraction techniques and analytical methods for isolation and characterization of lignans. *Plants, 11*(17), 2323. [Crossref]

Pelegrin, S., Galtier, F., Chalançon, A., Gagnol, J. P., Barbanel, A. M., Pélissier, Y., … Chevassus, H. (2019). Effects of *Nigella sativa* seeds (black cumin) on insulin secretion and lipid profile: A pilot study in healthy volunteers. *British Journal of Clinical Pharmacology, 85*(7), 1607–1611. [Crossref]

Pereira, G. A., Chaves, D. S. D. A., Silva, T. M. E., Motta, R. E. D. A., Silva, A. B. R. D., Patricio, T. C. D. C., … Karpiński, T. M. (2023). Antimicrobial activity of *Psidium guajava* aqueous extract against sensitive and resistant bacterial strains. *Microorganisms, 11*(7), 1784. [Crossref]

Pognan, F., Beilmann, M., Boonen, H. C., Czich, A., Dear, G., Hewitt, P., … Newham, P. (2023). The evolving role of investigative toxicology in the pharmaceutical industry. *Nature Reviews Drug Discovery, 22*(4), 317–335. [Crossref]

Polinati, R. M., Teodoro, A. J., Correa, M. G., Casanova, F. A., Passos, C. L. A., Silva, J. L., & Fialho, E. (2022). Effects of lycopene from guava (*Psidium guajava* L.) derived products on breast cancer cells. *Natural Product Research, 36*(5), 1405–1408. [Crossref]

Proença, C. E. B., Tuler, A. C., Lucas, E. J., Vasconcelos, T. N. D. C., de Faria, J. E. Q., Staggemeier, V. G., … da Costa, I. R. (2022). Diversity, phylogeny and evolution of the rapidly evolving genus *Psidium* L. (Myrtaceae, Myrteae). *Annals of Botany, 129*(4), 367–388. [Crossref]

Qin, X. J., Yu, Q., Yan, H., Khan, A., Feng, M. Y., Li, P. P., … Liu, H. Y. (2017). Meroterpenoids with antitumor activities from guava (*Psidium guajava*). *Journal of Agricultural and Food Chemistry, 65*(24), 4993–4999. [Crossref]

Qu, S., Dai, C., Shen, Z., Tang, Q., Wang, H., Zhai, B., … Hao, Z. (2019). Mechanism of synergy between tetracycline and quercetin against antibiotic resistant *Escherichia coli*. *Frontiers in Microbiology, 10*, 2536. [Crossref]

Rafati, M., Ghasemi, A., Saeedi, M., Habibi, E., Salehifar, E., Mosazadeh, M., & Maham, M. (2019). *Nigella sativa* L. for prevention of acute radiation dermatitis in breast cancer: A randomized, double-blind, placebo-controlled, clinical trial. *Complementary Therapies in Medicine, 47*, 102205. [Crossref]

Razmpoosh, E., Safi, S., Nadjarzadeh, A., Fallahzadeh, H., Abdollahi, N., Mazaheri, M., … Salehi-Abargouei, A. (2021). The effect of *Nigella sativa* supplementation on cardiovascular risk factors in obese and overweight women: A crossover, double-blind, placebo-controlled randomized clinical trial. *European Journal of Nutrition, 60*, 1863–1874. [Crossref]

Reyes-Jurado, F., Franco-Vega, A., Ramírez-Corona, N., Palou, E., & López-Malo, A. (2015). Essential oils: Antimicrobial activities, extraction methods, and their modeling. *Food Engineering Reviews, 7*, 275–297. [Crossref]

Said, S. A., Abdulbaset, A., El-Kholy, A. A., Besckales, O., & Sabri, N. A. (2022). The effect of *Nigella sativa* and vitamin D3 supplementation on the clinical outcome in COVID-19 patients: A randomized controlled clinical trial. *Frontiers in Pharmacology, 13*, 1011522. [Crossref]

Seghatoleslam, M., Alipour, F., Shafieian, R., Hassanzadeh, Z., Edalatmanesh, M. A., Sadeghnia, H. R., & Hosseini, M. (2016). The effects of *Nigella sativa* on neural damage after pentylenetetrazole induced seizures in rats. *Journal of Traditional and Complementary Medicine, 6*(3), 262–268. [Crossref]

Selvakumar, P., Seenivasan, S., Deshmukh, S. M., Ponnapalli, H., & Das, A. (2025). Environmental protection and policies. In *Renewable Energy and the Economic Welfare of Society* (pp. 71–102). IGI Global. [Crossref]

Shabbir, A., Butt, H. I., Shahzad, M., Arshad, H. M., & Waheed, I. (2016). Immunostimulatory effect of methanolic leaves extract of *Psidium guajava* (guava) on humoral and cell-mediated immunity in mice. *JAPS: Journal of Animal & Plant Sciences, 26*(5). *(No DOI provided)*

Shafodino, F. S., Lusilao, J. M., & Mwapagha, L. M. (2022). Phytochemical characterization and antimicrobial activity of *Nigella sativa* seeds. *PLoS ONE, 17*(8), e0272457. [Crossref]

Shetty, Y. S., Shankarapillai, R., Vivekanandan, G., Shetty, R. M., Reddy, C. S., Reddy, H., & Mangalekar, S. B. (2018). Evaluation of the efficacy of guava extract as an antimicrobial agent on periodontal pathogens. *Journal of Contemporary Dental Practice, 19*(6), 690–697. [Crossref]

Sousa Silveira, Z. D., Macêdo, N. S., Sampaio dos Santos, J. F., Sampaio de Freitas, T., Rodrigues dos Santos Barbosa, C., Júnior, D. L. D. S., … Martins, N. (2020). Evaluation of the antibacterial activity and efflux pump reversal of thymol and carvacrol against *Staphylococcus aureus* and their toxicity in *Drosophila*

melanogaster. *Molecules, 25*(9), 2103. [Crossref]

Srivastava, R., Dubey, N. K., Sharma, M., Kharkwal, H., Bajpai, R., & Srivastava, R. (2025). Boosting the human antiviral response in conjunction with natural plant products. *Frontiers in Natural Products, 3*, 1470639. [Crossref]

Stielow, M., Witczyńska, A., Kubryń, N., Fijałkowski, Ł., Nowaczyk, J., & Nowaczyk, A. (2023). The bioavailability of drugs—The current state of knowledge. *Molecules, 28*(24), 8038. [Crossref]

Streicher, L. M. (2021). Exploring the future of infectious disease treatment in a post-antibiotic era: A comparative review of alternative therapeutics. *Journal of Global Antimicrobial Resistance, 24*, 285–295. [Crossref]

Tan, Y., Lin, Q., Yao, J., Zhang, G., Peng, X., & Tian, J. (2023). *In vitro* outcomes of quercetin on *Candida albicans* planktonic and biofilm cells and *in vivo* effects on vulvovaginal candidiasis: Evidences of its mechanisms of action. *Phytomedicine, 114*, 154800. [Crossref]

Tella, T., Masola, B., & Mukaratirwa, S. (2019). The effect of *Psidium guajava* aqueous leaf extract on liver glycogen enzymes, hormone sensitive lipase and serum lipid profile in diabetic rats. *Biomedicine & Pharmacotherapy, 109*, 2441–2446. [Crossref]

Thomford, N. E., Dzobo, K., Chopera, D., Wonkam, A., Skelton, M., Blackhurst, D., ... & Dandara, C. (2015). Pharmacogenomics implications of using herbal medicinal plants on African populations in health transition. *Pharmaceuticals, 8*(3), 637–663. [Crossref]

Tian, L., Wang, X., Liu, R., Zhang, D., Wang, X., Sun, R., … Gong, G. (2021). Antibacterial mechanism of thymol against *Enterobacter sakazakii*. *Food Control, 123*, 107716. [Crossref]

Tiotsop, R. S., Mbaveng, A. T., Seukep, A. J., Matieta, V. Y., Nayim, P., Wamba, B. E., … Kuete, V. (2023). *Psidium guajava* (Myrtaceae) re-sensitizes multidrug-resistant *Pseudomonas aeruginosa* over-expressing MexAB-OprM efflux pumps to commonly prescribed antibiotics. *Investigational Medicinal Chemistry and Pharmacology, 6*(2), 80. [Crossref]

Ugbogu, E. A., Emmanuel, O., Uche, M. E., Dike, E. D., Okoro, B. C., Ibe, C., … Ugbogu, O. C. (2022). The ethnobotanical, phytochemistry and pharmacological activities of *Psidium guajava* L. *Arabian Journal of Chemistry, 15*(5), 103759. [Crossref]

Ullah, F., Ayaz, M., Sadiq, A., Ullah, F., Hussain, I., Shahid, M., … Devkota, H. P. (2020). Potential role of plant extracts and phytochemicals against foodborne pathogens. *Applied Sciences, 10*(13), 4597. [Crossref]

Upadhyay, S. K., & Singh, S. P. (Eds.). (2023). *Plants as bioreactors for industrial molecules*. John Wiley & Sons. [Crossref]

Uzzan, S., Rostevanov, I. S., Rubin, E., Benguigui, O., Marazka, S., Kaplanski, J., … Azab, A. N. (2024). Chronic treatment with *Nigella sativa* oil exerts antimanic properties and reduces brain inflammation in rats. *International Journal of Molecular Sciences, 25*(3), 1823. [Crossref]

Vaou, N., Stavropoulou, E., Voidarou, C., Tsakris, Z., Rozos, G., Tsigalou, C., & Bezirtzoglou, E. (2022). Interactions between medical plant-derived bioactive compounds: Focus on antimicrobial combination effects. *Antibiotics, 11*(8), 1014. [Crossref]

Vasconcelos, A. G., das G. N. Amorim, A., Dos Santos, R. C., Souza, J. M. T., de Souza, L. K. M., de S. L. Araújo, T., … de S. A. Leite, J. R. (2017). Lycopene rich extract from red guava (*Psidium guajava* L.) displays anti-inflammatory and antioxidant profile by reducing suggestive hallmarks of acute inflammatory response in mice. *Food Research International, 99*, 959–968. [Crossref]

Vermaak, C. (2020). *The effect of Psidium guajava L. (herbal extract, mother tincture and 3cH) on multi-drug resistant Pseudomonas aeruginosa, in vitro* [Doctoral dissertation, University of Johannesburg].

Wang, L., Wang, D., Wu, X., Xu, R., & Li, Y. (2020). Antiviral mechanism of carvacrol on HSV-2 infectivity through inhibition of RIP3-mediated programmed cell necrosis pathway and ubiquitin-proteasome system in BSC-1 cells. *BMC Infectious Diseases, 20*, Article 327. [Crossref]

Wang, M., Zhan, X., Ma, X., Wang, R., Guo, D., Zhang, Y., ... & Shi, C. (2022).

Antibacterial activity of thymoquinone against *Shigella flexneri* and its effect on biofilm formation. *Foodborne Pathogens and Disease, 19*(11), 767–778. [Crossref]

Wang, M., Zhang, S., Li, R., & Zhao, Q. (2024). Unraveling the specialized metabolic pathways in medicinal plant genomes: A review. *Frontiers in Plant Science, 15*, 1459533. [Crossref]

Wei, J., Wang, B., Chen, Y., Wang, Q., Ahmed, A. F., Zhang, Y., & Kang, W. (2022). The immunomodulatory effects of active ingredients from *Nigella sativa* in RAW264.7 cells through NF-κB/MAPK signaling pathways. *Frontiers in Nutrition, 9*, 899797. [Crossref]

Wei, Y., Ji, X. J., & Cao, M. (Eds.). (2024). *Engineering biology for microbial biosynthesis of plant-derived bioactive compounds*. Elsevier.

Wijesundara, N. M., Lee, S. F., Cheng, Z., Davidson, R., & Rupasinghe, H. V. (2021). Carvacrol exhibits rapid bactericidal activity against *Streptococcus pyogenes* through cell membrane damage. *Scientific Reports, 11*(1), 1487. [Crossref]

Wijesundara, N. M., Lee, S. F., Cheng, Z., Davidson, R., Langelaan, D. N., & Rupasinghe, H. V. (2022). Bactericidal activity of carvacrol against *Streptococcus pyogenes* involves alteration of membrane fluidity and integrity through interaction with membrane phospholipids. *Pharmaceutics, 14*(10), 1992. [Crossref]

Wu, Y., Bai, J., Zhong, K., Huang, Y., Qi, H., Jiang, Y., & Gao, H. (2016). Antibacterial activity and membrane-disruptive mechanism of 3-p-trans-coumaroyl-2-hydroxyquinic acid, a novel phenolic compound from pine needles of *Cedrus deodara*, against *Staphylococcus aureus*. *Molecules, 21*(8), 1084. [Crossref]

Yin, L., Liang, C., Wei, W., Huang, S., Ren, Y., Geng, Y., ... & Ouyang, P. (2022). The antibacterial activity of thymol against drug-resistant *Streptococcus iniae* and its protective effect on channel catfish (*Ictalurus punctatus*). *Frontiers in Microbiology, 13*, 914868. [Crossref]

Yu, Q., Wang, C., Zhang, X., Chen, H., Wu, M. X., & Lu, M. (2024). Photochemical strategies toward precision targeting against multidrug-resistant bacterial infections. *ACS Nano*. [Crossref]

Zhang, H., Zhang, J., Lang, Z., Botella, J. R., & Zhu, J. K. (2017). Genome editing—principles and applications for functional genomics research and crop improvement. *Critical Reviews in Plant Sciences, 36*(4), 291–309. [Crossref]

Zhang, W., Wang, J., Chen, Y., Zheng, H., Xie, B., & Sun, Z. (2018). Flavonoid compounds and antibacterial mechanisms of different parts of white guava (*Psidium guajava* L. cv. Pearl). *Natural Product Research, 34*, 1621–1625. [Crossref]

Zhu, C., Lei, M., Andargie, M., Zeng, J., & Li, J. (2019). Antifungal activity and mechanism of action of tannic acid against *Penicillium digitatum*. *Physiological and Molecular Plant Pathology, 107*, 46–50. [Crossref]

Zhu, X., Ouyang, W., Pan, C., Gao, Z., Han, Y., Song, M., ... & Cao, Y. (2019). Identification of a new benzophenone from *Psidium guajava* L. leaves and its antineoplastic effects on human colon cancer cells. *Food & Function, 10*(7), 4189–4198. [Crossref]