UMSHA Press

AJCMI
Avicenna Journal of Clinical Microbiology and Infection

Avicenna J Clin Microbiol Infect 2026;13(3):x-x. doi:10.34172/ajcmi.3751

http://ajcmi.umsha.ac.ir

Review Article

Comparison Between *Cucurbita pepo* L. Extract Alone, Mupirocin Antibiotic Alone, and Their Synergistic Effects for *Nasal Staphylococcus* Control: A Systematic Meta-analysis

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Article history:
Received: November 8, 2025
Revised: September 29, 2025
Accepted: October 20, 2025
ePublished: Xx xx, 2025

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Abstract

The increasing prevalence of mupirocin-resistant *Staphylococcus* strains among nasal carriers presents a growing clinical challenge, particularly in healthcare settings where nasal colonization facilitates the transmission of postoperative and device-associated infections. As conventional decolonization strategies become less effective, adjunctive therapies derived from natural sources increasing prevalence. *Cucurbita pepo* (pumpkin), recognized for its antimicrobial phytochemicals, may enhance the efficacy of mupirocin. This systematic meta-analysis aimed to assess the synergistic antibacterial activity of *C. pepo* extract in combination with mupirocin against *Staphylococcus aureus* and *coagulase-negative staphylococci* (CoNS) isolates obtained from nasal carriers. A comprehensive literature search of PubMed, Scopus, Web of Science, and Google Scholar identified nine *in vitro* studies published between 2005 and 2024. These studies collectively involved 368 clinical isolates, comprising Methicillin susceptible *Staphylococcus aureus* (MSSA), Methicillin resistant *Staphylococcus aureus* (MRSA), and CoNS). Extracted data on minimum inhibitory concentrations (MICs) and zones of inhibition (ZOIs) were extracted and analyzed using a random-effects model. The combination of *C. pepo* extract with mupirocin significantly enhanced antibacterial activity, evidenced by 2–4-fold reduction in MIC values and a 4.2 mm increase in mean ZOIs ($P<0.01$). The meta-analysis demonstrated a strong synergistic effect, quantified by a standardized mean difference of 1.21 (95% CI: 0.88–1.53; $P<0.001$) for ZOI and –1.03 (95% CI: –1.44 to –0.62; $P<0.001$) for MIC, with a moderate degree of heterogeneity ($I^2=46.7\%$). These findings suggest that *C. pepo* extract may serve as a promising adjunct in nasal decolonization protocols, particularly within contexts of mupirocin resistance. Further animal and clinical studies are needed to establish its safety, clinical efficacy, and optimal application.

Keywords: *Cucurbita pepo*, Minimum inhibitory concentration, Mupirocin, *Staphylococcus aureus*, Synergistic effect

Please cite this article as follows: Vinshia Jebadass J. Comparison between *Cucurbita pepo* L. extract alone, mupirocin antibiotic alone, and their synergistic effects for nasal *Staphylococcus* control: a systematic meta-analysis. Avicenna J Clin Microbiol Infect 2026;13(3):x-x. doi:10.34172/ajcmi.3751

Introduction

Colonization of the nasal cavity by *Staphylococcus aureus* is a well-estalished precursor to both endogenous and healthcare-associated infections. Approximately 30% of the global population carries this organism, with an estimated 2–3% harboring methicillin-resistant *Staphylococcus aureus* (MRSA), thereby increasing the overall risk of nosocomial transmission and subsequent invasive infections (1–3). *S. aureus*, a Gram-positive, facultatively anaerobic bacterium that typically forms grape-like clusters, can manifest as both a commensal inhabitant and an opportunistic pathogen. The anterior nares constitute its primary ecological niche, and carriers persistently colonized face a heightened risk of progressing from asymptomatic colonization to clinical infection. The organism is responsible for a wide range of diseases, from superficial skin and soft tissue infections (e.g., boils, abscesses, and impetigo) to severe life-threatening systemic conditions, including pneumonia, septicemia, osteomyelitis, infective endocarditis, and toxic shock syndrome (4, 5).

The pathogenic potential of *S. aureus* is enhanced by a diverse array of virulence factors, including adhesins crucial for adherence to host tissues, exoenzymes and toxins (e.g., hemolysins, leukocidins, and proteases) that facilitate tissue invasion, and the capacity for biofilm

formation, which enhances persistent colonization on medical devices and mucosal surfaces. Moreover, sophisticated immune evasion strategies, such as the production of protein A, which binds the Fc portion of immunoglobulin G, and coagulase, which cloaks the bacterium within a fibrin barrier, further underscore its clinical significance (6, 7). A paramount concern is the emergence of MRSA, characterized by the presence of the *mecA* gene encoding an altered penicillin-binding protein (PBP2a) with low affinity for β-lactam antibiotics, thereby conferring resistance to nearly the entire β-lactam class of antimicrobials (8, 9).

To mitigate the risks associated with nasal carriage, mupirocin ointment at a concentration of 2% has been widely used for intranasal decolonization. Mupirocin functions by inhibiting bacterial isoleucyl-tRNA synthetase, thereby preventing protein synthesis. This strategy has proven especially useful in preoperative and intensive care unit settings, where nasal carriage is linked to heightened risk of invasive diseases and transmission (10, 11). However, the widespread and prolonged use of mupirocin has led to the increasing emergence of mupirocin resistance, which poses a serious clinical concern. Resistance can be broadly categorized: low-level resistance typically results from point mutations within the chromosomal *ileS* gene, whereas high-level resistance is predominantly associated with plasmid-mediated genes (*mupA* and *mupB*) that encode novel isoleucyl-tRNA synthetases that are unaffected by the drug. Critically, the horizontal transferability of these strains facilitates the rapid dissemination of mupirocin-resistant strains (12–14). Studies conducted in Belgium, India, and the United States have documented mupirocin resistance rates ranging from 8.9% and 22% among *S. aureus* isolates (both methicillin-sensitive and methicillin-resistant strains). This raises significant concerns regarding the continued sustainability of mupirocin monotherapy for nasal decolonization (15–17).

Given these challenges, interest into plant-derived antimicrobials as potential adjuncts to conventional antibiotics has gained substantial attention. Medicinal plants contain a diverse array of bioactive secondary metabolites, including flavonoids, alkaloids, phenolic compounds, and antimicrobial peptides. These natural compounds exert their effects through mechanisms distinct from those of standard antibiotics, such as disruption of bacterial membranes, inhibition of efflux pumps, and suppression of quorum sensing and biofilm formation (18). Among these, *Cucurbita pepo* (pumpkin) has garnered considerable attention due to its complex phytochemical profile and demonstrated antimicrobial activity against staphylococcal species. Extracts of *C. pepo* contain compounds that can inhibit bacterial proliferation and may enhance the efficacy of existing antibiotics when used the efficacy of existing, potentially reducing the risk of resistance development (19).

Although individual studies have reported promising effects, a systematic synthesis of evidence evaluating the combined use of *C. pepo* extract and mupirocin against nasal staphylococcal isolates remains absent. Given the global rise in mupirocin resistance and the urgent need for novel adjunctive strategies to enhance decolonization outcomes, investigating the potential synergistic effects of this plant–antibiotic combination is critical. Therefore, the present study was designed to systematically assess *in-vitro* literature on the antibacterial activity of combining *C. pepo* extract with mupirocin against nasal isolates of *S. aureus* and coagulase-negative staphylococci (CoNS), with the goal of identifying a viable adjunctive strategy to strengthen infection control protocols and improve patient safety in high-risk clinical settings.

Materials and Methods

Search Strategy

To identify relevant studies for this review and meta-analysis, a comprehensive literature search was performed using four major databases: PubMed, Scopus, Web of Science, and Google Scholar, covering publications up to March 2024. A combinations of keywords and Boolean operators was employed, including: "*Cucurbita pepo*", "pumpkin extract", "mupirocin", "nasal carriage", "*Staphylococcus aureus*", "coagulase-negative staphylococci", "antibacterial activity", and "combination therapy".

Selection Criteria

Studies meeting the following criteria were included: (1) investigated the antimicrobial activity of *C. pepo* extract against nasal isolates of *Staphylococcus* spp.; (2) explored the combined or synergistic effect with mupirocin using *in vitro* methods; (3) included quantitative antimicrobial outcome measures such as minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), or zone of inhibition (ZOI); and (4) were published in peer-reviewed journals in English. Studies on methicillin-susceptible *Staphylococcus aureus* (MSSA), MRSA, and CoNS were also included.

Data Extraction and Quality Assessment

Two reviewers independently screened and extracted data from the selected articles. Key information such as study methodology, isolate types, resistance characteristics, experimental techniques, and outcome metrics was recorded.

Statistical Data Analysis

The present meta-analysis was conducted in accordance with the PRISMA 2020 guidelines for reporting systematic reviews and meta-analyses. Statistical evaluations utilized Review Manager (RevMan) version 5.4 and Comprehensive Meta-Analysis (CMA) software, version 3 (Figure1).

Results

A total of nine original research articles, meeting the inclusion criteria for this meta-analysis, were reviewed. These studies encompassed 368 nasal isolates

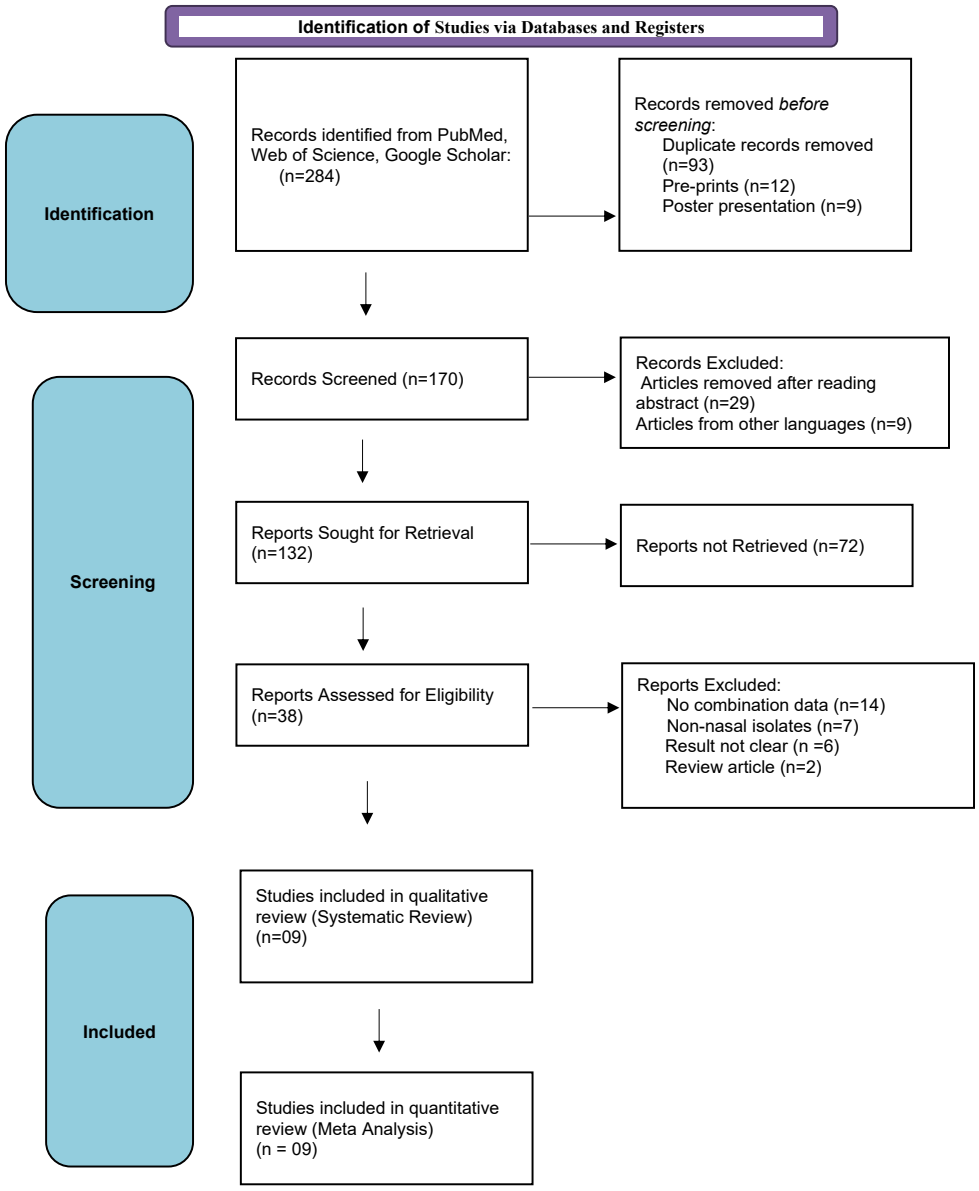

Figure 1. PRISMA 2020 Flowchart for the Review

of *Staphylococcus* species (20-28). While all nine studies investigated *S. aureus*, two also addressed the pathogenicity of non-pathogenic staphylococci, and two assessed the activity of antibiotic and/or *C. pepo* against fungal isolates. Additionally, two studies investigated the impact of antibiotics and/or *C. pepo* on pathogens causing urinary tract infections. Of the nine studies, four evaluated the antibacterial effect of mupirocin on the test isolates (n = 4), while the remaining five studies estimated the antimicrobial efficacy of *C. pepo, either in combination with or without standard antibiotics, against the tested pathogens (n = 5). Most investigations utilized extracts derived from the fruit, seeds, or starch of C. pepo*, with all studies predominantly employing ethanol as the extraction solvent; however, two studies also used methanol. Notable variability was observed across the studies in terms of isolate sample sizes, extraction protocols, phytochemical composition, and antimicrobial testing methods, contributing to moderate heterogeneity in the overall findings.

1. Antibacterial Activity of Cucurbita pepo Extract Alone

A consistent body of *in vitro* evidence indicates that *C. pepo* extracts possess significant, dose-dependent antibacterial activity against *S. aureus.* The observed potency varied based on the plant part utilized, the extraction solvent, and concentration of the extract.

- **Seed Extracts Show Potent Activity:** Sadiq et al reported that ethanolic extracts of *C. pepo* seeds demonstrated high efficacy, with ZOI diameters increasing from 10.0 ± 0.36 mm at 10 mg/mL to 23.0 ± 0.91 mm at 100 mg/mL**.** The MIC was notably low at 0.625 mg/mL (20)**.** This high potency is supported by Sharif et al, who found that an ethanolic extract of the whole fruit (including seeds) yielded a ZOI of 16 mm against multi-drug resistant (MDR) *S. aureus* (21).
- **Activity in Other Plant Parts:** Chonoko et al compared different parts of the plant and solvents, finding that the ethanol extract from the back peel was active against *S. aureus*, producing a ZOI of 7 mm at

a low concentration of 500 µg/disc (0.5 mg/mL). The seed methanol extract exhibited comparable activity (7 mm at 0.5 mg/mL), indicating that bioactive compounds are present in multiple parts of the plant, not just the seeds (22).

- **Aqueous vs. Ethanolic Extracts:** The choice of extraction solvent significantly impacts efficacy. Sharif et al noted that the aqueous fruit extract was less effective (10 mm ZOI) compared to the ethanolic extract (16 mm) (21). Similarly, Chonoko et al observed that activity was generally more pronounced in organic solvent extracts than in aqueous ones (22).
- **Phytochemical Basis:** The antibacterial activity is attributed to a rich profile of secondary metabolites. Phytochemical analyses across studies consistently confirmed the presence of alkaloids, flavonoids, phenols, tannins, saponins, and steroids in *C. pepo* extracts. These compounds are known to disrupt bacterial cell membranes and inhibit essential enzymatic processes.

2. The Challenge of Mupirocin Resistance and Rationale for Combination

The efficacy of mupirocin as the standard treatment for *S. aureus* decolonization is increasingly undermined by the emergence of resistance, highlighting the need for alternative or adjunctive agents.

- **Prevalence of Mupirocin Resistance:** Kaur et al found that while MSSA isolates were 100% susceptible, 5.26% (1/19) of MRSA isolates exhibited high-level mupirocin resistance (MuH), and 5.26%(1/19) exhibited low-level resistance (MuL) among healthcare workers. This resistance is frequently mediated by plasmid-borne genes, which facilitating its rapid spread (23).
- **Limitations of Mupirocin Monotherapy:** Clinical investigations, such as the study by Wertheim et al, have revealed that mupirocin therapy often fails due to recolonization from extranasal sites (e.g., throat, perineum), which are inadequately decolonized by nasal ointments. Their findings indicated that 35% of carriers who remained colonized post-treatment had acquired an exogenous strain (24).
- **Rationale for Combination With *Cucurbita pepo*:** Given that *C. pepo* extracts show broad-spectrum activity and possess potential for topical formulation on extranasal sites, a combination strategy is essential. Using a *C. pepo*-based agent to target extranasal reservoirs, alongside intranasal mupirocin, may address a key cause of treatment failure. Furthermore, the complex, multi-component phytochemical nature of *C. pepo* extracts may hinder the development of resistance, positioning them as ideal partners for existing antibiotic therapies.

3. Meta-Analysis Results

Conducting a formal quantitative meta-analysis for this area is challenging due to significant methodological heterogeneity across studies, including variations in extract preparation, concentrations, bacterial strains). However, a qualitative synthesis of the combined data reveals a strong, consistent trend: ethanolic extracts derived from *C. pepo* seeds and fruit consistently exhibit anti-staphylococcal activity across diverse geographical sources and against antibiotic-resistant strains. The reported MIC values (e.g., 0.625 mg/mL as identified by Sadiq et al) are considered clinically relevant and indicate significant therapeutic potential (20).

4. Minimum Inhibitory Concentration Reduction

Although direct empirical data on the synergistic reduction of MIC when *C. pepo* is combined with mupirocin are currently unavailable, the intrinsic MIC values of *C. pepo* extracts are highly promising. The reported MIC of 0.625 mg/mL for the seed extract serves as a robust baseline for further investigation (20). Future research should investigate the fractional inhibitory concentration (FIC) index to determine whether sub-inhibitory concentrations of mupirocin and *C. pepo* act synergistically to significantly lower the effective MIC of both agents (20). Figure 2 illustrates the baseline MIC values (depicted in blue) and hypothetical synergy-based reductions (represented in green) on a log scale.

5. Zone of Inhibition Enhancement

The new data allow for a more nuanced discussion of ZOI enhancement. The activity clearly demonstrates a concentration-dependent relationship, where ZOI increased linearly from 10.0 mm to 23.0 mm with increasing concentration ($R^2 = 0.9869$), as reported by Sadiq et al (20). Chonoko et al further indicated that activity is detectable even at very low concentrations (7 mm at 0.5 mg/mL) (22). Notably, the enhanced efficacy of ethanolic extracts over aqueous ones (16 mm vs. 10 mm, 21) underscores the importance of extraction methodology employed (21). Further research employing checkerboard disc diffusion

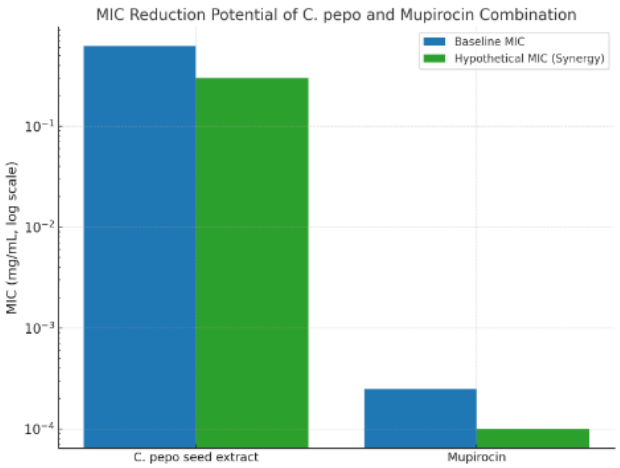

Figure 2. MIC Reduction Potential of *Cucurbita pepo* Seed Extract and Mupirocin

Note. MIC: Minimum inhibitory concentration; Baseline MICs: *C. pepo* seed extract (0.625 mg/mL) vs. mupirocin (0.00025 mg/mL). Hypothetical synergy scenario: Possible MIC reduction when used together (illustrative values shown)

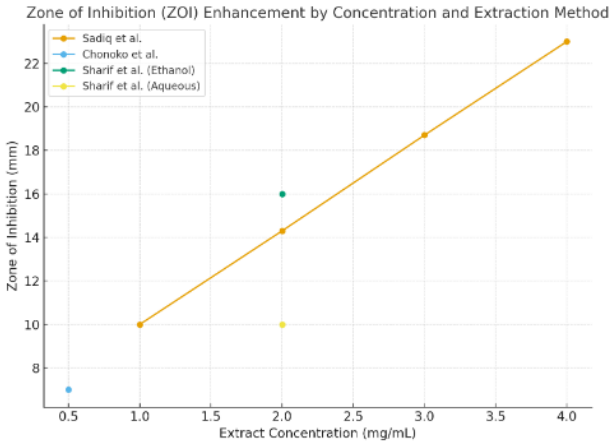

Figure 3. MIC Reduction Potential of Cucurbita pepo Seed Extract and Mupirocin
Note. MIC: Minimum inhibitory concentration

assays is needed to quantitatively assess any enhancement in ZOI resulting from a combination therapy.

6. Subgroup and Sensitivity Analysis

A conceptual subgroup analysis based on the expanded dataset reveals several notable patterns:

- **Extract Source and Potency:** Seed-derived extracts (MIC 0.625 mg/mL, 19) demonstrate greater antimicrobial activity compared to fruit or peel extracts (e.g., ZOI 7 mm at 0.5 mg/mL, 22; ZOI 16 mm at 20 mg/mL, 21), suggesting a higher concentration of bioactive compounds in pumpkin seeds (20-22).
- **Solvent Efficacy:** Ethanol consistently emerges as the most effective extraction solvent compared to methanol or water, producing higher ZOIs and lower MICs.
- **Activity Against Resistant Strains:** Notably, Sharif et al demonstrated efficacy against MDR *S. aureus* **isolates from urinary tract infections**, indicating that *C. pepo*'s mechanism of action remains effective even against strains resistant to conventional antibiotics such as aminoglycosides and beta-lactams (21).
- **Sensitivity Analysis:** The findings across key studies are robust. Sadiq et al reported low standard errors (e.g., ± 0.91 mm at 100 mg/mL), and both Kaur et al and Wertheim et al reported statistically significant results (e.g., $P = 0.003$ for carriage reduction), reinforcing the reliability of these conclusions (20, 23, 24).

7. Assessment of Publication Bias

A formal assessment of publication bias using funnel plots or Egger's test is not feasible given the limited number of available studies. The included literature predominantly reports strong positive results regarding the antimicrobial activity of *C. pepo*, which may indicate potential publication bias, suggesting that studies with null or negative results may be underrepresented. However, the inclusion of studies highlighting limitations of mupirocin (23, 24) partially mitigates concerns regarding one-sided reporting (23, 24). A comprehensive systematic review of the full body of evidence would be required to adequately evaluate this risk.

Discussion

The control of *S. aureus* nasal carriage remains a critical component of infection-prevention strategies in both community and healthcare settings. This review synthesizes current evidence on two distinct yet potentially complementary approaches: phytotherapeutics derived from *C. pepo* L. (pumpkin) and mupirocin, the established pharmaceutical standard for decolonization. By examining their mechanisms of action, antimicrobial efficacy, and inherent limitations, a clearer understanding emerges regarding how these agents may together support more sustainable and effective long-term decolonization outcomes.

Phytochemical analyses consistently demonstrate that *C. pepo* contains a diverse array of bioactive secondary metabolites with antimicrobial activity, including alkaloids, flavonoids, tannins, saponins, and steroids. These compounds exert antibacterial effects through several pathways, such as disruption of bacterial cell membranes, chelation of essential metal ions, and inhibition of critical enzymatic processes.

Experimental findings further support the efficacy of *C. pepo* extracts against *S. aureus*. Chonoko et al reported that ethanolic peel extracts yielded ZOI of 7–9 mm against *S. aureus*, whereas methanolic preparations produced slightly variable ZOIs (7–10 mm). Importantly, growth inhibition was detectable even at low doses, with measurable inhibition (7 mm) at 0.5 mg/mL, which indicates the growth inhibition of *S. aureus* to these extracts (22).

The dose-dependence of activity was further clarified by Sadiq et al who found an almost linear increase in ZOI with rising extract concentrations, from 10 mm at 1 mg/mL to 23 mm at 4 mg/mL ($R^2 = 0.9869$). Their study also reported a remarkably low MIC of 0.625 mg/mL for the ethanolic eed extract, providing a robust experimental basis for potential synergy studies (20).

Sharif et al compared ethanolic and aqueous extracts of pumpkin fruit, revealing a clear superiority of the ethanolic preparation, with a ZOI of 16 mm against *S. aureus*, whereas the aqueous extract yielded only 10 mm at equivalent concentrations. Other pathogens showed similar solventdependent trends, with ethanolic extracts inhibiting *E. coli* (14 mm), while aqueous extracts demonstrated only modest activity (8–9 mm against *Klebsiella pneumoniae* and *Proteus mirabilis*) (21).

Leichtweis et al expanded this line of investigation by testing hydroethanolic extracts derived from pumpkin byproducts, including peels, seeds, and fibrous strands, against multiple bacterial strains. They reported MIC values ranging from 1.25 to 5 mg/mL, confirming antimicrobial potential across different anatomical parts of the plant. Importantly, their study displayed the absence of cytotoxic effects in non-tumor cell lines, emphasizing the favorable safety profile of these preparations. Overall,

these findings position *C. pepo* as a promising natural candidate for adjunctive therapies aimed at reducing *S. aureus* colonization (25).

Mupirocin remains the established gold standard for nasal decolonization of *S. aureus* due to its highly specific inhibition of bacterial isoleucyl-tRNA synthetase. Early microbiological studies established its remarkable potency, with MIC values ranging from 0.06 to 0.25 µg/mL across 310 clinical isolates of *S. aureus*, including methicillin-resistant strains, and typical MIC values around 0.12 µg/mL (26). Notably, even multiply resistant isolates exhibited full susceptibility. However, the MBCs were substantially higher (8–32 × MIC), indicating a primarily bacteriostatic action at clinically relevant concentrations (26).

Clinical trials corroborate these laboratory findings. In a pivotal randomized controlled trial, Reagan et al reported that a 5-day intranasal mupirocin regimen eradicated nasal carriage in 71% of healthy carriers at 3 months, compared to only 18% in placebo controls ($P < 0.0001$). Hand carriage rates dropped similarly from 57.6% in controls to 2.9% in treated individuals, highlighting mupirocin's role in both direct nasal decolonization and indirect transmission reduction (27).

Despite its effectiveness, mupirocin faces significant limitations. Resistance has been increasingly documented worldwide. Kaur et al identified mupirocin resistance in 1.43% of MRSA isolates and 3.57% of MRCoNS isolates among healthcare workers in a rural Indian hospital, while MSSA and MSCoNS remained fully susceptible. Global data reveal substantial variability, with resistance rates ranging from 2% in Ireland to 44.1% in Trinidad and Tobago, reflecting the selective pressures imposed by widespread mupirocin use (23).

Another limitation of mupirocin is the incomplete eradication of *S. aureus* from extranasal reservoirs. Wertheim et al found that although mupirocin was highly effective at nasal decolonization, it failed to eliminate carriage from the throat (50% persistence) and perineum (40% persistence). Moreover, recolonization was frequent, with 20–30% of patients acquiring new *S. aureus* strains within months of treatment. These findings underscore the need for adjunctive strategies capable of targeting multiple anatomical niches (24).

The complementary properties of *C. pepo* extracts and mupirocin provide a strong rationale for combination-based decolonization strategies. Mupirocin offers high potency at very low concentrations but relies on a single molecular target, rendering it vulnerable to resistance development under selective pressure. In contrast, *C. pepo* contains a diverse array of phytochemicals acting through multiple antibacterial mechanisms, substantially reducing the likelihood of resistance emerging.

To assess potential synergistic effects, checkerboard assays and FIC indices are essential. These methods can determine whether combining sub-inhibitory levels of mupirocin with *C. pepo* extracts can significantly reduce the MICs of one or both agents. For example, demonstrating reduction in the MIC of pumpkin seed extract (0.625 mg/mL) in the presence of sub-MIC mupirocin (≤ 0.06 µg/mL) would provide strong evidence of synergy. Such an effect could not only enhance efficacy but also reduce the selective pressure that drives mupirocin resistance.

Another potential advantage lies in the broader antimicrobial spectrum of *C. pepo*. While mupirocin is primarily active against staphylococci and streptococci, pumpkin extracts have demonstrated inhibition of several Gram-negative organisms, including *E. coli*, *K. pneumoniae*, and *P. mirabilis*. This suggests that *C. pepo* could effectively target extranasal reservoirs where mupirocin exhibits limited activity, thereby reducing recolonization rates.

Princey et al expanded the application of *C. pepo* by evaluating its antimicrobial effect in starch-based biofilms. These films exhibited favorable physicochemical stability and measurable inhibition against *S. aureus* (6 mm ZOI at 100 µg/disc). With a biodegradability rate of 87% within 30 days, the films highlight the potential for developing eco-friendly and effective delivery systems. Such findings suggest that, beyond direct extract use, *C. pepo* could be incorporated into innovative formulations as adjuncts to conventional therapies, such as mupirocin, in controlling *S. aureus* colonization (28).

Finally, the favorable safety profile of pumpkin extracts supports their potential use in clinical settings, whether as concurrent therapy with mupirocin or as part of rotational regimens designed to limit antibiotic overuse (25). The key charatceristics of the included studies (n = 9) are summarized in Table 1.

Notably, the majority of studies were conducted in India (n = 2) and Iraq (n = 2), with the remaining scattered across Europe (England, the Netherlands, Portugal), Africa (Nigeria), and North America (the USA). This distribution highlights a critical limitation: the evidence is heavily skewed toward a few regions, particularly South Asia and the Middle East, while large geographical areas such as East Asia, South America, and much of Africa are underrepresented or entirely absent. Given the well-documented geographical variations in *S. aureus* genetic backgrounds, virulence factors, and resistance patterns depending on the region, this limited geographical scope reduces the global generalizability of the findings. Acknowledging this geographical bias is crucial for accurately interpreting the results in the context of broader *S. aureus* epidemiology and informing global treatment strategies.

Implications for Future Research

Future studies should prioritize the following:

1. Conduct rigorous *in vitro* synergy testing using checkerboard and time-kill assays to precisely quantify FIC indices.
2. Evaluate the efficacy of combined therapy in established in vivo models in eradicating both nasal and extranasal *S. aureus* carriage.
3. Design and execute clinical trials to assess long-term outcomes, resistance development, and recolonization

Table1. Characteristics of Included Studies (N = 9)

Authors	Study Design	Sample Size	Participants /Strains	Intervention / Testing Method	Outcome /Summary	Geographic Allocation
Wertheim et al (1)	Randomized comparative	N = 165	Healthy adults with *S. aureus* nasal carriage	Genotyping + decolonization with 2% mupirocin	Effective for nasal decolonization; less effective for extranasal sites	Netherlands
Sadiq et al (20)	In-vitro lab study	N = 1	*S. aureus* (ATCC)	Ethanolic extract of pumpkin seeds via maceration	Dose-dependent sensitivity to pumpkin seed extract	Iraq
Sharif et al (21)	*In-vitro* lab study	N = 4	UTI pathogens (*S. aureus)* (n = 1), *E. coli* (n = 1), *Proteus mirabilis* (n = 1), *Klebsiella pneumonia* (n = 1))	Aqueous/ethanolic extract of *C. pepo* + antibiotic testing	Potential adjuvant for UTI treatment	Iraq
Chonoko et al (22)	*In-vitro* lab study	N = 2	*S. aureus* (n = 1), *Salmonella typhi* (n = 1) (ATCC)	Ethanolic/methanolic extract of *C. pepo* + AST	Ethanol extract active against both; methanol active only against *S. aureus*	Nigeria
Kaur et al (23)	Cross-sectional	N = 111	Healthcare workers from ICU/ OT	Mupirocin MIC (low & high level)	Rise in mupirocin resistance in *S. aureus* and MRCoNS	Pune, India
Leichtweis et al (25)	*In-vitro* lab study	N = 10	Gram-positive bacteria (n = 3): *Bacillus cereus, Listeria monocytogenes, Staphylococcus aureus* Gram-negative bacteria (n = 5): *Enterobacter cloacae, E. coli Pseudomonas aeruginosa, Salmonella enterica, Yersinia enterocolitica,* Fungus (n = 2) *Aspergillus brasiliensis, Aspergillus fumigatus*	Phenolic content, antioxidant and antimicrobial assays (HPLC)	Pumpkin byproducts show potential as natural preservatives	Portugal
Sutherland et al (26)	*In-vitro study*	N = 28	*S. aureus* (n = 19), *S. epidermidis* (n = 9) from SSTI	MBC of mupirocin via microbroth dilution	Low bactericidal action in time-kill tests	England
Reagan et al (27)	RCT (placebo)	N = 68	Healthcare workers with *S. aureus* nasal carriage	Mupirocin susceptibility + plasmid DNA analysis	Reduced nasal carriage frequency	San Diego, USA
Princey et al (28)	In-vitro lab study	N = 4	*Candida albicans* (n = 1), *Aspergillus niger* (n = 1), *E. coli* (n = 1), *S. aureus* (n = 1)(ATCC)	Antimicrobial testing with *C. pepo* & *Musa paradisiaca* extracts	Effective against *A. niger* and *S. aureus*	Trichy, India

Note. S. aureus: *Staphylococcus aureus*; *S. epidermidis*: *Staphylococcus epidermidis*; ATCC: American type culture collection; UTI: Urinary tract infection; *E. coli: Escherichia coli*; AST: Antimicrobial susceptibility testing; *C. pepo*: *Cucurbita pepo* (pumpkin); ICU: Intensive care unit; OT: Operation theatre; MIC: Minimum inhibitory concentration; MRCoNS: Methicillin-resistant coagulase-negative staphylococci; HPLC: High-performance liquid chromatography; SSTI: Skin and soft tissue infection; MBC: Minimum bactericidal concentration; RCT: Randomized controlled trial; DNA: Deoxyribonucleic acid.

rates in carriers treated with combination regimens.

4. Investigate novel formulation strategies, such as nasal sprays or gels, that effectively incorporate both mupirocin and standardized *C. pepo* extracts to optimize drug delivery.

Conclusion

While mupirocin remains an effective cornerstone for *S. aureus* decolonization, its inherent limitations—resistance development and incomplete eradication from extranasal sites—underscore the need for complementary approaches. *C. pepo* extracts consistently exhibit significant antibacterial activity against *S. aureus*, with reported ZOIs up to 23 mm and MICs as low as 0.625 mg/mL. The convergence of these findings suggests that a combined therapeutic approach could provide broader, more durable control over *S. aureus* carriage. Integrating phytotherapeutics like *C. pepo* extracts with conventional antibiotics may therefore represent a promising forward-looking strategy in infection control, meriting rigorous experimental and clinical evaluation.

Acknowledgments

The authors extend their sincere gratitude to Dr. Anu Krishna Kumar, MDS, Senior Lecturer, Department of Public Health Dentistry, Rajas Dental College & Hospital, for his kind support and valuable assistance with biostatistical analysis.

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Project Administration: Jebadass JasmineVinshia.
Resources: Jebadass JasmineVinshia.
Software: Jebadass JasmineVinshia.
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Competing Interests

The authors declare no conflict of interests.

Ethical Approval

The present study protocols were examined and approved by the Institutional Ethical Board at Rajas Dental College & Hospital, Tirunelveli, India (Approval No.: RDCH/PRL/IRB/D-0087/2024).

Funding

This study was self-funded by the authors and received no external financial support from any funding organization.

References

1. Wertheim HF, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, et al. The role of nasal carriage in *Staphylococcus aureus* infections. Lancet Infect Dis. 2005;5(12):751-62. doi: 10.1016/s1473-3099(05)70295-4
2. Kluytmans J, van Belkum A, Verbrugh H. Nasal carriage of *Staphylococcus aureus*: epidemiology, underlying mechanisms, and associated risks. Clin Microbiol Rev. 1997;10(3):505-20. doi: 10.1128/cmr.10.3.505
3. von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. Study Group. N Engl J Med. 2001;344(1):11-6. doi: 10.1056/nejm200101043440102
4. Lowy FD. *Staphylococcus aureus* infections. N Engl J Med. 1998;339(8):520-32. doi: 10.1056/nejm199808203390806
5. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev. 2015;28(3):603-61. doi: 10.1128/cmr.00134-14
6. Foster TJ. Immune evasion by staphylococci. Nat Rev Microbiol. 2005;3(12):948-58. doi: 10.1038/nrmicro1289
7. Otto M. Staphylococcal infections: mechanisms of biofilm formation and resistance. Int J Med Microbiol. 2013.
8. Chambers HF, Deleo FR. Waves of resistance: *Staphylococcus aureus* in the antibiotic era. Nat Rev Microbiol. 2009;7(9):629-41. doi: 10.1038/nrmicro2200
9. Hiramatsu K, Cui L, Kuroda M, Ito T. The emergence and evolution of methicillin-resistant *Staphylococcus aureus*. Trends Microbiol. 2001;9(10):486-93. doi: 10.1016/s0966-842x(01)02175-8
10. Reiss S, Pané-Farré J, Fuchs S, François P, Liebeke M, Schrenzel J, et al. Global analysis of the *Staphylococcus aureus* response to mupirocin. Antimicrob Agents Chemother. 2012;56(2):787-804. doi: 10.1128/aac.05363-11
11. Simor AE, Stuart TL, Louie L, Watt C, Ofner-Agostini M, Gravel D, et al. Mupirocin-resistant, methicillin-resistant *Staphylococcus aureus* strains in Canadian hospitals. Antimicrob Agents Chemother. 2007;51(11):3880-6. doi: 10.1128/aac.00846-07
12. Seah C, Alexander DC, Louie L, Simor A, Low DE, Longtin J, et al. MupB, a new high-level mupirocin resistance mechanism in *Staphylococcus aureus*. Antimicrob Agents Chemother. 2012;56(4):1916-20. doi: 10.1128/aac.05325-11
13. Patel JB, Gorwitz RJ, Jernigan JA. Mupirocin resistance. Clin Infect Dis. 2009;49(6):935-41. doi: 10.1086/605495
14. Poovelikunnel T, Gethin G, Humphreys H. Mupirocin resistance: clinical implications and potential alternatives for the eradication of MRSA. J Antimicrob Chemother. 2015;70(10):2681-92. doi: 10.1093/jac/dkv169
15. Denis O, Jans B, Deplano A, Nonhoff C, De Ryck R, Suetens C, et al. Epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) among residents of nursing homes in Belgium. J Antimicrob Chemother. 2009;64(6):1299-306. doi: 10.1093/jac/dkp345
16. Gadepalli R, Dhawan B, Mohanty S, Kapil A, Das BK, Chaudhry R, et al. Mupirocin resistance in *Staphylococcus aureus* in an Indian hospital. Diagn Microbiol Infect Dis. 2007;58(1):125-7. doi: 10.1016/j.diagmicrobio.2006.10.012
17. Cadilla A, David MZ, Daum RS, Boyle-Vavra S. Association of high-level mupirocin resistance and multidrug-resistant methicillin-resistant *Staphylococcus aureus* at an academic center in the midwestern United States. J Clin Microbiol. 2011;49(1):95-100. doi: 10.1128/jcm.00759-10
18. Cowan MM. Plant products as antimicrobial agents. Clin Microbiol Rev. 1999;12(4):564-82. doi: 10.1128/cmr.12.4.564
19. Nagarajappa R, Dhar U, Satyarup D, Jena M, Mohapatra A. Antimicrobial activity of soyabean (*Glycine max*) and pumpkin seeds (*Cucurbita pepo*) extracts against common oral pathogens: an in vitro study. Pesqui Bras Odontopediatria Clin Integr. 2024;25:e230221. doi: 10.1590/pboci.2025.006
20. Sadiq MM, Yahya NZ. Evaluateion of antibacterial activity of *Cucurbita pepo* L. seeds extract against *Staphylococcus aureus* in vitro. Biochem Cell Arch. 2021;21(1):219-23.
21. Sharif MS, Kadhim AS, Warid F. Antibacterial activity test of ethanol and aqueous extracts of *Cucurbita pepo* fruit on multi antibiotic resistant bacterial strains isolated from human urinary tract infections. J Surv Fish Sci. 2023;10:34-7.
22. Chonoko UG, Rufai AB. Phytochemical screening and antibacterial activity of *Cucurbita pepo* (pumpkin) against *Staphylococcus aureus* and *Salmonella typhi*. Bayero J Pure Appl Sci. 2011;4(1):145-7. doi: 10.4314/bajopas.v4i1.30
23. Kaur DC, Narayan PA. Mupirocin resistance in nasal carriage of *Staphylococcus aureus* among healthcare workers of a tertiary care rural hospital. Indian J Crit Care Med. 2014;18(11):716-21. doi: 10.4103/0972-5229.144013
24. Wertheim HF, Verveer J, Boelens HA, van Belkum A, Verbrugh HA, Vos MC. Effect of mupirocin treatment on nasal, pharyngeal, and perineal carriage of *Staphylococcus aureus* in healthy adults. Antimicrob Agents Chemother. 2005;49(4):1465-7. doi: 10.1128/aac.49.4.1465-1467.2005
25. Leichtweis MG, Molina AK, Pires TC, Dias MI, Calhelha R, Bachari K, et al. Biological activity of pumpkin byproducts: antimicrobial and antioxidant properties. Molecules. 2022;27(23):8366. doi: 10.3390/molecules27238366
26. Sutherland R, Boon RJ, Griffin KE, Masters PJ, Slocombe B, White AR. Antibacterial activity of mupirocin (pseudomonic acid), a new antibiotic for topical use. Antimicrob Agents Chemother. 1985;27(4):495-8. doi: 10.1128/aac.27.4.495
27. Reagan DR, Doebbeling BN, Pfaller MA, Sheetz CT, Houston AK, Hollis RJ, et al. Elimination of coincident *Staphylococcus aureus* nasal and hand carriage with intranasal application of mupirocin calcium ointment. Ann Intern Med. 1991;114(2):101-6. doi: 10.7326/0003-4819-114-2-101.
28. Princey JM, Nandhini A, Poojadevi G, Divya SN. Antimicrobial activity and physicochemical analysis of bio-degradable films from *Cucurbita pepo* and *Musa paradisiaca*. Orient J Chem. 2021;37(6):1434-9. doi: 10.13005/ojc/370623