INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Synergistic Multi-Herb Approaches for Reversing Microbial Biofilms in Chronic Infections

Shruti Bijwe*, Shreeya Hambarde, Mayuri Randive, Khushi Raikwad, Arpita Bhajipale, Nishant Awandekar, Millind Umekar

Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur, Maharashtra, India-441002

ARTICLE INFO

Published: 11 Jan 2026

Keywords:
Biofilms; Chronic infections; Phytochemicals; Herbal synergy; Quorum sensing inhibition; EPS disruption; Persister cells; Nanoparticle delivery; Polyherbal formulations; Antimicrobial resistance.

DOI:
10.5281/zenodo.18213434

ABSTRACT

Chronic infections are largely sustained by microbial biofilms, complex, multicellular matrices that confer antimicrobial tolerance and immune evasion. Conventional antibiotic regimens fail to eradicate these resilient structures due to limited penetration, metabolic dormancy, and efflux-mediated resistance. In recent years, phytochemicals have emerged as promising anti-biofilm agents through diverse mechanisms, including quorum-sensing inhibition, extracellular polymeric substance (EPS) disruption, and persister-cell eradication. Compounds such as curcumin, berberine, allicin, cinnamaldehyde, and catechins act at sub-inhibitory concentrations to suppress virulence and enhance antibiotic susceptibility. Multi-herb or polyherbal combinations further potentiate efficacy via synergistic interactions, simultaneously targeting quorum sensing, adhesion, and EPS synthesis while minimising resistance risks. Delivery innovations such as herbal nanoparticles, nanofibers, and mucoadhesive gels improve bioavailability, sustained release, and site-specific action against chronic wounds, oral, and urinary tract biofilms. This review synthesises current evidence on synergistic multi-herb strategies and highlights their mechanistic roles in disrupting biofilm integrity, downregulating virulence gene expression, and reactivating persister metabolism. Despite significant in vitro advances, translational challenges persist due to limited standardisation, dose optimisation, and clinical validation. Integrating polyherbal therapeutics with advanced delivery systems represents a novel, multi-targeted approach for combating chronic infections, reducing antibiotic reliance, and supporting host immune resilience. Future research should focus on systematic synergy modelling, pharmacokinetic profiling, and in vivo evaluation to establish safe, effective phytotherapeutic interventions for biofilm-associated diseases.

***Corresponding Author:** Shruti Bijwe
Address: *Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur, Maharashtra, India-441002*
Email : shrutibijwe29@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

INTRODUCTION

Chronic infections persist due to bacterial biofilms, structured communities embedded in an extracellular matrix that shield microbes from host defences and treatments (1). These biofilms affect 65-80% of human infections, like cystic fibrosis and implant-related issues (2). Biofilms cause prolonged inflammation and recurrence, complicating clinical management in wounds, catheters, and dental plaques (3). Antibiotics fail against biofilms due to poor matrix penetration and the slow growth of persister cells (4). Biofilms show up to 1000-fold increased tolerance compared to planktonic cells (5). Efflux pumps and altered metabolism further reduce the efficacy of antibiotics, leading to persistent infections despite high-dose regimens (6). Herbal phytochemicals like berberine, curcumin, quercetin, and baicalin inhibit quorum sensing, adhesion, and EPS production (7). They disrupt biofilms at sub-MIC levels without fostering resistance (8). Compounds such as cryptotanshinone and mangiferin target virulence genes in pathogens like *P. aeruginosa* and *S. aureus* (9). Multi-herb combinations enhance efficacy through synergistic mechanisms like QS inhibition plus anti-adhesion (10). They reduce biofilm biomass more than single agents and minimise resistance risks (11). Polyherbal formulations mimic traditional medicine, improving penetration and multitarget action (12). This review assesses the synergistic effects of phytochemicals on biofilm disruption in chronic infections (13). It synthesises mechanisms, efficacy data, and clinical translation potential to guide novel herbal therapies (14).

1.1 Mechanisms of Biofilm Formation

Biofilm formation follows a structured lifecycle (15). Initial attachment of planktonic bacteria to a surface occurs first (16). This progresses to irreversible adhesion and microcolony formation (17). Maturation involves proliferation and EPS production, creating a three-dimensional matrix (18). The cycle concludes with dispersal, where cells revert to planktonic form due to nutrient depletion or signalling (19). Quorum sensing (QS) enables bacterial communication via autoinducer molecules like N-acyl-homoserine lactones (20). QS regulates gene expression based on population density (21). QS triggers EPS production, virulence factors, and biofilm maturation through coordinated collective behaviour (22). It plays a vital role in biofilm architecture and antibiotic tolerance (23). EPS provides structural integrity, adhesion, and protection against antibiotics and host defences. During maturation, EPS production increases to create water channels for nutrient flow and waste removal. Persister cells are dormant, antibiotic-tolerant subpopulations within biofilms. They form in higher numbers during biofilm culture than during planktonic growth. Persister cells contribute to recurrence post-treatment. Biofilms cause 65-80% of chronic infections, including cystic fibrosis and implant-associated osteomyelitis (24).

2. ANTI-BIOFILM MECHANISMS OF HERBS

2.1 QS Inhibition

Herbal compounds like berberine, curcumin, and garlic-derived ajoene block quorum sensing by antagonising autoinducer receptors such as LasR in *P. aeruginosa* and Agr in *S. aureus* (25). This disrupts coordinated behaviours essential for biofilm initiation and maturation without killing planktonic cells (26). QS inhibitors from herbs like *Rosa rugosa* tea polyphenols reduce violacein production in *Chromobacterium violaceum* reporter strains by over 70% (27).

2.2 EPS Disruption

Phytochemicals such as tannins from *Punica granatum* and flavonoids from green tea destabilise the EPS matrix by binding polysaccharides and eDNA (28). They reduce biofilm biomass by 50-80% in *S. aureus* and *Candida* models(29).

Cranberry proanthocyanidins inhibit EPS synthesis enzymes, creating structural voids that enhance antibiotic penetration (30). Enzyme-mimicking polyphenols from *Herba patriniae* degrade mature EPS scaffolds (31).

2.3 Persister Cell Eradication

Carvacrol from oregano and thymol penetrate dormant persister cells, disrupting membrane potential and ATP synthesis (32). They achieve 4-5 log reductions in *E. coli* and *P. aeruginosa* persisters(33). Alkaloids like sanguinarine from *Sanguinaria canadensis* target toxin-antitoxin modules, reactivating metabolic pathways in persisters (34). Combined herbal extracts show synergy with antibiotics, eradicating 99% of persisters that survive ampicillin alone (35).

2.4 Gene Expression Modulation

Quercetin and resveratrol downregulate biofilm-associated genes (*pel*, *algD*, *ica*) by 60-90% through histone deacetylase inhibition and sRNA interference (36). *Polygonum chinense* extracts suppress the ica operon in *S. aureus*, reducing PIA production essential for adhesion (37). Epigallocatechin gallate modulates global regulators like RpoS, shifting bacteria toward planktonic growth (38).

2.5 Fermentation-Enhanced Bioactive Compounds

Fermented herbal products like kimchi-derived phenolics and *Ginkgo biloba* extracts increase anti-biofilm potency 2-5 fold via microbial biotransformation (39). Lactic acid fermentation of garlic enhances allicin derivatives that inhibit QS 3x more effectively than fresh extracts (40). Traditional fermented medicines like *Tripterygium wilfordii* show 80% biofilm reduction in *MRSA* due to novel isoflavone metabolites (41).

3. SYNERGISTIC MULTI-HERB APPROACHES

3.1 Definition and Concept of Herbal Synergy

Herbal synergy refers to the combined action of multiple plant extracts or phytochemicals that produce therapeutic effects greater than those of individual herbs alone. This synergism may occur through complementary mechanisms such as enhanced bioavailability, multi-target interactions, or improved antimicrobial potency (42). In the context of biofilms, synergy helps target the structurally and functionally diverse layers of microbial communities more effectively than single-herb formulations (43).

3.2 Examples of Herb Combinations Targeting Biofilms

Several multi-herb combinations have shown enhanced antibiofilm effects, such as curcumin + piperine, where piperine increases curcumin's penetration and activity against EPS-producing bacteria (43). Garlic (allicin) + gingerol-rich extracts demonstrate synergistic inhibition of quorum sensing and bacterial adhesion (44). Combinations like berberine + tea polyphenols also display enhanced biofilm disruption and suppression of virulence pathways (45). These synergistic pairs highlight the potential of multi-herb formulations in overcoming biofilm-related chronic infections.

3.3 Mechanistic Classification: Layer-Wise Biofilm Disruption

Multi-herb synergy can be classified based on the specific biofilm layer or component each herb targets:

- **EPS Matrix Disruption:** phytochemicals such as eugenol and cinnamaldehyde weaken the structural integrity of the EPS layer (48).
- **Quorum Sensing Inhibition:** compounds like curcumin and catechins block signalling pathways, reducing virulence and biofilm maturation (49).
- **Persister Cell Targeting:** alkaloids such as berberine and reserpine exhibit activity against dormant persister cells within biofilms (50).
- **Immune Modulation:** herbs like turmeric, neem, and ashwagandha enhance host immune responses, supporting clearance of chronic infections (51).

Together, these mechanisms demonstrate how multi-herb formulations can comprehensively weaken, disrupt, and eliminate biofilms.

3.4 Advantages Over Single-Herb Therapy

Multi-herb formulations provide several benefits over single-herb approaches, including broader antimicrobial activity, reduced resistance development, and enhanced effects at lower doses (52). Synergistic herb combinations allow simultaneous targeting of multiple biofilm pathways: EPS degradation, quorum-sensing suppression, cell membrane disruption, and immune enhancement, leading to more efficient biofilm eradication (53). Multi-herb strategies also lower toxicity and improve therapeutic safety compared to high-dose monotherapies (54).

4. DELIVERY SYSTEMS FOR ENHANCED EFFICACY

4.1 Nanofiber-Based Herbal Delivery

Nanofiber matrices provide a high surface area and controlled release environment for herbal bioactives, enabling sustained delivery at infection sites. Electrospun nanofibers loaded with phytochemicals such as curcumin, neem extract, or essential oils show improved penetration into biofilm layers and enhanced antimicrobial activity compared to free extracts (51,52). Their porous structure allows deeper diffusion into biofilms, making them highly effective for chronic wound infections.

4.2 Mucoadhesive Gels

Herbal mucoadhesive gels prolong the retention time of phytochemicals on mucosal surfaces such as the oral cavity, nasal mucosa, or vaginal membranes. This extended contact enhances the antibiofilm action of herbs like aloe vera, liquorice, curcumin, and neem, allowing continuous release at the infection site (53). Mucoadhesive polymers such as Carbopol, xanthan gum, and chitosan further enhance penetration through biofilm EPS while improving patient compliance (54).

4.3 Herbal Nanoparticles

Nanoparticle-based herbal formulations—such as curcumin nanoparticles, berberine-loaded chitosan nanoparticles, and silver–herbal hybrid nanoparticles—significantly increase bioavailability and cell uptake of phytochemicals (55). Due to their nanoscale size, these particles can penetrate dense biofilm matrices and disrupt microbial adhesion, quorum sensing, and metabolic pathways more efficiently than conventional extracts (56). Nanoencapsulation

also protects unstable herbal compounds from degradation.

4.4 Role in Targeted Biofilm Disruption

Advanced delivery systems enhance targeted action against specific biofilm components. Nanoparticles and nanofibers can be engineered to preferentially bind bacterial surfaces, degrade EPS, or release phytochemicals in response to infection-specific conditions such as pH or enzymes (56). These targeted systems provide multi-layer disruption, EPS breakdown, inhibition of quorum sensing, and eradication of persister cells, making them highly effective for chronic infections (57). Mucoadhesive platforms further localise these effects at mucosal biofilm sites.

5. KEY HERBS WITH MULTI-TARGET ANTI-BIOFILM ACTIVITY

1. **Curcumin**

Curcumin inhibits quorum sensing, suppresses EPS matrix synthesis, and increases membrane permeability in *Pseudomonas aeruginosa* and *Staphylococcus aureus* (58,59).

Demonstrates synergistic disruption when combined with antibiotics and other herbs. (60).

2. **Berberine**

Berberine interferes with microbial signalling pathways (LuxS, LasR), reducing biofilm thickness and metabolic activity(61).

Shows strong synergy with flavonoids, curcumin, and antibiotics, improving penetration into mature biofilms(62).

3. **Allicin (Garlic-derived)**

Allicin penetrates microbial cell walls, disrupts thiol-containing enzymes, and inhibits EPS formation(63).

Effective against multi-drug-resistant (MDR) staphylococcal and fungal biofilms(64).

4. **Cinnamaldehyde**

Damages biofilm architecture by breaking hydrogen-bond networks and downregulating adhesion genes (fimA, curli)(65).

Inhibits quorum–sensing–regulated virulence factors in gram-negative pathogens(70).

5. **Tea Polyphenols (EGCG & Catechins)**

EGCG reduces cell adhesion, inhibits amyloid-like fibrils in the biofilm matrix, and potentiates antibiotic uptake(71).

Prevents initial colonisation and reduces multidrug efflux pump activity in biofilm-forming bacteria(72).

6. **Liquorice Flavonoids (Glycyrrhizin, Licochalcone A)**

Licochalcone A targets metabolic pathways involved in EPS synthesis and biofilm maturation(73).

Glycyrrhizin destabilises membrane integrity and downregulates persister-cell formation. (74).

Other Emerging Phytochemicals

1. **Boswellic acids**

Reduce oxidative stress and inhibit EPS synthesis in chronic inflammatory biofilms(75).

2. **Thymol and Carvacrol (from thyme & oregano)**

Causes rapid membrane depolarisation and collapse of metabolic activity inside mature biofilms(76).

3. **Baicalin (Scutellaria baicalensis)**

Acts as a quorum-quenching agent and enhances antibiotic sensitivity(77).

6. RESEARCH GAPS AND FUTURE DIRECTIONS

Lack of Standardised Anti-Biofilm Assays

Current studies rely on variable in vitro methods (microtiter plates, crystal violet, CLSM), limiting comparability across laboratories(78).

No universal guidelines exist for evaluating herbal anti-biofilm activity, leading to inconsistent reporting of MIC, MBIC, and MBEC values(79).

Need for In Vivo and Clinical Studies

Most evidence for herbal anti-biofilm effects comes from in vitro models; animal models and human trials remain limited(80).

Complex host–immune interactions in chronic infections cannot be captured in laboratory biofilm models alone(81).

Optimisation of Synergistic Multi-Herb Combinations

Few studies systematically evaluate dose response, ratio optimisation, or pharmacokinetic compatibility of combined herbs.

Synergy is often reported without mechanistic integration (quorum sensing + EPS inhibition + membrane disruption)(82).

Integration with Conventional Therapy

Combining phytochemicals with antibiotics shows promise, but standardised combinational protocols and safety profiles are underdeveloped(84).

Herb drug interactions, especially CYP-mediated ones, require detailed investigation before clinical translation.

Potential Translational Applications

Advanced delivery systems (nanogels, mucoadhesive systems, nanoparticles) require regulatory evaluation for herbal formulations.

Multi-targeted herbal therapeutics could be integrated into personalised medicine approaches for chronic infections(83).

Table 1. Documented Multi-Herb Combinations Showing Synergistic Anti-Biofilm Effects

Herb Combination	Synergistic Mechanism	Biofilm Type Targeted	Study Outcome	Reference
Curcumin + Berberine	QS inhibition + membrane damage	*P. aeruginosa*	2–3× higher biofilm reduction vs. single herbs	(84)
Garlic + Ginger	EPS degradation + virulence inhibition	Mixed oral biofilms	Significant reduction in adhesion	(85)
Green tea polyphenols + Liquorice	Adhesion inhibition + anti-inflammatory	Dental plaque	Enhanced inhibition of biofilm biomass	(86)
Cinnamaldehyde + Eugenol	QS disruption + membrane permeability	*S. mutans*	Reduction in EPS and acidogenicity	(87)

Turmeric + Neem	Anti-inflammatory + antimicrobial synergy	Wound biofilms	Faster wound healing and biofilm control	(88)

Table 2. Herbal Delivery Systems and Their Effectiveness Against Biofilms

Delivery System	Herbal Extract/ Compound	Target Site	Improvement in Efficacy	Reference
Nanofiber patch	Curcumin	Chronic wound biofilms	Sustained release, deeper penetration	(89)
Mucoadhesive gel	Licorice extract	Oral biofilms	Improved retention, reduced inflammation	(90)
Herbal nanoparticles	Berberine NPs	Multi-species biofilms	Enhanced 2× penetration into EPS	(91)
Nanoemulsion	Cinnamaldehyde	Dental plaque	Increased stability & QS inhibition	(92)
Hydrogel	Green tea catechins	UTI biofilms	Controlled delivery, reduced recurrence	(93)

7. CONCLUSION

Multi-herb formulations offer a promising approach for overcoming biofilm-associated chronic infections by simultaneously targeting multiple microbial pathways.

Evidence indicates that combining herbs enhances antibiofilm efficacy through synergistic effects, enabling EPS degradation, quorum-sensing inhibition, reduced bacterial adhesion, and enhanced immune modulation.

Multi-herb synergy provides multi-layered biofilm disruption, including targeting persister cells, inhibiting virulence gene expression, and destabilising microbial membrane integrity.

Herbal combinations also promote host tissue repair, anti-inflammatory responses, and modulation of oxidative stress mechanisms not achieved by conventional antibiotics alone.

Integrating multi-herb strategies with advanced delivery systems (nanogels, nanoparticles, mucoadhesive gels) may significantly improve therapeutic outcomes in chronic wounds, oral infections, UTIs, and respiratory biofilm infections.

These approaches can reduce antibiotic dependence, lower antimicrobial resistance, and serve as safer, multi-target alternatives for long-term management of persistent infection.

REFERENCES

1. Miyaue, S., Suzuki, E., Komiyama, Y., Kondo, Y., Morikawa, M., & Maeda, S. (2018). Bacterial memory of persisters: Bacterial persister cells can retain their phenotype for days or weeks after withdrawal from colony-biofilm culture. Frontiers in Microbiology, 9(JUN), 379354. https://doi.org/10.3389/FMICB.2018.01396/BIBTEX
2. Rather, M. A., Gupta, K., & Mandal, M. (2021). Microbial biofilm: formation, architecture, antibiotic resistance, and control strategies. Brazilian Journal of Microbiology, 52(4), 1701. https://doi.org/10.1007/S42770-021-00624-X
3. Mishra, R., Panda, A. K., de Mandal, S., Shakeel, M., Bisht, S. S., & Khan, J. (2020). Natural Anti-biofilm Agents: Strategies to Control Biofilm-Forming Pathogens. Frontiers in Microbiology, 11, 566325.

https://doi.org/10.3389/FMICB.2020.566325/FULL

4. Samrot, A. v., Mohamed, A. A., Faradjeva, E., Jie, L. S., Sze, C. H., Arif, A., Sean, T. C., Michael, E. N., Mun, C. Y., Qi, N. X., Mok, P. L., & Kumar, S. S. (2021). Mechanisms and Impact of Biofilms and Targeting of Biofilms Using Bioactive Compounds—A Review. Medicina, 57(8), 839. https://doi.org/10.3390/MEDICINA57080839
5. Harriott, M. M. (2019). Biofilms and Antibiotics. Reference Module in Biomedical Sciences. https://doi.org/10.1016/B978-0-12-801238-3.62124-4
6. Almatroudi, A., & Almatroudi, A. (2024). Investigating Biofilms: Advanced Methods for Comprehending Microbial Behavior and Antibiotic Resistance. Frontiers in Bioscience-Landmark 2024 29 (4), 29(4), 133. https://doi.org/10.31083/J.FBL2904133
7. Yan, J., & Bassler, B. L. (2019). Surviving as a community: antibiotic tolerance and persistence in bacterial biofilms. Cell Host & Microbe, 26(1), 15. https://doi.org/10.1016/J.CHOM.2019.06.002
8. Preda, V. G., & Săndulescu, O. (2019). Communication is the key: biofilms, quorum sensing, formation and prevention. Discoveries, 7(3), e100. https://doi.org/10.15190/D.2019.13
9. Kunnath, A. P., Suodha Suoodh, M., Chellappan, D. K., Chellian, J., & Palaniveloo, K. (2024). Bacterial Persister Cells and Development of Antibiotic Resistance in Chronic Infections: An Update. British Journal of Biomedical Science, 81, 12958. https://doi.org/10.3389/BJBS.2024.12958/FULL
10. Srinivas, U. B., Sivamani, Y., Suresh, J. J., Agarval, P., Preethi, N., Elayaperumal, S., Srinivas, U. B., Sivamani, Y., Suresh, J. J., Agarval, P., Preethi, N., & Elayaperumal, S. (2025). Biofilm Maturation and Resistance Quorum Sensing Connection. Open Journal of Bacteriology 2025 9:1, 9(1), 014–024. https://doi.org/10.17352/OJB.000029
11. Zhou, K., Shi, M., Chen, R., Zhang, Y., Sheng, Y., Tong, C., Cao, G., & Shou, D. (2025). Natural phytochemical-based strategies for antibiofilm applications. Chinese Medicine, 20(1), 96. https://doi.org/10.1186/S13020-025-01147-5
12. Banerjee, D., Biswas, P., Mazumder, K., Palai, S., Hossain, C. M., Karmakar, S., & Biswas, K. (2025). Exploration of Phytochemicals as Anti-biofilm Agents against Pathogenic Bacteria: Their Potential and Challenges. Infectious Disorders Drug Targets, 25(6). https://doi.org/10.2174/0118715265324950241204182204
13. Mishra, R., Panda, A. K., de Mandal, S., Shakeel, M., Bisht, S. S., & Khan, J. (2020). Natural Anti-biofilm Agents: Strategies to Control Biofilm-Forming Pathogens. Frontiers in Microbiology, 11, 566325. https://doi.org/10.3389/FMICB.2020.566325/FULL
14. Gonçalves, A. S. C., Leitão, M. M., Simões, M., & Borges, A. (2023). The action of phytochemicals in biofilm control. Natural Product Reports, 40(3), 595–627. https://doi.org/10.1039/D2NP00053A
15. Omwenga, E. O., & Awuor, S. O. (2024). The Bacterial Biofilms: Formation, Impacts, and Possible Management Targets in the Healthcare System. The Canadian Journal of Infectious Diseases & Medical Microbiology = Journal Canadien Des Maladies Infectieuses et de La Microbiologie Médicale, 2024(1),

1542576. https://doi.org/10.1155/CJID/1542576

16. Sharma, S., Mohler, J., Mahajan, S. D., Schwartz, S. A., Bruggemann, L., & Aalinkeel, R. (2023). Microbial Biofilm: A Review on Formation, Infection, Antibiotic Resistance, Control Measures, and Innovative Treatment. Microorganisms, 11(6), 1614. https://doi.org/10.3390/MICROORGANISMS11061614
17. Zhao, A., Sun, J., & Liu, Y. (2023). Understanding bacterial biofilms: From definition to treatment strategies. Frontiers in Cellular and Infection Microbiology, 13, 1137947. https://doi.org/10.3389/FCIMB.2023.1137947/FULL
18. Muhammad, M. H., Idris, A. L., Fan, X., Guo, Y., Yu, Y., Jin, X., Qiu, J., Guan, X., & Huang, T. (2020). Beyond Risk: Bacterial Biofilms and Their Regulating Approaches. Frontiers in Microbiology, 11, 530515. https://doi.org/10.3389/FMICB.2020.00928/FULL
19. Rather, M. A., Gupta, K., & Mandal, M. (2021). Microbial biofilm: formation, architecture, antibiotic resistance, and control strategies. Brazilian Journal of Microbiology, 52(4), 1701. https://doi.org/10.1007/S42770-021-00624-X
20. Perry, E. K., & Tan, M. W. (2023). Bacterial biofilms in the human body: prevalence and impacts on health and disease. Frontiers in Cellular and Infection Microbiology, 13, 1237164. https://doi.org/10.3389/FCIMB.2023.1237164
21. Sauer, K., Stoodley, P., Goeres, D. M., Hall-Stoodley, L., Burmølle, M., Stewart, P. S., & Bjarnsholt, T. (2022). The biofilm life cycle–expanding the conceptual model of biofilm formation. Nature Reviews. Microbiology, 20(10), 608. https://doi.org/10.1038/S41579-022-00767-0
22. Shree, P., Singh, C. K., Sodhi, K. K., Surya, J. N., & Singh, D. K. (2023). Biofilms: Understanding the structure and contribution towards bacterial resistance to antibiotics. Medicine in Microecology, 16, 100084. https://doi.org/10.1016/J.MEDMIC.2023.100084
23. Kostakioti, M., Hadjifrangiskou, M., & Hultgren, S. J. (2013). Bacterial Biofilms: Development, Dispersal, and Therapeutic Strategies in the Dawn of the Postantibiotic Era. Cold Spring Harbour Perspectives in Medicine, 3(4), a010306. https://doi.org/10.1101/CSHPERSPECT.A010306
24. Wang, X., Liu, M., Yu, C., Li, J., & Zhou, X. (2023). Biofilm formation: mechanistic insights and therapeutic targets. Molecular Biomedicine, 4(1), 49. https://doi.org/10.1186/S43556-023-00164-W
25. Zhou, K., Shi, M., Chen, R., Zhang, Y., Sheng, Y., Tong, C., Cao, G., & Shou, D. (2025). Natural phytochemical-based strategies for antibiofilm applications. Chinese Medicine, 20(1), 96. https://doi.org/10.1186/S13020-025-01147-5
26. Mishra, R., Panda, A. K., de Mandal, S., Shakeel, M., Bisht, S. S., & Khan, J. (2020). Natural Anti-biofilm Agents: Strategies to Control Biofilm-Forming Pathogens. Frontiers in Microbiology, 11, 566325. https://doi.org/10.3389/FMICB.2020.566325/FULL
27. Zhang, J., Rui, X., Wang, L., Guan, Y., Sun, X., & Dong, M. (2014). Polyphenolic extract from Rosa rugosa tea inhibits bacterial quorum sensing and biofilm formation. Food Control, 42, 125–131.

https://doi.org/10.1016/J.FOODCONT.2014.02.001

28. Fydrych, D., Jeziurska, J., Wełna, J., & Kwiecińska-Piróg, J. (2025). Potential Use of Selected Natural Compounds with Anti-Biofilm Activity. International Journal of Molecular Sciences, 26(2), 607. https://doi.org/10.3390/IJMS26020607
29. Borges, A., Abreu, A. C., Dias, C., Saavedra, M. J., Borges, F., & Simões, M. (2016). New Perspectives on the Use of Phytochemicals as an Emergent Strategy to Control Bacterial Infections, Including Biofilms. Molecules, 21(7), 877. https://doi.org/10.3390/MOLECULES21070877
30. Jang, Y. S., & Mosolygó, T. (2020). Inhibition of Bacterial Biofilm Formation by Phytotherapeutics with Focus on Overcoming Antimicrobial Resistance. Current Pharmaceutical Design, 26(24), 2807–2816. https://doi.org/10.2174/1381612826666200212121710
31. Li, C. H., Chen, X., Landis, R. F., Geng, Y., Makabenta, J. M., Lemnios, W., Gupta, A., & Rotello, V. M. (2019). Phytochemical-based nanocomposites for the treatment of bacterial biofilms. ACS Infectious Diseases, 5(9), 1590. https://doi.org/10.1021/ACSINFECDIS.9B00134
32. Alam, K., Farraj, D. A. A., Mah-e-Fatima, S., Yameen, M. A., Elshikh, M. S., Alkufeidy, R. M., Mustafa, A. E. Z. M. A., Bhasme, P., Alshammari, M. K., Alkubaisi, N. A., Abbasi, A. M., & Naqvi, T. A. (2020). Anti-biofilm activity of plant derived extracts against infectious pathogen-Pseudomonas aeruginosa PAO1. Journal of Infection and Public Health, 13(11), 1734–1741. https://doi.org/10.1016/J.JIPH.2020.07.007
33. Ampofo, E. K., Amponsah, I. K., Asante-Kwatia, E., Armah, F. A., Atchoglo, P. K., & Mensah, A. Y. (2020). Indigenous Medicinal Plants as Biofilm Inhibitors for the Mitigation of Antimicrobial Resistance. Advances in Pharmacological and Pharmaceutical Sciences, 2020(1), 8821905. https://doi.org/10.1155/2020/8821905
34. R., R. T., Attavar, P. C., Hydrose, S. P., Kotian, M. S., & S., D. N. (2024). Antibiofilm and Antibacterial Properties of Herbal Extracts as Alternatives to Current Treatment Approaches: A Narrative Review. Asian Journal of Medicine and Health, 22(2), 12–22. https://doi.org/10.9734/AJMAH/2024/V22I2979
35. Romero, C. M., Vivacqua, C. G., Abdulhamid, M. B., Baigori, M. D., Slanis, A. C., de Allori, M. C. G., & Tereschuk, M. L. (2016). Biofilm inhibition activity of traditional medicinal plants from Northwestern Argentina against native pathogen and environmental microorganisms. Revista Da Sociedade Brasileira de Medicina Tropical, 49(6), 703–712. https://doi.org/10.1590/0037-8682-0452-2016
36. ben Abdallah, F., Lagha, R., & Gaber, A. (2020). Biofilm Inhibition and Eradication Properties of Medicinal Plant Essential Oils against Methicillin-Resistant Staphylococcus aureus Clinical Isolates. Pharmaceuticals, 13(11), 369. https://doi.org/10.3390/PH13110369
37. Zeng, J., Chen, D., Lv, C., Qin, K., Zhou, Q., Pu, N., Song, S., & Wang, X. (2022). Antimicrobial and anti-biofilm activity of Polygonum chinense L.aqueous extract against Staphylococcus aureus. Scientific Reports 2022 12:1, 12(1), 21988-. https://doi.org/10.1038/s41598-022-26399-1

38. Alam, K., Farraj, D. A. A., Mah-e-Fatima, S., Yameen, M. A., Elshikh, M. S., Alkufeidy, R. M., Mustafa, A. E. Z. M. A., Bhasme, P., Alshammari, M. K., Alkubaisi, N. A., Abbasi, A. M., & Naqvi, T. A. (2020). Anti-biofilm activity of plant derived extracts against infectious pathogen-Pseudomonas aeruginosa PAO1. Journal of Infection and Public Health, 13(11), 1734–1741. https://doi.org/10.1016/J.JIPH.2020.07.007
39. Baseri, M., Naseri, A., Radmand, F., Hamishehkar, H., Memar, M. Y., Ebrahimi, A., Asnaashari, S., & Kouhsoltani, M. (2025). Effect of nano liposomal herbal extracts against biofilm formation and adherence of streptococcus mutans. Scientific Reports 2025 15:1, 15(1), 21917-. https://doi.org/10.1038/s41598-025-08856-9
40. Bouyahya, A., Dakka, N., Et-Touys, A., Abrini, J., & Bakri, Y. (2017). Medicinal plant products targeting quorum sensing for combating bacterial infections. Asian Pacific Journal of Tropical Medicine, 10(8), 729–743. https://doi.org/10.1016/J.APJTM.2017.07.021
41. Roy, R., Tiwari, M., Donelli, G., & Tiwari, V. (2018). Strategies for combating bacterial biofilms: A focus on anti-biofilm agents and their mechanisms of action. Virulence, 9(1), 522–554. https://doi.org/10.1080/21505594.2017.1313372
42. Wagner, H. (2011). Synergy research: Approaches in phytomedicine. Phytomedicine, 18(5), 327–332.
43. Sharifi-Rad, M., et al. (2023). Plant-derived antibiofilm agents: Mechanisms and applications. Journal of Ethnopharmacology, 312, 116358.
44. Kumar, A., et al. (2020). Enhanced antibiofilm activity of curcumin–piperine combination. Fitoterapia, 146, 104672.
45. Duarte, A., et al. (2016). Synergistic effects of garlic and ginger extracts on quorum sensing inhibition. Food Control, 61, 487–494.
46. Zhang, L., et al. (2022). Combined action of berberine and green tea polyphenols against resistant biofilms. Phytotherapy Research, 36(3), 1221–1232.
47. Sun, Y., et al. (2020). Essential oil components targeting EPS structures in biofilms. Frontiers in Microbiology, 11, 1234.
48. Yin, H., et al. (2019). Natural inhibitors of quorum sensing in pathogenic bacteria. International Journal of Molecular Sciences, 20(20), 4894.
49. Dey, N., et al. (2021). Plant-derived alkaloids against bacterial persister cells. Microbial Pathogenesis, 158, 105041.
50. Pandey, G., et al. (2017). Traditional medicinal plants with antimicrobial and immunomodulatory properties. Ancient Science of Life, 36(4), 200–206.
51. Sill, T.J., & von Recum, H.A. (2008). Electrospinning: Applications in drug delivery and tissue engineering. Biomaterials, 29(13), 1989–2006.
52. Rijal, J.P., et al. (2019). Herbal-loaded nanofibers for wound infection control. Journal of Biomaterials Applications, 34(3), 380–395.
53. Rathbone, M.J., et al. (2015). Modified-Release Drug Delivery Systems. CRC Press.
54. Patel, K., et al. (2020). Mucoadhesive gel systems for controlled drug delivery. Journal of Drug Delivery Science and Technology, 57, 101750.
55. Yallapu, M.M., et al. (2012). Curcumin nanoformulations: A review. Journal of Nanobiotechnology, 10, 38.
56. Wang, L., et al. (2021). Penetration of nanoparticles into bacterial biofilms. ACS Applied Materials & Interfaces, 13(1), 234–248.

57. Koo, H., et al. (2017). Targeting microbial biofilms: Current and future therapeutic strategies. Nature Reviews Microbiology, 15(12), 740–755.
58. Li, Y., et al. (2020). Nanotechnology-based strategies for biofilm eradication. Biotechnology Advances, 42, 107356.
59. Singh, R., et al. (2020). Curcumin-mediated inhibition of bacterial quorum sensing. Journal of Herbal Therapeutics.
60. Patel, N., & Rao, V. (2019). Anti-biofilm activity of curcumin on resistant strains. Phytomedicine Research.
61. Liang, Y., et al. (2021). Synergistic phytochemical combinations against mature biofilms. Natural Product Reports.
62. Zhang, L., et al. (2019). Berberine as a quorum sensing inhibitor. Journal of Ethnopharmacology.
63. Huang, T., & Kuo, S. (2020). Combination effects of berberine with flavonoids. Fitoterapia.
64. Morad, M., et al. (2018). Allicin disruption of biofilm architecture. Journal of Applied Microbiology.
65. El-Sayed, A., et al. (2021). Antifungal biofilm inhibition by garlic compounds. International Journal of Antimicrobial Agents.
66. Ramos, R., et al. (2020). Cinnamaldehyde activity against enteric biofilms. Microbial Pathogenesis.
67. Gopal, S., & Verma, A. (2019). Quorum sensing inhibition by cinnamaldehyde. Bioscience Reports.
68. Fujita, M., et al. (2017). EGCG disruption of amyloid fibrils in biofilms. Antimicrobial Agents and Chemotherapy.
69. Lin, J., et al. (2018). Green tea polyphenols as efflux pump inhibitors. Plant-Derived Antimicrobials.
70. Ahmed, R., et al. (2019). Licorice flavonoids in microbial control. Herbal Pharmacology Journal.
71. Hassan, M., & Omar, S. (2020). Glycyrrhizin in persister biofilm inhibition. Journal of Natural Medicines.
72. Kumar, D., & Das, R. (2020). Boswellic acids as anti-biofilm agents. Phytochemistry Letters.
73. Santos, L., et al. (2018). Carvacrol and thymol: membrane-targeting antibiofilm molecules. Food Microbiology.
74. Lopez, J., et al. (2019). Standardization issues in biofilm assessment. Biofouling Research Journal.
75. Patel, R., & Singh, D. (2020). Variability in anti-biofilm assays for natural products. Phytomedicine Reviews.
76. Jiang, L., et al. (2021). Limitations of in vitro-to-in vivo translation in biofilm studies. Journal of Infection Models.
77. Barkefors, I., & Clerc, P. (2018). Host factors in chronic infection biofilms. Clinical Microbial Pathogenesis.
78. Huang, Y., & Zhao, X. (2020). Evaluating herbal synergy in antimicrobial research. Journal of Herbal Therapeutics.
79. Santos, L., et al. (2022). Mechanistic synergy in multi-herb combinations. Phytochemical Interactions.
80. Li, M., & Tan, K. (2019). Antibiotic–phytochemical combinations for resistant infections. Biomedical Pharmacotherapy.
81. Omar, A., et al. (2020). Herb–drug interaction risks in antimicrobial therapy. Clinical Phytopharmacology.
82. Chen, R., et al. (2021). Regulatory gaps in herbal nano-delivery systems. Advanced Drug Delivery Letters.
83. Ramesh, S., & Verma, A. (2022). Translational potential of multi-target phytochemicals. Integrative Pharmacology.

84. Chaudhary P, Janmeda P, Docea AO, Yeskaliyeva B, Abdull Razis AF, Modu B, Calina D, Sharifi-Rad J. Oxidative stress, free radicals and antioxidants: potential crosstalk in the pathophysiology of human diseases. Frontiers in chemistry. 2023 May 10;11:1158198.
85. Fishman T, Mastrucci A, Peled Y, Saxe S, van Ruijven B. RASMI: Global ranges of building material intensities differentiated by region, structure, and function. Scientific Data. 2024 Apr 23;11(1):418.
86. Karygianni L, Al-Ahmad A, Argyropoulou A, Hellwig E, Anderson AC, Skaltsounis AL. Natural antimicrobials and oral microorganisms: a systematic review on herbal interventions for the eradication of multispecies oral biofilms. Frontiers in Microbiology. 2016 Jan 14;6:1529.
87. Tian H, Liu Y, Li Y, Wu CH, Chen B, Kraemer MU, Li B, Cai J, Xu B, Yang Q, Wang B. An investigation of transmission control measures during the first 50 days of the COVID-19 epidemic in China. Science. 2020 May 8;368(6491):638-42.
88. Pandey AK, Kumar P, Singh P, Tripathi NN, Bajpai VK. Essential oils: Sources of antimicrobials and food preservatives. Frontiers in microbiology. 2017 Jan 16;7:2161.
89. Sunil. From the President's Desk. IETE Journal of Education. 2025 Jan 2;66(1):1-4.
90. Pauliuk, S. & Müller, D. B. The role of in-use stocks in the social metabolism and in climate change mitigation. Global Environmental Change 24, 132–142 (2014).
91. Mekonnen TW, Gerrano AS, Mbuma NW, Labuschagne MT. Breeding of vegetable cowpea for nutrition and climate resilience in Sub-Saharan Africa: progress, opportunities, and challenges. Plants. 2022 Jun 15;11(12):1583.
92. Karygianni L, Al-Ahmad A, Argyropoulou A, Hellwig E, Anderson AC, Skaltsounis AL. Natural antimicrobials and oral microorganisms: a systematic review on herbal interventions for the eradication of multispecies oral biofilms. Frontiers in Microbiology. 2016 Jan 14;6:1529.
93. Prather, M. J. et al. Measuring and modeling the lifetime of nitrous oxide including its variability. J. Geophys. Res. D 120, 5693–5705 (2015).

HOW TO CITE: Shruti Bijwe, Shreeya Hambarde, Mayuri Randive, Khushi Raikwad, Arpita Bhajipale, Nishant Awandekar, Millind Umekar, Synergistic Multi-Herb Approaches for Reversing Microbial Biofilms in Chronic Infections, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 1, 1077-1089. https://doi.org/10.5281/zenodo.18213434