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# Sustainable Management of Surgical Site Infection Pathogens: Leveraging Multitrophic Phytobiome Interactions of Urtica dioica and Chamaemelum nobile

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**ABSTRACT:** Surgical site infections (SSIs) are still among the most frequent healthcare-associated infections and are a major cause of postoperative morbidity, mortality, prolonged hospitalization, and increased healthcare costs globally. The increasing occurrence of multidrug-resistant (MDR) pathogens such as Staphylococcus aureus and Pseudomonas aeruginosa, together with their ability to form biofilms, has significantly reduced the effectiveness of conventional antibiotics and exacerbated the global antimicrobial resistance (AMR) crisis. This review discusses the potential of Urtica dioica (stinging nettle) and Chamaemelum nobile (Roman chamomile) as phytobiome-driven therapeutic resources for sustainable management of SSIs. The review covers the current evidence on the antimicrobial, antibiofilm, quorum-sensing inhibitory, efflux pump inhibitory, anti-inflammatory, antioxidant, and wound-healing properties of these medicinal plants, highlighting the synergistic contributions of multitrophic plant–microbe interactions. Advances in metagenomics, metabolomics, and other multi-omics technologies significantly elucidate the functions of the phytobiome and facilitate the discovery of new antibacterial substances. U. dioica and C. nobile could be eco-friendly multitarget therapeutics to combat MDR SSI pathogens, reducing antibiotic reliance and environmental impact when integrating phytobiome science with sustainable healthcare and the One Health framework.

## 1. INTRODUCTION

Surgical site infections (SSIs) continue to be a significant global health concern, increasing morbidity, lengthening hospital stays, and raising medical expenses. Among the most common causative organisms are MDR *S. aureus* and *P. aeruginosa*. These bacteria exhibit several resistance mechanisms, including the development of biofilms, the activity of efflux pumps, and the enzymatic degradation of antibiotics, all of which diminish the effectiveness of conventional treatments (Allegranzi et al., 2016; Tacconelli et al., 2018). The search for sustainable alternative antibacterial techniques has intensified due to the rapid increase in antimicrobial resistance (AMR) (Du et al., 2024). As a source of bioactive substances with antibacterial, anti-inflammatory, antioxidant, and wound-healing qualities, medicinal plants have drawn more and more attention. *C. nobile* is rich in terpenoids and flavonoids, such as α-bisabolol, chamazulene, and apigenin, which have antibacterial, antioxidant, and tissue-regenerative properties, while *U. dioica* contains flavonoids, phenolic acids, lignans, and lectins with proven activity against multidrug-resistant

pathogens (Kregiel et al., 2018; Rahmani et al., 2024). These phytochemicals are potential options for treating MDR infections because they act through mechanisms such as membrane disruption, inhibition of nucleic acid synthesis, biofilm inhibition, and interference with quorum sensing (Breijyeh and Karaman, 2024). Recent progress in phytobiome research has recognized medicinal plants as holobionts of the host plant and its associated endophytic and rhizosphere microbiota, thereby increasing their therapeutic potential. These microbial communities often produce bioactive substances that supplement those of the host plant and assist in secondary metabolite biosynthesis, pathogen control, and plant defence (Leach et al., 2017). Thus, phytobiome-mediated interactions provide a practical and sustainable approach to developing novel antimicrobial therapies for MDR SSI pathogens (Marchut-Mikołajczyk et al., 2023).

### 1.1 Background and Global Burden of Surgical Site Infections (SSIs): Defining the Clinical Challenge and the Rise of MDR Pathogens in Hospital Settings

SSIs are one of the most common infections associated with health care, occurring within 30 days of surgery or up to a year after surgery involving implants (Allegranzi et al., 2016). Although surgical techniques have improved significantly, and there have been advancements in infection control, SSIs remain a considerable cause of morbidity, mortality, increased length of hospitalization, and medical costs. LMICs disproportionately incur high costs owing to poor infection control measures and poor health care infrastructure (WHO, 2023; Zewdu et al., 2025). Approximately 20–25% of healthcare-associated infections globally are SSIs, which occur in a range of 2-5% in developed countries and greater than 30% in some LMICs (Zewdu et al., 2025; GBD 2023, 2026; Singh et al., 2026). Because of their aggressiveness, capacity to produce biofilms, and MDR phenotypes, *S. aureus* (especially methicillin-resistant *S. aureus* [MRSA]) and *P. aeruginosa* are the most clinically concerning of the common causal organisms (Khan et al., 2023; Flemming et al., 2016). AMR's quick rise has made managing SSI even more difficult. The efficacy of conventional antibiotics is significantly diminished by resistance mechanisms such as β-lactamase production, efflux pump activation, target-site modification, and biofilm formation. Additionally, the growing frequency of extensively drug-resistant (XDR) strains highlights the critical need for sustainable alternative antimicrobial strategies (Du et al., 2024; Murray et al., 2022; Gverić Grginić et al., 2026).

### 1.2 The Crisis of Antimicrobial Resistance: Limitations of Conventional Antibiotics and the Need for Sustainable, "Green" Alternatives

Because of the extensive and improper use of antibiotics in human medicine, agriculture, veterinary care, and aquaculture, antimicrobial resistance (AMR) is one of the most significant risks to global health (Murray et al., 2022). The treatment of SSIs and other nosocomial infections has been significantly hampered by the development of antibiotic resistance in important healthcare-associated bacteria, such as *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii* (WHO, 2023).

Numerous mechanisms, including β-lactamase synthesis, target-site alteration, decreased membrane permeability, efflux pump overexpression, and biofilm development, mediate bacterial resistance (Munita and Arias, 2016). Because they shield bacterial colonies from medicines and host immune responses, biofilms provide a significant therapeutic challenge and encourage recurring and persistent infections (Flemming et al., 2016). Globally, the proliferation of MDR and XDR infections has raised healthcare expenses and deaths, further restricting treatment options (Murray et al., 2022). Antibiotic residues released into the environment contribute to the spread of antimicrobial resistance genes, which goes beyond clinical issues and highlights the significance of a One Health strategy that incorporates environmental, animal, and human health (Larsson and Flach, 2022).

### 1.3 The Phytobiome Paradigm: Shifting Focus from Isolated Phytochemicals to Multitrophic Interactions (Endophytes, Rhizobacteria, and Host Plant)

The isolation and identification of specific bioactive chemicals that are responsible for therapeutic efficacy has been the main focus of traditional phytopharmacological research. Despite the promising antibacterial and anti-inflammatory properties of phytochemicals such as flavonoids, alkaloids, terpenoids, phenolic acids, and tannins, it appears increasingly clear that the medicinal value of plants extends beyond just the chemistry of these components (Leach et al., 2017). The phytobiome paradigm, in which the plant is viewed as a holobiont that interacts dynamically with different microorganisms along with the environment, is one such outcome of this revelation. The host plant, along with the associated microbiomes such as the rhizosphere microorganisms, endophytes, phyllosphere microorganisms, mycorrhizae, insects, the soil conditions, and the climate factors, is included within the phytobiome that influences the health and fitness of the plant. The therapeutic potential

of plants is influenced by these multitrophic interactions, regulating immunity, stress resistance, nutrient absorption, and synthesis of bioactive compounds.

The plant growth-promoting rhizobacteria (PGPR) and endophytes are among the most important phytobiome components. The beneficial microbes can induce the production of flavonoids, phenolics, terpenoids, and other defense-related secondary metabolites via signaling pathways that involve jasmonic acid, salicylic acid, ethylene, and reactive oxygen species (Li et al., 2022). Alkaloids, peptides, polyketides, and volatile organic compounds are among the antimicrobial metabolites that endophytic bacteria and fungi may directly contribute. Many of these chemicals have the ability to combat diseases that are resistant to many drugs.

## 2. ETIOLOGY OF SSI PATHOGENS AND RESISTANCE MECHANISMS

SSIs are among the most common healthcare-associated infections and contribute to post-operative morbidity and mortality, prolonged hospital stays, and increased health care costs (Allegranzi et al., 2016). These are caused by microbial contamination of surgical wounds and depend on variables such as patient health status, the type of surgical procedure, infection-control practices, and post-operative care (WHO, 2023).

*S. aureus* is the leading pathogen for SSIs, but Gram-negative organisms such as *P. aeruginosa*, *E. coli*, *K. pneumoniae,* and *A. baumannii* are increasingly associated with severe and MDR infections (Seidelman et al., 2023). These pathogens have virulence traits such as toxin production, tissue adhesion, immune evasion, and biofilm formation that confer an advantage to persist in surgical wounds.

The growing prevalence of AMR among SSI pathogens adds further complexity to treatment. Resistance is mediated by genetic changes and horizontal gene transfer that lead to mechanisms such as β-lactamase production, target modification, efflux pump activation, decreased permeability of the membrane, and biofilm-mediated protection (Munita et al., 2016). This may limit the efficacy of antibiotics and further increase the burden of MDR infections associated with surgery worldwide (Murray et al., 2022).

### 2.1 Profile of Dominant SSI Pathogens: Focused Discussion on *Staphylococcus aureus* and *Pseudomonas aeruginosa*

Most SSIs arise from opportunistic pathogens that have the ability to invade wound sites, resist host defences, and form antibiotic resistance. These include *S. aureus* and *P. aeruginosa*, as they are the most common due to their virulence, biofilm formation capability, and MDR nature (Seidelman et al., 2023).

*S. aureus* is a Gram-positive organism and a facultative pathogen that normally inhabits the skin and mucosa of humans. After surgery, it may penetrate into damaged tissues and lead to infection through the production of many virulence factors, such as adhesins, toxins, proteases, and evasion proteins (Turner et al., 2019). Its ability to produce biofilms on wounds and medical devices makes it more pathogenic by causing the host's immune response to increase (Roy et al., 2018). The mecA gene, which encodes the altered penicillin-binding protein (PBP2a), is primarily accountable for the emergence of MRSA, which has resulted in the reduced effectiveness of β-lactam antibiotics and caused more illness and deaths (Turner et al., 2019).

*P. aeruginosa* is an opportunistic Gram-negative bacterium that commonly occurs in hospital and environmental settings. Infection through burns, chronic wounds, and surgery is commonly associated with it (Pang et al., 2019). Exotoxin A, elastase, phospholipases, pyocyanin, and the type III secretion system are some of the numerous virulence factors that the pathogen uses to cause tissue injury and evade the immune system (Klockgether and Tümmler, 2017). The capability of forming robust biofilms that consist of alginate and other extracellular polymeric substances, which protect bacteria from the host immune system and antibiotics, plays an important role in its survival (Thi et al., 2020).

### 2.2 Biofilm Formation: The Primary Barrier in Surgical Wound Healing and How it Evades Standard Treatment

All the mentioned factors, like failure of antimicrobial therapy, delay in wound healing, and persistence of SSI, are greatly affected by biofilm formation. Biofilms allow microbial adherence to wound sites, sutures, implants, and other medical devices because they represent organized microorganisms within an extracellular matrix that is composed of polysaccharides, proteins, lipids, and extracellular DNA (eDNA) (Koo et al., 2017; Uberoi et al., 2024). Microbes within biofilms are much more resilient

against antibiotics, host immune defenses, and environmental stresses compared to free-living cells, thereby posing problems in the treatment of infections (Flemming et al., 2016; Uberoi et al., 2024).

Attachment, Microcolony Formation, Maturation, and Dissemination constitute the sequential stages of the process of biofilm formation. Following surgical procedures, pathogens such as *S. aureus* and *P. aeruginosa* may infect and colonize the exposed surfaces. The bacteria produce the EPS components that enable the formation of microbial colonies (Thi et al., 2020; Goswami et al., 2023). The persistence and survival of microbes become possible because of the creation of various microenvironments by mature biofilms characterized by gradients of nutrients and oxygen (Flemming et al., 2016).

Biofilms create chronic inflammation and disrupt the process of tissue repair, thus hampering wound healing by inhibiting fibroblast proliferation, collagen formation, angiogenesis, and epithelialization through sustained release of inflammatory mediators, reactive oxygen species, and degradation enzymes (Uberoi et al., 2024; Malone et al., 2017). Consequently, wound infections associated with biofilms lead to poor outcomes, healing delay, and reinfection.

The remarkable amount of resistance to antimicrobial agents in biofilms, which may be up to 1,000-fold greater than in planktonic cells, is what distinguishes biofilms (Koo et al., 2017). Metabolic dormancy of persister cells, poor diffusion of antibiotics through the EPS matrix, and physiological mechanisms like efflux pumps and stress response systems are some of the factors responsible for the tolerance observed (Yan and Bassler, 2019; Liu et al., 2024). In addition to this, biofilms expedite the development of multidrug-resistant bacteria by allowing horizontal gene transfer and dissemination of resistance genes (Flemming et al., 2016; Liu et al., 2024).

Quorum sensing enhances the durability of biofilms by means of controlling bacterial communication, virulence factor expression, and biofilm formation. Although the agr system in *S. aureus* performs similar functions in terms of regulation, the Las, Rhl, and Pqs systems in *P. aeruginosa* control biofilm formation and virulence (Cheung et al., 2021). Overall, these characteristics contribute to the significance of biofilms as a key aspect of the pathophysiology of chronic SSI as well as an important focus for the development of new antimicrobial therapies.

## 3. BIOLOGICAL PROFILE: URTICA DIOICA AND CHAMAEMELUM NOBILE

Medicinal plants are being increasingly appreciated as sustainable sources for bioactive molecules that can be used against antibiotic resistance and chronic wounds. From this group, the plants *U. dioica* and *C. nobile* have various pharmacological activities like immunomodulatory, antibacterial, anti-inflammatory, antioxidant, and wound-healing properties (Kregiel et al., 2018; Arip et al., 2022). These plants contain a lot of phytochemicals and have complex microbial flora, which might influence the production of secondary metabolites and increase the pharmaceutical value.

Traditional medicine has widely utilized *U. dioica*, an herbaceous perennial plant that belongs to the family *Urticaceae*, for the treatment of injuries, inflammations, urinary tract infections, arthritis, and skin diseases (Papang et al., 2025). According to phytochemical research, the main components are flavonoids, phenolic acids, tannins, lignans, phytosterols, terpenoids, alkaloids, polysaccharides, and lectins (Papang et al., 2025; El Haouari and Rosado, 2019). They help contribute to the herb's anti-inflammatory, antioxidant, and antibacterial activity. Clinically important bacteria such as MRSA, MDR *P. aeruginosa*, *E. coli*, and *K.* pneumoniae are vulnerable to *U. dioica* extract (Kregiel et al., 2018). Some of the mechanisms proposed include bacterial membrane disruption, nucleic acid synthesis inhibition, induction of oxidative stress, interruption of quorum sensing, and biofilm production inhibition (Arip et al., 2022).

*C. nobile,* belonging to the Asteraceae family, is known for its applications in the treatment of ailments such as wounds, skin conditions, and inflammatory conditions. Its medicinal properties are primarily due to flavonoids, terpenoids, coumarins, phenolic acids, and essential oil constituents such as apigenin, luteolin, α-bisabolol, and chamazulene (Sharifi-Rad et al., 2018). The substances are tissue-regenerative, anti-inflammatory, antioxidant, and antibacterial. Numerous studies have demonstrated the inhibitory effects of chamomile extracts and essential oils against *S. aureus*, *P. aeruginosa*, *E. coli*, and fungal infections through mechanisms such as membrane rupture, enzyme inhibition, and interference with bacterial communication systems (Sharifi-Rad et al., 2018; Sah et al., 2022). Additionally, chamomile compounds promote wound healing by increasing fibroblast proliferation, collagen formation, angiogenesis, and inflammatory response control (Pandey et al., 2023).

### 3.1 Ethnobotanical Relevance: History of use in wound care and infection control

The use of medicinal plants for wound care and prevention of infection predates contemporary antimicrobial therapy and is a valuable source of therapeutic knowledge. Botanicals have been used for centuries in traditional health care systems to fight infection, reduce inflammation, and promote faster tissue repair. This has provided crucial leads for the development of novel anti-infective drugs capable of combating AMR (Breijyeh and Karaman, 2024; Cedillo-Cortezano et al., 2024).

*U. dioica* has been traditionally used in Middle Eastern, Asian, and European medical systems for the treatment of burns, wounds, ulcers, abscesses, and skin infections. Poultices and decoctions were applied directly to the affected areas to promote healing and to reduce inflammation. In a similar vein, *C. nobile* has been used for wound cleaning, burn and ulcer treatment, pain relief, and infection prevention since the ancient Egyptian, Greek, and Roman eras. Modern research showing the antibacterial, anti-inflammatory, antioxidant, and tissue-regenerative properties of its bioactive components has validated these ancient uses (Parente et al., 2025; Thakura and Kaura, 2024; Dai et al., 2023).

### 3.2 Bioactive Metabolites: A Comparative analysis of Polyphenols, terpenoids, and alkaloids present in both species

The various secondary metabolites found in medicinal plants are largely responsible for their therapeutic qualities. These metabolites have important pharmacological effects in humans and are involved in plant defence. The main classes of bioactives exhibiting antibacterial, antioxidant, anti-inflammatory, and wound-healing properties are polyphenols, terpenoids, and alkaloids. These chemicals are abundant in *U. dioica* and *C. nobile*, which have had success in countering MDR microorganisms in SSIs. The two plants have similar and unique metabolites in their phytochemical profiles, and their antibacterial activities and therapeutic values support their potential for long-term use in treatment for bacterial infections (Parente et al., 2025; Dai et al., 2023).

#### 3.2.1 Polyphenols

Polyphenols have some of the best antibacterial, antioxidant, anti-inflammatory, and wound-healing properties of all plant-derived compounds. They inhibit bacterial virulence, host tissue damage from oxidative stress, and facilitate tissue healing. *U. dioica* has an abundance of flavonoids and phenolic acids (such as quercetin, rutin, kaempferol, isorhamnetin, caffeic acid, chlorogenic acid, ferulic acid, and gallic acid) They rupture bacterial membranes, inhibit the production of nucleic acids, block the construction of biofilms, and lessen the oxidative stress response. These substances show activity against bacterial species. Rutin and quercetin have shown remarkable activity against important human pathogens like *P. aeruginosa* and *S. aureus* (Parente et al., 2025; Thakura and Kaura, 2024).

Polyphenolic compounds like apigenin, luteolin, quercetin, patuletin, eupafolin, and chlorogenic acid can be found in *C. nobile*. Although luteolin acts against biofilm formation and quorum sensing by bacteria, apigenin acts against inflammation and bacteria. This combination of flavonoids results in increased antibacterial action and helps to heal wounds due to the reduction of oxidative stress and inflammation. (Dai et al.,2023; Sobha et al., 2024).

#### 3.2.2 Terpenoids

Terpenoids play a vital role in enhancing the antibacterial, anti-inflammatory, antioxidant, and wound-healing properties of medicinal plants by functioning as secondary metabolites. These are constituents of several essential oils and function as natural defense systems against infections.

Monoterpenes, sesquiterpenes, diterpenes, triterpenes, and phytosterols such as β-sitosterol, stigmasterol, campesterol, and ursolic acid are among the terpenoids found in *U. dioica.* Triterpenoids, particularly ursolic acid, have exhibited antibacterial, antibiofilm, anti-inflammatory, and tissue regenerative activities (Parente et al., 2025).

Most of the bioactive components of *C. nobile's* essential oil are terpenoids. Important compounds include α-bisabolol, bisabolol oxides, farnesene, chamazulene, spiroethers, and various sesquiterpenes. α-bisabolol possesses potent antibacterial, anti-inflammatory, and wound-healing qualities, whereas chamazulene has strong antioxidant and anti-inflammatory qualities. These terpenoids enhance the antibacterial efficacy of *C. nobile* by rupturing bacterial membranes, inhibiting microbial adhesion, and decreasing the formation of biofilms (Cedillo-Cortezano et al., 2024; Dai et al., 2023).

### 3.2.3 Alkaloids and Nitrogen-Containing Bioactive Compounds

Compared to polyphenols and terpenoids, alkaloids and other nitrogen-containing metabolites are present in relatively tiny concentrations in *U. dioica* and *C. nobile*. These compounds, however, may increase the overall pharmacological activity of both plants.

Nitrogen-containing elements such as histamine, acetylcholine, serotonin, choline, and other alkaloid-like compounds are primarily found in the stinging trichomes of *U. dioica*. In addition to their function in the characteristic stinging reaction, these metabolites may have an indirect effect on antimicrobial defence by modulating inflammatory management, tissue repair, and host immune responses (Parente et al., 2025).

*C. nobile* possesses relatively few alkaloidal components, with only trace amounts of nitrogen-containing compounds, amino acid derivatives, and bioactive amides found. Their contribution to the plant's antibacterial action is believed to be minimal in comparison to the important activities of terpenoids and flavonoids. Alkaloids are therefore not believed to be the primary bioactive elements responsible for *C. nobile's* therapeutic efficacy (Dai et al., 2023).

## 4. MULTITROPHIC PHYTOBIOME INTERACTIONS

By viewing medicinal plants as holobionts made up of the host plant and its associated microbial communities, including endophytes, rhizosphere bacteria, fungi, archaea, and viruses, the concept of the phytobiome has changed our understanding of these plants (Leach et al., 2017). Such multitrophic interactions are essential for the growth, stress tolerance, disease resistance, and secondary metabolite biosynthesis in plants, which in turn influence the pharmacological properties of medicinal plants.

The phytobiome is comprised of the microbial communities within the rhizosphere, phyllosphere, endosphere, and the surrounding soil, in which continuous chemical signaling and metabolic interactions regulate plant defence and the production of bioactive metabolites including flavonoids, phenolics, terpenoids, and alkaloids (Trivedi et al., 2020). Hence, the therapeutic potential of medicinal plants is not only related to the plant genetics but also to their microbiota.

Endophytic and rhizosphere microorganisms promote the accumulation of secondary metabolites in medicinal plants such as *U. dioica* and *C. nobile* through nutrient mobilisation, phytohormone production, and induction of plant defence pathways (Pandey et al., 2023). Many endophytes also produce antimicrobial metabolites that complement host plant defences and contribute to the overall antimicrobial efficacy of plant extracts (Zotchev, 2024).

By inhibiting infections through competitive exclusion, generation of antimicrobial metabolites, induction of systemic resistance, and disruption of pathogen signaling, beneficial phytobiome members further defend plants (Trivedi et al., 2020). The antibacterial potential of medicinal plants is specifically increased by plant growth-promoting rhizobacteria (PGPR), which improve nutrient uptake and promote the manufacture of phenolics, flavonoids, and terpenoids (Backer et al., 2018). Similarly, endophytes that colonise interior tissues enhance plant fitness and may generate bioactive substances that share structural similarities with their hosts, making them promising long-term sources of innovative antimicrobial drugs (Zotchev, 2024; Kumari et al., 2023).

### 4.1 The Role of Endophytic Microorganisms: Diversity of Fungi and Bacteria Residing Within These Plants That Produce Novel Antimicrobial Compounds

Bacteria, fungi, and actinomycetes are examples of endophytic microorganisms that live inside plant tissues without causing illness and form mutualistic interactions that improve defence, growth, stress tolerance, and the generation of secondary metabolites (Compant et al., 2019). Advancements in metagenomics and metabolomics have redefined medicinal plants as holobionts, in which therapeutic characteristics come from interactions between the host plant and its accompanying microbiota rather than plant metabolism alone (Leach et al., 2017).

Endophytes live in roots, stems, leaves, flowers, and seeds, where they aid in nutrient acquisition, regulate phytohormone production, suppress infections, and encourage the creation of beneficial secondary metabolites. Bacillus, Pseudomonas, Streptomyces, Paenibacillus, and Burkholderia are the dominant bacterial endophytes, whereas frequent fungal species include Penicillium, Aspergillus, Fusarium, Alternaria, Trichoderma, and Colletotrichum (Kumari et al., 2023). Many of these bacteria

produce antibiotic, antioxidant, antiviral, and anti-inflammatory compounds, making them prospective sources of new therapies against antimicrobial-resistant infections (Zotchev, 2024).

Bacillus, Pseudomonas, Streptomyces, and Paenibacillus dominate *U. dioica's* endophytic communities, producing antibiotics, lipopeptides, siderophores, hydrolytic enzymes, and volatile organic chemicals that suppress microbial pathogens (Parente et al., 2025). *C. nobile* has bacterial and fungal endophytes that aid in plant defence and the manufacture of pharmacologically significant substances such as α-bisabolol, chamazulene, and apigenin derivatives (Dai et al., 2023). The fact that these plants have long been used medicinally to treat wounds and infections may be explained by these interactions.

Antibiotics, bacteriocins, lytic enzymes, biosurfactants, siderophores, and volatile chemical molecules are all produced by endophytic microbes. Additionally, they compete with pathogens for ecological niches and resources and trigger host defence responses. When taken as a whole, these activities increase the antibacterial effectiveness of medicinal plants and emphasise endophytes as crucial resources for creating long-term treatments against microorganisms that cause surgery site infections that are resistant to drugs.

### 4.2 Rhizosphere Signaling: How Plant Microbe Interactions Influence the Synthesis of Secondary Metabolites

The rhizosphere, the small zone of soil surrounding plant roots, is a highly dynamic ecological interface at which plants and microbes communicate via complex chemical signaling. These interactions affect plant development, defence, and secondary metabolite biosynthesis, which are involved in the therapeutic properties of plants such as *U. dioica* and *C. nobile* (Trivedi et al., 2020).

Plant roots release a wide variety of exudates including sugars, amino acids, organic acids, phenolics, flavonoids, terpenoids, and phytohormones, which selectively recruit beneficial microbial populations in the rhizosphere (Sasse et al., 2018). These microbes form reciprocal relationships through continuous biochemical signaling that improve nutrient acquisition, prevent infections, and modulate plant metabolism.

PGPR include Bacillus, Pseudomonas, Paenibacillus, Azospirillum, and Rhizobium species, which are among the most important rhizosphere microorganisms. PGPR, besides improving plant nutrition via nitrogen fixation, phosphate solubilisation, siderophore and phytohormone synthesis, also activates defence pathways involving ethylene (ET), salicylic acid (SA), and jasmonic acid (JA), leading to production of secondary metabolites (Li et al., 2022; Backer et al., 2018). Activation of such pathways causes the production of greater amounts of antioxidants and antibacterials in the form of flavonoids, phenolic acids, terpenoids, and alkaloids.

Promotion of flavonoid production by microorganisms in *U. dioica* enhances antibacterial and antibiofilm effects through the formation of more substances like rutin, kaempferol, quercetin, and phenolic acids. Similarly, terpenoid synthesis in *C. nobile* is stimulated through interaction between plants and microbes, resulting in the accumulation of such chemicals as α-bisabolol, chamazulene, farnesene, and others, making the plant possess antibacterial and wound-healing properties (Li et al., 2022).

AMF increase the process of synthesis of secondary metabolites through the improvement of absorption of nutrients, the photosynthesis process, and activation of signaling pathways involved in defense responses, resulting in higher content of flavonoids, terpenoids, alkaloids, and phenolic acids (Begum et al., 2019). Additionally, the production of lipopeptides, volatile organic compounds (VOCs), siderophores, quorum-sensing molecules, and microbial phytohormones is a source of microbial metabolites that act as signaling molecules that directly regulate the genes for the synthesis of secondary metabolites (Trivedi, 2020).

### 4.3 Omics Insights: Utilizing Metagenomics and Metabolomics to Decode the Phytobiome's Defense Against Human Pathogens

The recent discoveries in metagenomics and metabolomics have completely transformed medicinal plant research by recognizing medicinal plants as phytobiome systems in which plants and microbes collectively affect their defense responses and production of secondary metabolites. The discovery of new antibiotics for MDR pathogens is facilitated by the use of such omics techniques, which provide a comprehensive understanding of the taxonomic composition, functional capabilities, and metabolism of the microbial communities associated with plants (Trivedi et al., 2020; Wang et al., 2024).

Through the discovery of functional genes and gene clusters responsible for the production of antimicrobial agents, siderophores, quorum quenchers, and biofilm inhibitors, metagenomics helps to study the microbes inhabiting the rhizosphere, endosphere, and phyllosphere without culturing them. Plant-associated microbes contain a variety of biosynthetic pathways that can produce natural compounds with activity against MDR infections, such as S. aureus and P. aeruginosa, according to genome-mining studies (Zotchev, 2024; Spooren et al., 2024).

By employing analytical tools like LC-MS, GC-MS, and NMR to profile the small chemicals generated within phytobiome systems, metabolomics enhances these discoveries. Several studies have found that plant-microbe interactions promote the synthesis of antimicrobial metabolites like α-bisabolol, chamazulene, apigenin, and luteolin in *C. nobile* and quercetin, rutin, chlorogenic acid, and caffeic acid in *U. dioica* (Parente et al., 2025; Thakura and Kaura, 2024).

## 5. MECHANISM OF ACTION AGAINST SSI PATHOGENS

A wide range of phytochemicals and phytobiome-derived compounds that target several bacterial activities at once mediate the antibacterial action of *U. dioica* and *C. nobile* against SSI pathogens. These bioactive substances have multitarget mechanisms that lessen the chance of resistance development and are especially efficient against MDR pathogens like *S. aureus* and *P. aeruginosa*, in contrast to conventional antibiotics, which usually operate on a single cellular target (Munita and Arias, 2016; Pang et al., 2019).

Bacterial cell wall and membrane rupture is one of the main mechanisms. These include terpenoids, flavonoids, and polyphenols that increase membrane permeability, impairing essential cellular functions and causing exudation of cellular contents. While flavonoids like quercetin and rutin from *U. dioica* interfere with membrane-associated enzymes and transport mechanisms, terpenoids like α-bisabolol and chamazulene from *C. nobile* mainly destabilise bacterial membranes (Thakura and Kaura, 2024; Dai et al., 2023).

By inhibiting bacterial adhesion, EPS generation, and biofilm maturation, these phytochemicals help prevent the formation of biofilms. They also break existing biofilms to increase antimicrobial resistance. Furthermore, a number of flavonoids and phenolic acids disrupt quorum-sensing systems that control motility, virulence, toxin generation, and biofilm formation, reducing bacterial pathogenicity without applying significant selective pressure for resistance.

Additional antimicrobial strategies include production of intracellular oxidative stress, regulation of enzymes involved in DNA replication, protein synthesis, and energy consumption, and suppression of bacterial virulence pathways (Sharifi-Rad et al., 2018).

At the same time, these metabolites' antioxidant qualities shield host tissues from oxidative damage, promoting wound healing. Phytobiome-associated bacteria produce bacteriocins, lipopeptides, hydrolytic enzymes, siderophores, and volatile organic molecules that enhance antimicrobial action in addition to phytochemicals supplied from plants. These microbial secondary metabolites support durable treatments against MDR SSI pathogens by inhibiting pathogen growth, competing for nutrients, and improving plant defense mechanisms (Pandey et al., 2023; Zotchev, 2024).

### 5.1 Disruption of Quorum Sensing: How Phytocompounds Blind Bacteria to Prevent Biofilm Assembly

Quorum sensing refers to cell density-dependent communication in which bacteria produce and detect signal molecules called autoinducers to regulate bacterial virulence, biofilm formation, motility, and antimicrobial resistance. QS is a key factor in the pathogenicity and persistence of MDR pathogens such as *S. aureus* and *P. aeruginosa* in SSIs (Pang et al., 2019; Silva et al., 2023).

Biofilm maturation and virulence in *P. aeruginosa* are regulated by the Las, Rhl, Pqs, and Iqs regulatory systems. Toxin production and biofilm dynamics in *S. aureus* are regulated by the accessory gene regulator (agr) system (Thi et al., 2020). Quorum-sensing inhibitors (QSIs) reduce bacterial virulence without directly affecting bacterial viability, and therefore reduce the selective pressure for development of resistance in contrast to conventional antibiotics. Phytochemicals of plant origin, such as flavonoids, phenolic acids, terpenoids, and constituents of essential oils, affect QS by inhibiting signal synthesis, degrading signaling molecules, blocking receptor binding, or repressing expression of genes regulated by QS (Vashistha et al., 2023; Bhattacharya et al., 2023). In *U. dioica,* flavonoids such as quercetin, rutin, kaempferol, and isorhamnetin reduce QS-regulated genes involved in bacterial adhesion, EPS production, and biofilm maturation. According to reports, quercetin inhibits *P.*

*aeruginosa* LasR and RhlR signaling pathways, which lowers the synthesis of pyocyanin, elastase, and other virulence factors (Gonçalves et al., 2023).

Similarly, terpenoids (α-bisabolol, chamazulene) and flavonoids (apigenin, luteolin) found in *C. nobile* disrupt QS signaling, prevent biofilm-associated gene expression, and lessen bacterial pathogenicity (Sharifi-Rad et al., 2018; Dai et al., 2023). These phytochemicals inhibit biofilm formation and increase bacterial vulnerability to host immunological responses and antimicrobial drugs by interfering with QS in the early phases of colonisation (Roy et al., 2018; Silva et al., 2023).

### 5.2 Membrane Permeabilization and Efflux Pump Inhibition: Technical Breakdown of How These Extracts Neutralize Resistant Strains

Resistance to MDR bacteria, particularly that of *S. aureus* and *P. aeruginosa*, occurs through active efflux of toxic substances and preservation of cell membrane integrity. Resistance to antimicrobials in SSIs is mainly due to reduced membrane permeability and expression of efflux pumps, which prevents antibiotic accumulation inside the cell. An increasing amount of evidence points to the ability of phytochemicals obtained from *U. dioica* and *C. nobile* to interfere with these mechanisms through membrane destruction and inhibition of efflux pumps, leading to higher levels of antimicrobial retention and increased susceptibility to antimicrobials (Pang et al., 2019; Ghosh et al., 2025).

#### 5.2.1 Membrane Permeabilization

Energy generation, signal transduction, nutrient transfer, and cellular homeostasis rely on the membranes of bacterial cells. The association of these phytochemicals with phospholipids of the bacterial membrane and related proteins brings about the disruption of the membrane structure, leading to increased membrane permeability, leakage of cell contents, loss of membrane potential, and ultimately cell death (Gonçalves et al., 2023).

Flavonoids present in *U. dioica*, like quercetin, rutin, kaempferol, and isorhamnetin, inhibit bacterial energy metabolism by altering the membrane fluidity, causing leakage of ions and cellular macromolecules, and damaging enzymes on the membrane associated with electron transfer and ATP formation (Parente et al., 2025). In a similar way, compounds found in terpenoids and essential oils like farnesene, chamazulene, and α-bisabolol act on bacterial cell membranes, causing disruptions in their structures and permeability, which is needed for ATP production. The interaction is also seen between these agents and lipopolysaccharides in Gram-negative bacteria such as *P. aeruginosa*, making it easier for antimicrobials to enter the cell (Dai et al., 2023). In addition to their direct bactericidal actions, membrane-permeabilizing phytochemicals show synergistic efficacy against MDR bacteria with reduced membrane permeability by enhancing the absorption of co-administered antimicrobial medicines (Gonçalves et al., 2023).

#### 5.2.2 Efflux Pump Inhibition

Efflux pumps are transmembrane transport proteins that aggressively eliminate toxic materials from bacterial cells, reducing intracellular antibiotic concentrations and promoting multidrug resistance. Important efflux systems include the NorA transporter in *S. aureus* and the Resistance-Nodulation-Division (RND) family pumps, including MexAB-OprM, MexCD-OprJ, and MexEF-OprN in *P. aeruginosa* (Pang et al., 2019).

Plant-derived flavonoids like quercetin and kaempferol act as natural efflux pump inhibitors through their interactions with transporter proteins, interruption of energy-dependent transport, or downregulation of efflux-associated gene expression. These processes boost the intracellular buildup of antimicrobial medications and render bacteria more vulnerable to conventional antibiotics (Ghosh et al., 2025). Additionally, terpenoids and phenols affect the proton motive force required by many efflux pumps in bacteria, particularly the RND family in Gram-negative bacteria. Permeabilization of the membrane, along with inhibition of the efflux pump, increases the ability of the phytochemicals to act on drug-resistant microorganisms (Gonçalves et al., 2023).

#### 5.2.3 Implication for MDR SSI Pathogens

Combination of membrane permeability and efflux pump inhibition is key to successfully tackling multidrug resistance in SSI cases. Inhibition of the NorA efflux pump and damage to the membrane make *S. aureus* more sensitive to fluoroquinolones, β-lactams, and other antimicrobial agents. Similarly, in *P. aeruginosa*, intracellular antibiotic accumulation is increased, and biofilm-

associated resistance is decreased when outer membrane function is compromised and RND efflux mechanisms are suppressed (Pang et al., 2019; Silva et al., 2023).

### 5.3 Anti-inflammatory and Pro-coagulant Properties: Holistic Benefits for Surgical Wound Recovery

Promoting wound healing and eliminating infections are both necessary for the effective management of SSIs. The complementary antibacterial, anti-inflammatory, antioxidant, wound-healing, and hemostatic qualities of *U. dioica* and *C. nobile* promote tissue regeneration and enhance healing results (Salehi et al., 2020).

Pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 are produced in excess when *S. aureus* and *P. aeruginosa* infections persist, delaying the healing of wounds. The bioactive compounds of *U. dioica* and *C. nobile* reduce these inflammatory mediators by inhibiting key signaling pathways such as nuclear factor-ϰB (NF-ϰB) and cyclooxygenase (COX), which decreases tissue damage and promotes repair (Sharifi-Rad et al., 2018). Flavonoids, phenolic acids, and polysaccharides from *U. dioica* reduce the expression of inflammatory mediators, while terpenoids and flavonoids such as α-bisabolol, chamazulene, apigenin, and luteolin from *C. nobile* further reduce inflammation and enhance tissue regeneration (Salehi et al., 2020).

Additionally, both plants are abundant in antioxidant phytochemicals that scavenge reactive oxygen species (ROS), preventing oxidative damage to fibroblasts, keratinocytes, and endothelial cells while promoting collagen deposition, angiogenesis, and re-epithelialization (Kregiel et al., 2018; Salehi et al., 2020). *C. nobile* indirectly promotes wound healing by reducing inflammation and increasing fibroblast proliferation and collagen synthesis. *U. dioica* exhibits haemostatic activity attributed to vitamin K, tannins, minerals, and bioactive proteins that help maintain platelet function and stabilise clots (Sharifi-Rad et al., 2018; Taheri et al., 2022).

## 6. SUSTAINABLE MANAGEMENT AND ENVIRONMENTAL INTEGRATION

The global increase in AMR and the environmental impact of the overuse of antibiotics have driven the search for long-term solutions to control infection. Pharmaceutical residues released into soil and aquatic habitats promote the proliferation of antimicrobial resistance genes, which highlights the need for environmentally sustainable strategies for the control of SSIs (Murray et al., 2022; Larsson and Flach, 2022).

Medicinal plants like *U. dioica* and *C. nobile* have long-term potential for antibacterial activity due to their renewable nature, biodegradability, and varied phytochemical composition. Unlike conventional antibiotics, which target particular cellular processes, plant-derived metabolites such as flavonoids, phenolic acids, and terpenoids function through a variety of mechanisms, such as membrane disruption, biofilm inhibition, quorum-sensing interference, and efflux pump inhibition. This multitarget action may maintain broad-spectrum antibacterial efficacy while reducing selective pressure for resistance development (Ghosh et al., 2025; Angelini, 2024).

## 7. TRANSLATIONAL CHALLENGES AND FUTURE PERSPECTIVES

Despite the promising antibacterial, antibiofilm, anti-inflammatory, and wound-healing properties of *U. dioica* and *C. nobile*, a number of problems hinder their clinical translation for SSIs. There are currently few properly planned human trials evaluating therapeutic standardisation, pharmacokinetics, safety, and efficacy; the majority of the evidence comes from in vitro studies and animal models (Angelini, 2024; Atanasov et al., 2021).

One major limitation is the diversity in phytochemical content caused by differences in genotype, environmental conditions, growing techniques, harvesting stage, and associated microbiota. Because of this, ensuring consistent effectiveness becomes difficult due to this variability, stressing the importance of metabolomics profiling, chemical fingerprinting, and good quality control methods (Wang et al., 2024).

The lack of information regarding interactions in the phytobiome is yet another problem. The production of secondary metabolites as well as antibacterial activity are both affected by endophytes and rhizosphere microorganisms; however, the mechanism behind these processes is not yet clear. To find the essential plant-microbe interactions and the bioactive compounds they contain which suppress pathogens, it would be needed to use an integrated approach of multi-omics techniques like proteomics, metagenomics, metabolomics, and metatranscriptomics (Trivedi et al., 2020; Vannier et al., 2019).

In addition, extensive pharmacological and toxicological studies are required for clinical applications to examine the relevant aspects, including bioavailability, pharmacokinetics, optimal dosing, long-term safety, and potential herb–drug interactions. This is especially important for patients who are taking multiple medications (Taheri et al., 2022; Atanasov et al., 2021). Emerging technologies can further increase the stability and bioavailability of the bioactive chemical in order to increase targeted delivery into the infected wound, thus improving the treatment of biofilm-associated diseases (Fadaka et al., 2021; Wang et al., 2024).

## 8. CONCLUSION

The increasing number of surgical site infections (SSI) caused by multidrug-resistant (MDR) bacteria, especially *S. aureus* and *P. aeruginosa*, is a growing concern and a serious threat to public health. Although phytochemicals originating from plants have demonstrated considerable antimicrobial properties, recent studies have suggested that multitrophic phytobiome interactions between host plants, endophytes, rhizosphere microorganisms, and the environment play a critical role in their therapeutic efficiency. Therapeutic application of these medicinal plants is based on the fact that they are holobionts, where their microbiota participates in the formation of different bioactive compounds.

*U. dioica* and *C. nobile* could be considered as promising phytobiome-derived sources for the management of SSI due to their antibacterial, antibiofilm, quorum-sensing inhibitory, efflux pump inhibitory, antioxidant, anti-inflammatory, and wound-healing activities. The production, standardisation, and therapeutic efficacy of plant-derived antimicrobials can be improved by combining phytobiome science with developments in metagenomics, metabolomics, microbiome engineering, and green extraction technologies.

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## AUTHOR CONTRIBUTIONS

**Atul Singh:** Conceptualization, Writing, Writing-Review, Investigation.

**Mukta Sharma:** Supervision, Writing-Review, Editing.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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