2.0

REVIEW OF LITERATURE

The skin barrier protects the human body from invasion by exogenous factors and pathogenic microorganisms. A break in this barrier exposes the underlying tissue to microbial contamination, which can lead to infection, delayed healing, and further loss of tissue and organ integrity. Delayed wound healing and chronic wounds are associated with comorbidities, including diabetes, advanced age, immunosuppression and autoimmune disease. The wound microbiota can influence each stage of the multi-factorial repair process and influence the likelihood of an infection. Pathogens that commonly infect wounds, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, express specialized virulence factors that facilitate adherence and invasion. Biofilm formation and other polymicrobial interactions contribute to host immunity evasion and resistance to antimicrobial therapies. Hence, there is a prerequisite to develope a unique strategy to combat microbial infections at the wound site to promote wound healing processes (Uberoi *et al*., 2024). This review dwells on the impact of microbial infections at the wound site and the possible strategies to combat wound infections are discussed under the following headings.

2.1. Wound and Wound infections

2.2. Wound microbiota

2.3. Biofilm-forming bacteria

2.4. Antibiotics: a frontline defense against bacterial infections

2.5. Mode of actions and targets for antibacterial drugs

2.5.1. Inhibitors of cell wall biosynthesis

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2.5.3. Inhibitors of membrane function

2.5.4. Inhibitors of nucleic acid synthesis

2.5.5. Inhibitors of metabolic pathways

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2.1. Wound and Wound infections

Infectious diseases are mainly dependent on the nature of the organisms and the complexity of the human system. Depending on this, pathogenic organisms can be classified into five main types namely viruses, bacteria, fungi, protozoa, and worms. These organisms are evolutionarily dynamic and different infectious agents cause markedly different diseases thus reflecting the diverse processes of the action. Among those bacterial infections compose a significant proportion of global infectious diseases hence hurting human welfare and the economy. Bacteria cause emerging infectious diseases and it has been recognized as an important outcome of host-pathogen evolution leading to serious public health consequences. Infectious diseases are the leading cause of morbidity and mortality in worldwide, especially in developing countries. Bacteria possess the genetic ability to acquire and to transmit resistance to therapeutic agents. Due to the excessive use of antimicrobial drugs for the treatment of bacterial infections in humans, bacteria have developed several resistance

mechanisms such as target site modification, expression of the efflux pumps and metabolic inactivation, which contribute to the multidrug resistance fungi (Reygaert, 2018).

Each year, millions globally experience acute and chronic wounds, creating significant health concerns and resource burdens. The primary goal in wound management and treatment is to achieve rapid skin healing with optimal functional and aesthetic outcomes. Advances in understanding wound pathophysiology have sparked interest in multifunctional wound dressings that offer physical protection and maintain an optimal moisture environment. Acute wounds typically heal through a systematic process involving inflammation, migration, proliferation, and remodeling phases, quickly restoring skin barrier functions. However, not all wounds heal efficiently, leading to major economic and ethical challenges. In acute wounds, fibroblasts are typically spindle-shaped and elongated, actively participating in the healing process by aiding in wound contraction and closure. They exhibit high proliferative activity, producing collagen and extracellular matrix components essential for tissue repair. In contrast, fibroblasts in chronic wounds often appear irregular and disorganized, with reduced functionality. This results in lower proliferative activity and collagen production, contributing to impaired healing and prolonged inflammation. Chronic wounds, therefore, represent a significant clinical challenge, often requiring advanced therapeutic strategies to manage underlying dysfunctions and promote proper tissue regeneration (Demidova-Rice *et al.,* 2012).

Wound infections specifically occur when pathogenic microorganisms invade a wound, leading to local and sometimes systemic infection (Figure 1). Several factors increase the likelihood of wound infections, including the extent and nature of the wound, the presence of foreign bodies, and patient-related factors such as age, immune status, and comorbid conditions like diabetes. Environmental factors, such as the cleanliness of the wound care setting and the use of aseptic techniques, also play a crucial role (Ahovan *et al.,* 2022; Gilbert, 2020; Guo and Dipietro, 2010).

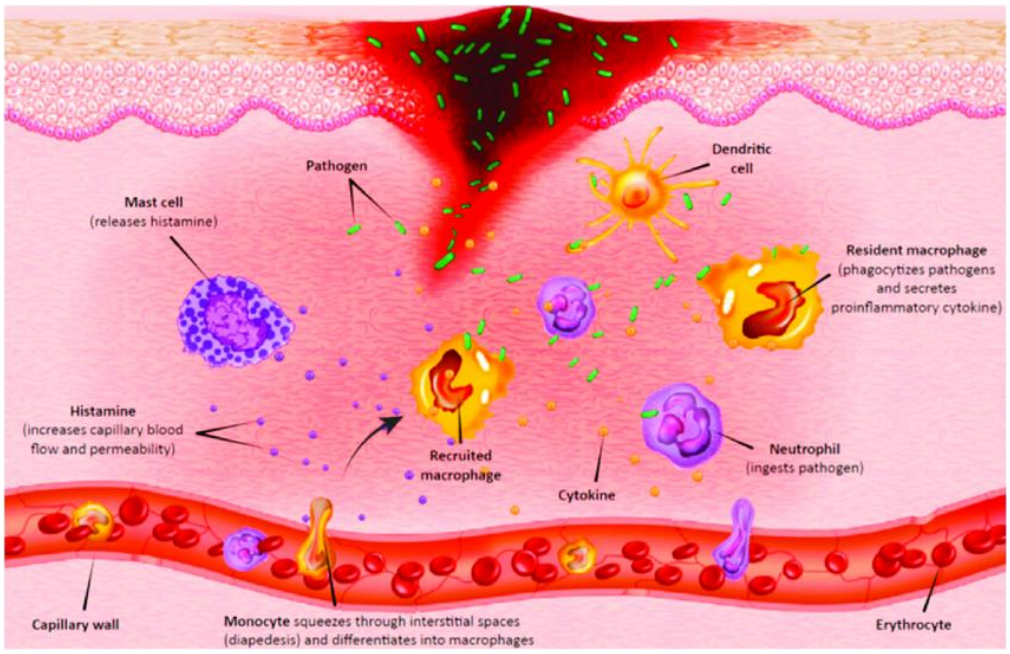

Figure 1: Wound infections by invasion of pathogens and action of the immune system in the host

As the global population ages, chronic wounds have emerged as a significant healthcare challenge. Wounds that do not heal and attain anatomical and functional integrity within a month are typically classified as chronic wounds. Common types of chronic wounds encompass diabetic ulcers, pressure injuries, and venous stasis ulcers. Standard treatments involve removing dead tissue from the wound, using appropriate wound dressings, and administering antimicrobial agents either through intravenous or local application (Wu *et al*., 2019). Chronic wounds often experience impaired and delayed healing due to local factors such as contamination and complications like diabetic, vascular, arterial, and pressure ulcers. Consequently, these wounds require prolonged and intensive treatment with therapeutic agents to ensure optimal recovery (Han and Ceilley, 2017).

Wound infections are recognized as a significant complication in the healing process, often delaying recovery and contributing to increased morbidity and mortality rates (Negut *et al.,* 2018). These infections arise when bacteria or other pathogens colonize the wound bed, overwhelming the body's immune defenses. This colonization can result from various sources, including the patient's microbiome,

contact with healthcare providers, or exposure to contaminated hospital surfaces. Such infections disrupt the natural stages of healing, prolonging inflammation and potentially leading to chronic wounds, especially in immunocompromised or vulnerable patients. The World Health Organization (WHO) estimates that 20–25% of surgical wounds encounter infections each year, highlighting the widespread impact on patient outcomes and healthcare resources (Mota *et al.,* 2021).

2.2. Wound microbiota

In general, healthy skin possesses its own microbiota, encompassing millions of bacteria, fungi, and viruses. Figure 2 explains the wound microbiota. The predominant bacterial communities on the skin are attributed to phyla such as *Actinobacteria, Firmicutes, Bacteroidetes,* and *Proteobacteria*. At the time of injury, the resident bacteria in the skin and the exogenous bacteria penetrate the wound. The intruded bacterial strains proliferate and colonize at the site effectively. In the initial stages of wound occurrence, bacteria such as *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae*, *Escherichia coli, Proteus, Klebsiella, Pseudomonas, Acinetobacter, and Stenotrophomonas* are predominantly noted. These bacterial strains can exacerbate the healing process and lead to further complications if not properly managed. Across chronic wounds of different etiologies, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* are the most prevalent genera, representing 63% and 25%, respectively. In a study on chronic venous leg ulcers, Gram negative bacteria accounted for 51%, primarily represented by *Pseudomonas aeruginosa* followed by *Escherichia coli, Serratiamarcescens, Enterobacter cloacae,* and *Morganella morganii.* Gram-positive bacteria constituted 48.3%, with *Staphylococcus aureus* as the predominant species (Cavallo *et al.,* 2024; Okur *et al.,* 2020). Among various bacterial pathogens, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the two main pathogens often identified at the wound sites and promote the delaying of wound healing processes (Figure 3).

Pseudomonas aeruginosa is a highly virulent, rod-shaped bacterium classified as Gram-negative and belonging to the *Pseudomonadaceae* family.

It is widely distributed in various environments such as water, plants, soil, and animals. While it typically doesn't cause infections in healthy individuals, it poses a significant threat to those with compromised immune systems. In particular, *Pseudomonas aeruginosa* is known for its remarkable ability to form robust biofilms. These biofilms act as barriers to wound healing and contribute to the bacterium's high resistance to antimicrobial therapies. As a result, infections caused by *Pseudomonas aeruginosa* can be challenging to treat, especially in individuals with weakened immune responses (Vetrivel *et al.,* 2021).

Staphylococcus aureus is a Gram-positive bacterium known for causing a variety of infectious diseases in both humans and animals. These infections can vary from minor skin and soft tissue issues to more severe and potentially life-threatening conditions like blood stream infections (bacteremia/septicemia). Additionally, *Staphylococcus aureus* can form biofilms, which serve to slow down or block the diffusion of antimicrobial drugs, thereby impeding the drugs' effectiveness in reaching the cells within the biofilm structure (Idrees *et al.,* 2021).

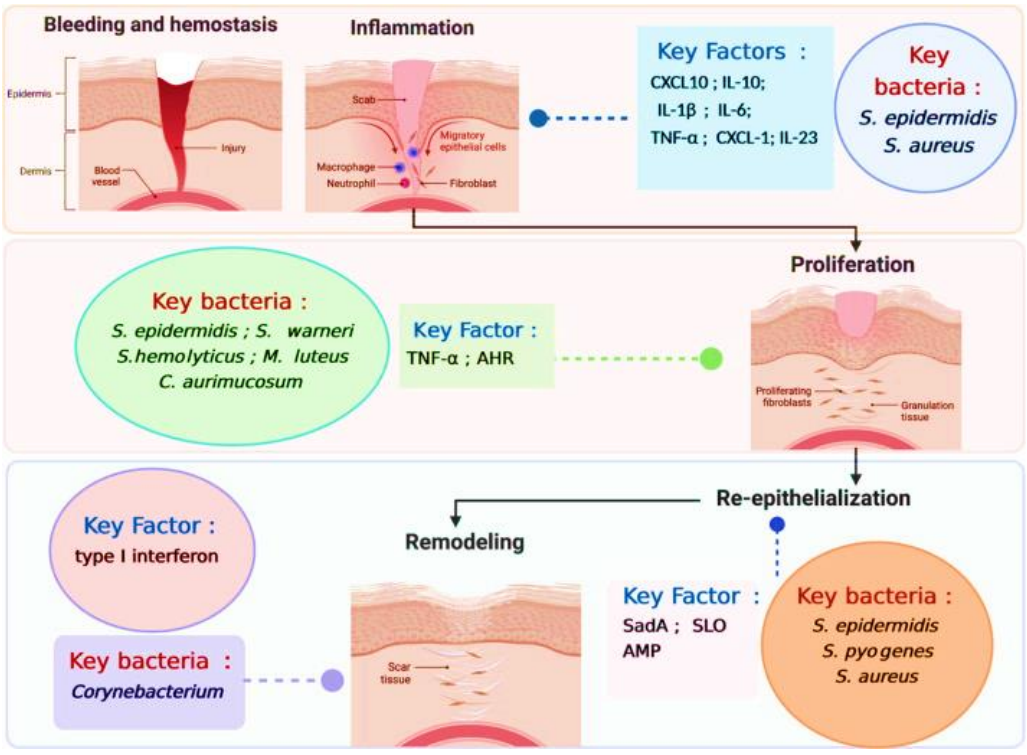

Figure 2: Wound microbiota responsible for impaired wound healing

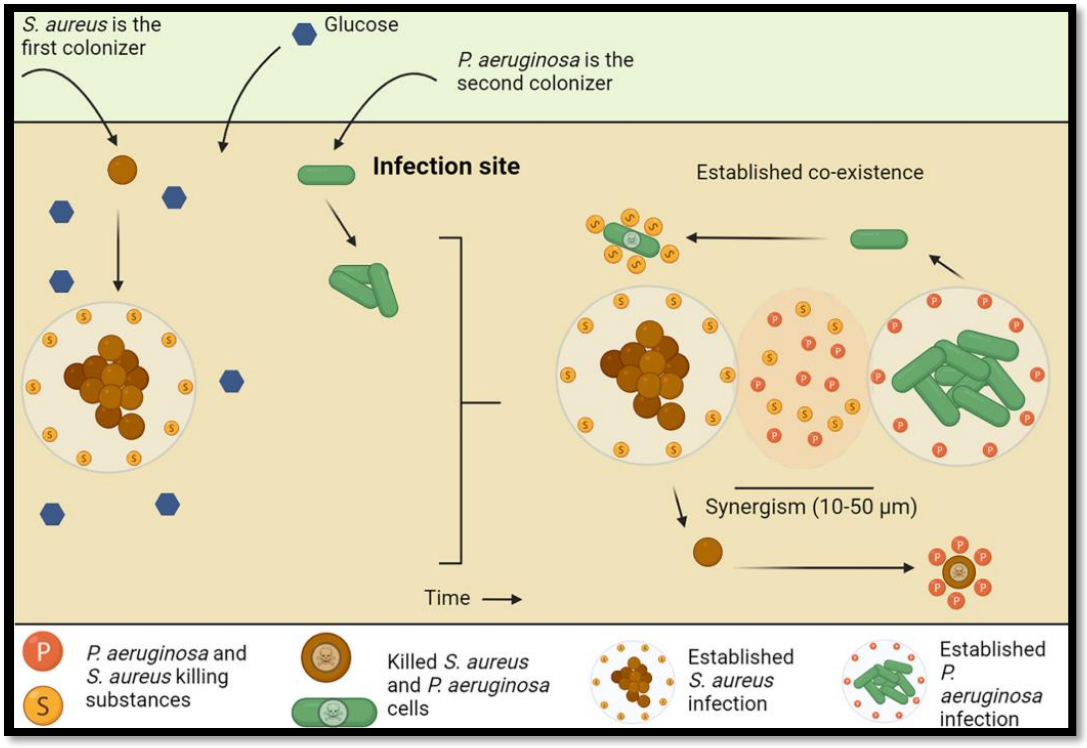

Figure 3: Colonization of *Staphylococcus aureus* and *Pseudomonas aeruginosa* at wound sites

2.3. Biofilm-forming bacteria

One of the preferred growth states for bacteria is a biofilm which exists in majority of bacteria. Naturally, microorganisms exist either as free-floating cells or enclosed within an architectural structure known as biofilms. Biofilms may be regarded as “Microbial communities consisting of various bacterial cells living in close association by encasing itself in an extracellular matrix made up of polymeric substances, adhered to a substratum or each other and exhibit an altered phenotype”. Biofilms are heterogenous, with 15% of cells usually in microcolonies and 85% comprising polymeric extracellular substances (Karygianni *et al.,* 2020; Donlan, 2002).

The biofilm matrix's composition varies among species but generally contains proteins, polysaccharides, and nucleic acids (Flemming *et al*., 2016). Biofilms are polymicrobial with a tremendous rivalry for nutrients and space (Figure 4). The cohabitation of numerous microbes on a surface promotes

cooperative behaviours such as metabolic cooperation, horizontal gene transfer, and other synergies leading to an increased potential for microorganisms to survive and exhibit resistance to antimicrobial agents (Goudarzi *et al.,* 2021). In such an environmental niche, the bacterial communities are regulated by various biological processes and use advanced genotypic events to promote different molecular mechanisms and phenotypes necessary for survival in the new environment during pathogenesis and antibiotic treatment (Jamal *et al.,* 2018). Biofilms form on many surfaces, including living tissues, hotels, industrial places, labs, wastewater channels, bathrooms, and indwelling medical devices. They are frequently found on hard surfaces immersed in or exposed to an aqueous solution. Nearly 99.9% of all microbes can develop biofilms on biotic and abiotic surfaces (Vetrivel *et al.,* 2021).

Biofilms, act as protective structures and significantly contribute to persistent infections that are often difficult to treat. These structures, which can resist both antibiotics and the immune system, play a crucial role in the development and severity of infections, especially those involving multiple types of microorganisms. Additionally, in polymicrobial wound infections, biofilms create an environment conducive to exchanging antibiotic resistance genes through mobile genetic elements, avoiding immune responses such as phagocytosis, and dampening inflammatory reactions. To elaborate further, the anaerobic conditions within biofilms favor the selection of persistent microbial strains, their hydrophobic nature facilitates the efflux of antibiotics and inflammatory cytokines, and the presence of multiple microorganisms fosters horizontal gene transfer (HGT) (Dehbashi *et al.,* 2024; Azevedo *et al.,* 2020; Metcalf and Bowler, 2020).

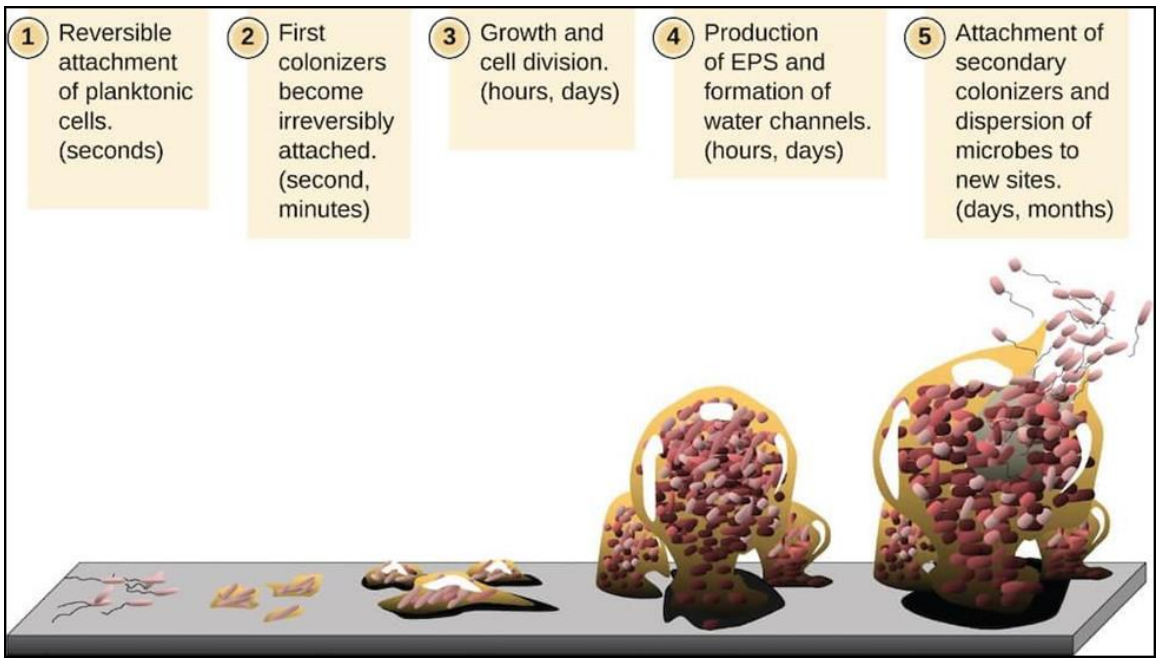

Figure 4: Mechanism of biofilm formation by pathogenic bacteria

The biofilm-producing bacteria present a formidable challenge from the treatment perspective (Figure 5). Of note, it becomes less susceptible to human immune defense mechanisms and also uses its own sophisticated mechanisms to develop resistance. Usually, biofilms can persist on surfaces over a longer period to boost the chronification of the wounds. Bacteria encased in biofilms are 1000 times more resistant to conventional antibiotics, thus, an effective strategy is required to eliminate the biofilm forming capabilities of the pathogens responsible for wound infections (Wolcott *et al*., 2010). Among the various bacteria responsible for wound infections, *Staphylococcus aureus* and *Psuedomonas aeruginosa* are considered as the most notorious pathogens with limited treatment options (Munyeshyaka *et al*., 2021).

Pathogens within biofilms can accelerate both chemical and biological reactions, leading to metal corrosion in pipelines and tanks. Additionally, when biofilms accumulate on surfaces such as plate heat exchangers and pipelines, they can impede heat transfer efficiency, particularly if they become sufficiently thick. Furthermore, certain populations of bacteria within biofilms exhibit

antibiotic resistance, which poses challenges in medical, agricultural, and industrial contexts. This resistance can complicate efforts to control microbial growth and manage infections, leading to the persistence and spread of microbial strains (Satpathy *et al.,* 2016).

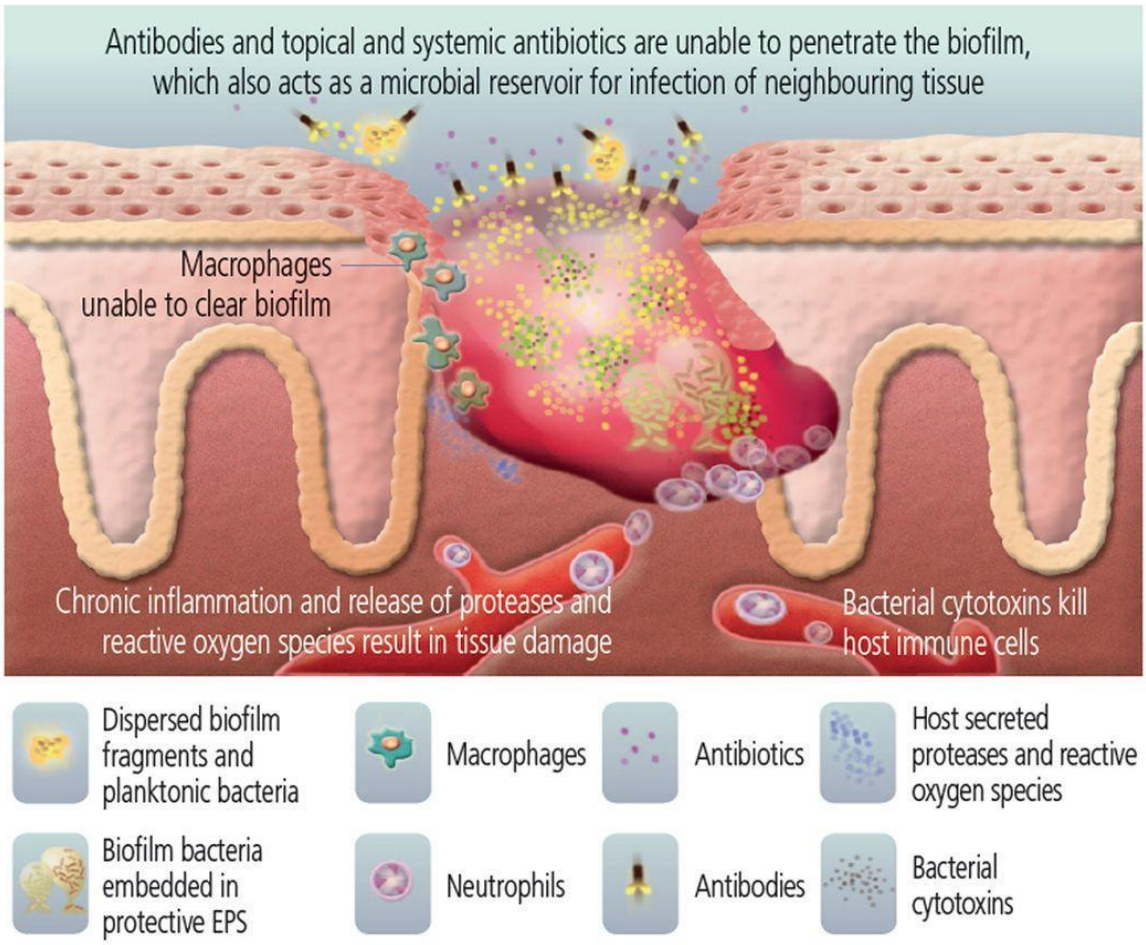

Figure 5: Bacterial biofilms as potential threat in fastidious wound healing processes

2.4. Antibiotics: a frontline defense against bacterial infections

The explosive growth in the use of antimicrobial therapy has provided a degree of control on microbial-related diseases in humans. Many studies revealed that various bacteriostatic or bactericidal antibiotics can assist wound closing, still their positive influence on wound healing is regularly unnoticed. Even if countless antibiotics are known to be effective against infection-producing microorganisms,

merely quinolones, tetracyclines, aminoglycosides and cephalosporins have been applied to produce antimicrobial wound dressings (Negut *et al*., 2018).

Empirical antibiotic therapy for virtually all infected wounds should be active against *Staphylococcus aureus,* as it is the most commonly isolated pathogen in most settings. Additional coverage for other organisms (potentially including aerobic Gram-negative and anaerobic organisms) may be appropriate for severe infections or for patients with findings that suggest these organisms. Selecting an antibiotic regimen, including the dose and route of administration, depends on many factors. For an acute, severe (e.g. accompanied by sepsis or rapid progression) wound infection, intravenous therapy is usually appropriate, often with a combination of bactericidal agents. When the infection has clinically responded and microbiological results are available, consider simplification (narrowing the spectrum of therapy), changing from intravenous to oral ('switch') therapy with an agent with good orally bioavailability, or stopping therapy if an alternative (non-infectious) cause has been established (Lalonde *et al*., 2022).

While systemic antibiotic therapy is appropriate for most clinically infected wounds, for superficial, mild infections topical antimicrobial (antibiotic and non-antibiotic) agents may have several potential benefits. Most noteworthy: a small amount can achieve high levels directly at the site of infection; it avoids systemic adverse effects; and, it allows use of agents that cannot be administered systemically. There is much regional and geographical variation in the use of topical antibiotics, and in resistance rates of pathogens to these agents. We advise avoiding using antibiotics (as opposed to antiseptics) topically for treating wound infections as there is limited evidence of their effectiveness and they often select for resistant colonizing bacteria. Furthermore, topical treatment may cause peri-wound skin irritation, rash, eczema or impairment of wound healing. Concerns also remain about possible cytotoxic effects of topical antimicrobials on the wound bed, especially with long-term treatment. A few topical antibiotics (e.g. fusidic acid, mupirocin, neomycin) may be appropriate to treat localized acute superficial skin infections, such as impetigo and folliculitis, but almost all other clinically infected wounds require systemic antibiotic therapy. Topical

metronidazole may be beneficial in reducing wound odour, but the evidence is weak (De Gaudio *et al*., 2011).

Topical antibiotics and antiseptic agents have been widely utilized for the prevention and treatment of localized skin and wound infections (Williamson *et al*., 2017). Molecular iodine stands out as one of the most powerful and versatile antimicrobial agents, renowned for its broad-spectrum effectiveness (Eggers, 2019). It is often incorporated into specialized delivery systems, such as cadexomer iodine, for targeted and sustained administration in wound care and skin treatments. Additionally, silver is another potent antimicrobial agent with broad-spectrum properties. It is commonly utilized in various types of dressings to promote healing in wounds that are affected by microbial infections (Woo *et al.*, 2021; Bruna *et al*., 2021).

Rifampicin (RIF), a hydrophobic semisynthetic antibiotic, is commonly used in the treatment of a large variety of bacterial infections, including those mediated by *Mycobacterium* spp., Gram-positive cocci (*Staphylococci* and *Streptococci*), and certain Gram-negative pathogens (Drapeau *et al*., 2010). RIF is always used in combination with other antibiotics to treat *Staphylococcus aureus*-associated bacterial infections due to its high susceptibility to develop resistance. On the other hand, ciprofloxacin (CIP) is a fluoroquinolone derivative that acts as an antibacterial agent inhibiting the growth of both Gram-positive and Gram-negative bacteria. It has been reported that its use on infected topical wounds improves wound healing (Zhang *et al*., 2018).

Chloramphenicol has a broad spectrum of activity against Gram positive and Gram negative bacteria, rickettsias, and *Chlamydia*. Chloramphenicol ointment is indicated for the treatment of bacterial conjunctivitis, but little evidence exists for its effectiveness in prophylaxis or treatment of wound infection. Despite this, it is regularly used in areas outside its main indication. Before our study, several of the investigating general practitioners had applied it to sutured wounds as prophylaxis against wound infection. A survey of plastic surgeons reported that 66% used chloramphenicol eye ointment in their practice,

mainly as prophylaxis against infection. The ointment has been used as an adhesive for replacement of the nail bed. A comprehensive Medline search found only one other study relating to the use of topical chloramphenicol ointment on wounds; this study investigated the application of chloramphenicol ointment to wounds after hip replacement (Das and Velpandian, 2019).

2.5. Mode of actions and targets for antibacterial drugs

The treatment of bacterial infections is increasingly complicated by the ability of bacteria to develop resistance to antimicrobial agents. Antimicrobial agents used for the treatment of bacterial infections are often categorized according to their principal mechanism of action. There are six major modes of action: (1) interference with cell wall synthesis, (2) inhibition of protein synthesis, (3) interference with nucleic acid synthesis, (4) inhibition of a metabolic pathway, (5) inhibition of membrane function, (6) inhibition of ATP Synthase. Therefore, according to its mechanism of action, the targets of antibacterial drugs include cell membrane, cell wall, protein synthesis, nucleic acid synthesis, and biological metabolic compound synthesis (Figure 6) (Reygaert, 2018; Bbosa *et al*., 2014).

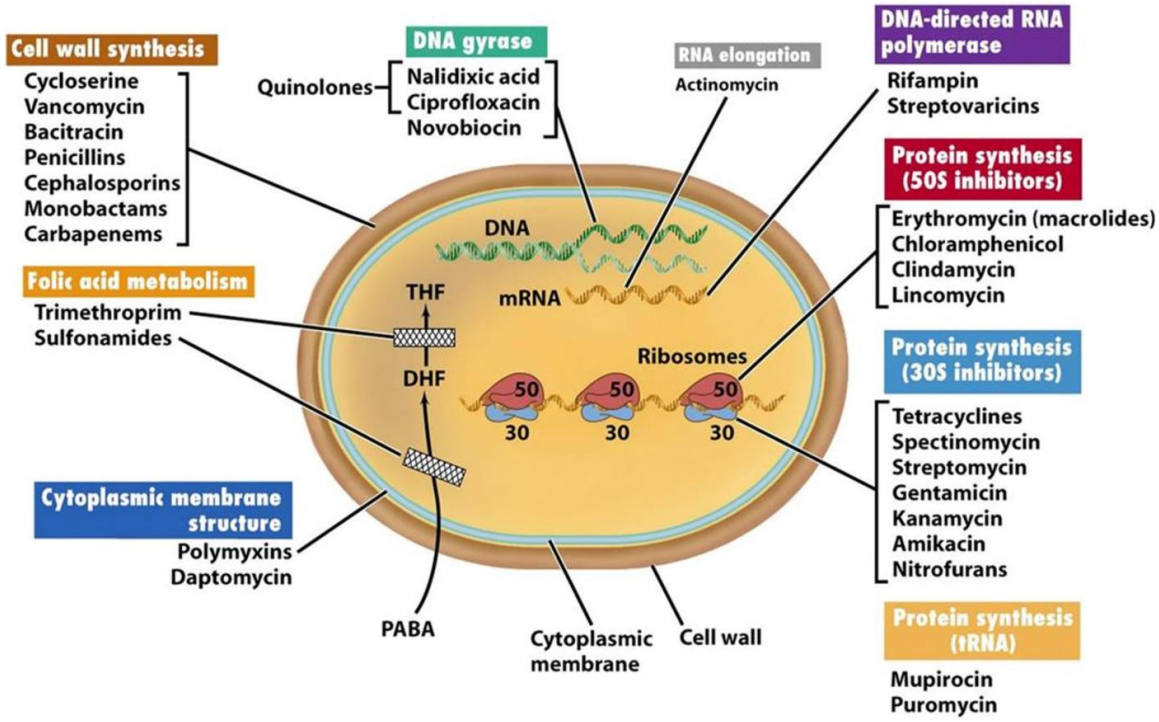

Figure 6: Mode of action of antibacterial drugs

2.5.1. Inhibitors of cell wall biosynthesis

Bacterial cells are surrounded by cell walls made of peptidoglycan. Peptidoglycan biosynthesis is essential to the integrity of the cell wall structure, and it is the outermost layer and the main component of the cell wall. Specific antibiotics interfere with the biosynthesis of peptidoglycans, thereby destroying the integrity of the cell wall. Since mammalian cells do not have the peptidoglycan wall structure, inhibition of cell wall peptidoglycan biosynthesis is a preferred target for the discovery of antibacterial agents, and at the same time has no significant negative impact on mammalian host cells (Silver, 2003).

2.5.2. Inhibitors of protein biosynthesis

Protein synthesis is a complex, multi-step process involving many enzymes and conformational alignment. However, most antibiotics interfere with the 30S or 50S subunits of the 70S bacterial ribosome to block bacterial protein synthesis. For example, tetracyclines, including doxycycline, prevent the binding of aminoacyl-tRNA by blocking the A (aminoacyl) site of the 30S ribosome. They are capable of inhibiting protein synthesis in both 70S and 80S (eukaryotic) ribosomes (Franklin and Snow, 1989).

2.5.3. Inhibitors of membrane function

The bacterial membrane provides selective permeability for cellular homeostasis and metabolic energy-transduction. Several antimicrobial agents interfere with multiple targets through the interaction of a lipophilic moiety with the bacterial membrane, leading to the destruction of membrane structures and functional impairment. At present, antibacterial agents directed against the cytoplasmic membrane components of bacteria have been reported, and they can act on both Gram-negative and Gram-positive bacteria (Epand *et al*., 2016).

2.5.4. Inhibitors of nucleic acid synthesis

Antibiotics can inhibit replication, transcription, and folate synthesis of microorganisms. Quinolone drugs can interfere with DNA synthesis by inhibiting topoisomerase, an enzyme involved in DNA replication. For example, the

second-generation quinolone drugs levofloxacin, norfloxacin, and ciprofloxacin are active against both Gram-negative and Gram-positive bacteria. There are also antibiotics that interfere with RNA synthesis by inhibiting RNA polymerases, such as doxorubicin and actinomycin D (dactinomycin). They interfere with bacterial and mammalian systems and are therefore most commonly used as antineoplastic and antitumor drugs, attacking rapidly growing malignant cells as well as normal cells (Franklin and Snow, 1989).

2.5.5. Inhibitors of metabolic pathways

Bacterial metabolism inhibitors are a class of antibiotics that target nucleic acid and amino acid synthesis pathways. Tetrahydro-folic Acid (TH4) is a key coenzyme used to synthesize nucleic acids and certain amino acids in all life forms. Bacteria synthesize their folic acid from the precursor para-aminobenzoic acid (PABA). Bacterial metabolism inhibitors affect bacterial metabolic pathways by interfering with bacterial TH4 synthesis (Kumar *et al*., 2022).

2.5.6. Inhibitor of ATP synthase

ATP synthase is the principal energy-generating enzyme in all organisms from bacteria to vertebrates through oxidative phosphorylation or photophosphorylation. Bacteria can produce ATP through substrate-level phosphorylation of fermentable carbon sources or oxidative phosphorylation using respiratory chains and ATP synthase. Some antibiotics have been found to inhibit oxidative phosphorylation of ATP synthase to affect the energy production of bacteria, which in turn kills bacteria (Althaher and Alwahsh, 2023).

2.6. Emergence of antimicrobial resistance and multidrug resistant strains

Antibiotic resistance is a worldwide concern because of its current and possible future impact on global health and the costs of national healthcare systems, mainly due to more limited treatment options. Antimicrobial resistance (AMR) is recognised by the World Health Organization (WHO) as a major global health threat to humanity, estimated to lead to 10 million deaths annually by 2050. In a recent systematic review of the global burden of AMR on health, four

sub-regions of Africa were all found to have rates of death attributable to bacterial AMR higher than any other global sub-region: Central, Eastern, Southern and Western Africa each had a AMR-attributable mortality rate of over 75/100,000. Globally, bacterial infections of the skin and subcutaneous tissues are the sixth highest infectious syndrome causing AMR-attributable death: only lower respiratory tract infections (LRTI), bloodstream infections, intra-abdominal infections, urinary tract infections and tuberculosis have higher AMR-attributable mortality (Monk *et al*., 2024).

Factors contributing to the growth of antibiotic resistance are complex, but clearly the rate of antibiotic resistance is directly related to the level of antibiotic use. This document is concerned only with clinical prescribing for humans, an area over which clinicians have more control and in which improvements may occur relatively quickly. Clinicians, as well as the public, must understand that antibiotic consumption is associated with the development of antibiotic resistance at not only the individual patient level, but also at community, national and regional levels. Prior treatment of a patient with commonly used antibiotics greatly increases that person's risk of infection with an antibiotic-resistant organism, which is directly responsible for increases in morbidity, length of hospitalization, mortality and cost of healthcare (Lipsky *et al*., 2016).

Despite the use of prophylactic antibiotics pre- and postoperatively and other preventive measures such as improved operating room ventilation, sterilization methods, use of barriers, and surgical technique, SSIs still remain a burden to postoperative patients. This has majorly been attributed to increasing emergence of antimicrobial resistance due to irrational use of antibiotics. This inappropriate use of antimicrobials increases selection pressure favoring emergence of pathogenic drug resistant bacteria (Hope *et al*., 2019).

The bacterial strains resistant to the majority of antibiotics (commonly known as “super-bugs”) are not only involved in cases of pneumonia and infections affecting the urinary tract and skin, but also in often clinically neglected eye infections. The main culprits are *Staphylococcus aureus* (and more recently,

Staphylococcus epidermidis), which are known to be resistant to methicillin, and *Neisseria gonorrhoeae*, which show increased resistance to penicillin, tetracycline, and, particularly, ciprofloxacin. However, other frequently encountered bacteria, such as *Enterococcus faecalis*, *Acinetobacter baumannii*, or *Pseudomonas aeruginosa*, have become increasingly resistant to some relatively new antibiotics as the latest-generation cephalosporins, carbapenems against Gram-negative bacteria, and daptomicin and glycopetides against Gram-positive bacteria. Similarly, this happened to the older antibiotics that are now sometimes seen as “last-chance drugs”, such as colistin, that can still be used against Gram-negative bacteria despite the clinical appearance of bacteria harboring the colistin-resistance mcr-1 gene. There has also been a dramatic increase in the resistance of *Enterobacteriaceae* (especially *Escherichia coli* and *Klebsiella* spp.), and recent data have indicated an increase in bacterial enzymes that give rise to multi-resistance to bectalactams, such as extended-spectrum β-lactamases (ESBL), and carbapenems, such as carbapenemases (KPC). Antibiotic resistance and biofilms are also associated with the pathogens causing eye infections, and factors such as prescribing antibiotics without identifying the germ, short-term treatments, and repeated exposure to the same antibiotic are now considered the main contributors to antibiotic resistance and treatment failure (Drago, 2019).

Chloramphenicol is a broad-spectrum antibiotic that had been partially abandoned in developed countries because its systemic administration is associated with fatal aplastic anemia but is now widely used in response to the continuing problem of multi-drug resistant pathogens. Chloramphenicol has been indeed often blamed for being a possible cause of aplastic anemia by postulating that the p-NO2 group of chloramphenicol is the structural feature underlying this adverse event, especially in case of viral hepatitis. This last eventuality causes an abnormal metabolism of this molecule, and the reduction of the nitrobenzene ring to a nitroso group on chloramphenicol may lead to potential DNA damages in the stem cell, and potentially to cell death (Das and Velpandian, 2019).

Other studies have hypothesized that, also, particular bacteria of the gut microbiota may metabolize chloramphenicol to toxic metabolites. Chloramphenicol and its fluorinated derivative florfenicol represent highly potent inhibitors of bacterial protein biosynthesis. As a consequence of the use of this drug in human and veterinary medicine, bacterial pathogens of various species and genera have developed and/or acquired resistance. Several mechanisms responsible for resistance to chloramphenicol can occur, i.e., pump efflux, acetyltransferases, or transposons, and other mobile genetic elements carrying resistance genes (Figure 7) (Drago, 2019).

Multi-drug resistance development in bacterial pathogens relies on several mechanisms, such as drug targ*et al*teration, action of enzymes on the drug metabolite, increased efflux of antibiotics, and biofilm formation. The role of biofilms in antimicrobial resistance (AMR) is incredibly intricate and can significantly contribute to resistance. Bacteria residing within a biofilm can display a 10 to 1,000-fold increase in antibiotic resistance compared to similar bacteria in aplanktonic state. However, nearly 75% of these same isolates were entirely resistant to vancomycin when tested within a biofilm. This pattern is also observed with organisms like *Klebsiella pneumoniae,* which may appear susceptible to certain antibiotics when tested in an aqueous solution but become highly resistant when tested within a biofilm (Weber *et al*., 2023). Treatment options exclusively targeting the biofilm regulatory genes are scarce, and the identification of novel drug metabolites with such capabilities could be beneficial for treating wound infections. Gram-positive bacteria utilize strategies such as altering target sites, deploying efflux pumps, producing enzymes like β-lactamases to degrade antibiotics, and forming biofilms that protect them from antibiotics and the host's immune response. On the other hand, Gram-negative bacteria rely on their outer membrane's selective permeability to limit antibiotic entry, utilize efflux pumps, modify porins to restrict antibiotic uptake, and produce enzymes that break down antibiotics. These mechanisms collectively contribute to the significant challenge of treating infections caused by resistant bacterial strains (Figure 8).

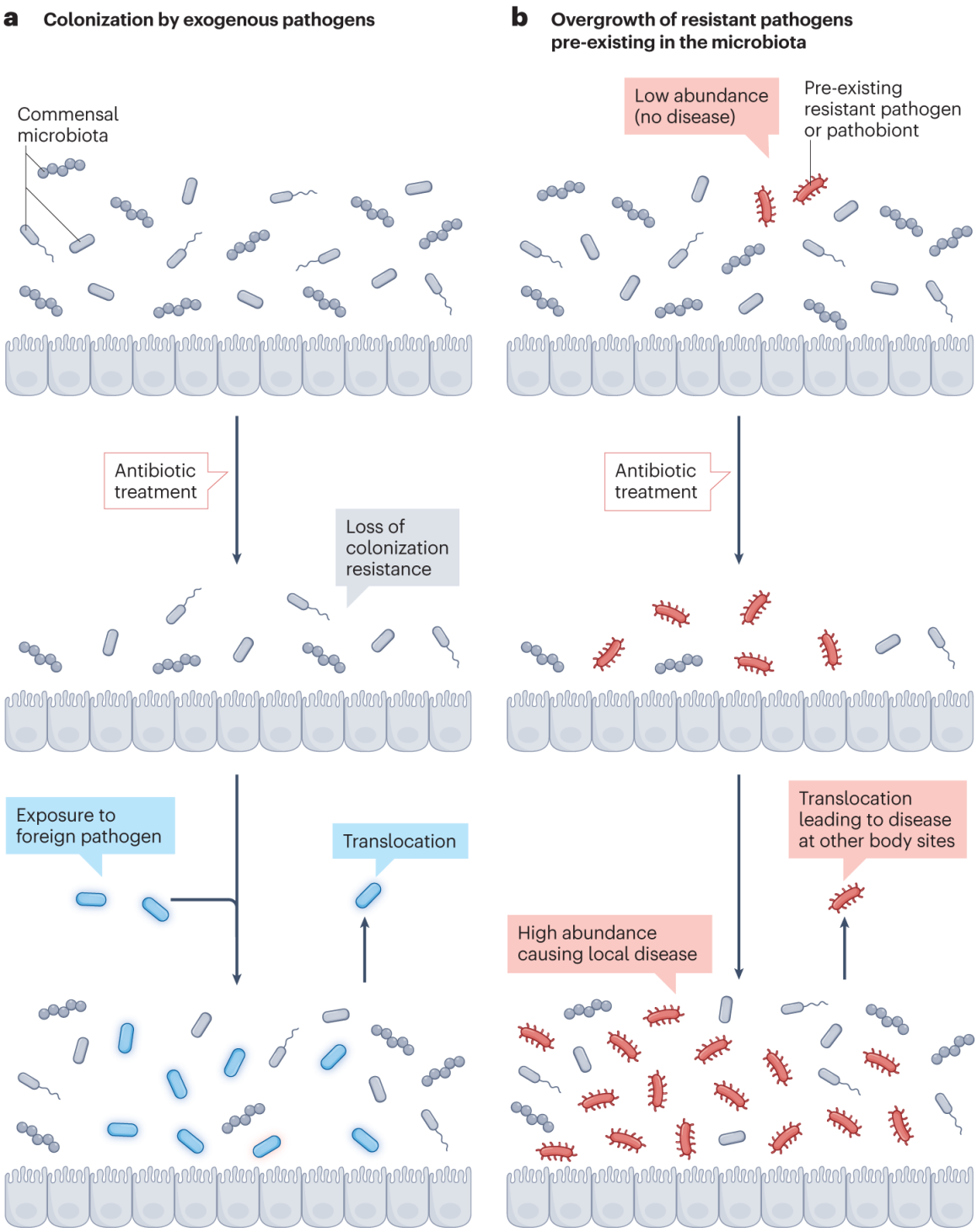

Figure 7: Antibiotic-induced collateral damage to the wound microbiota and associated infections

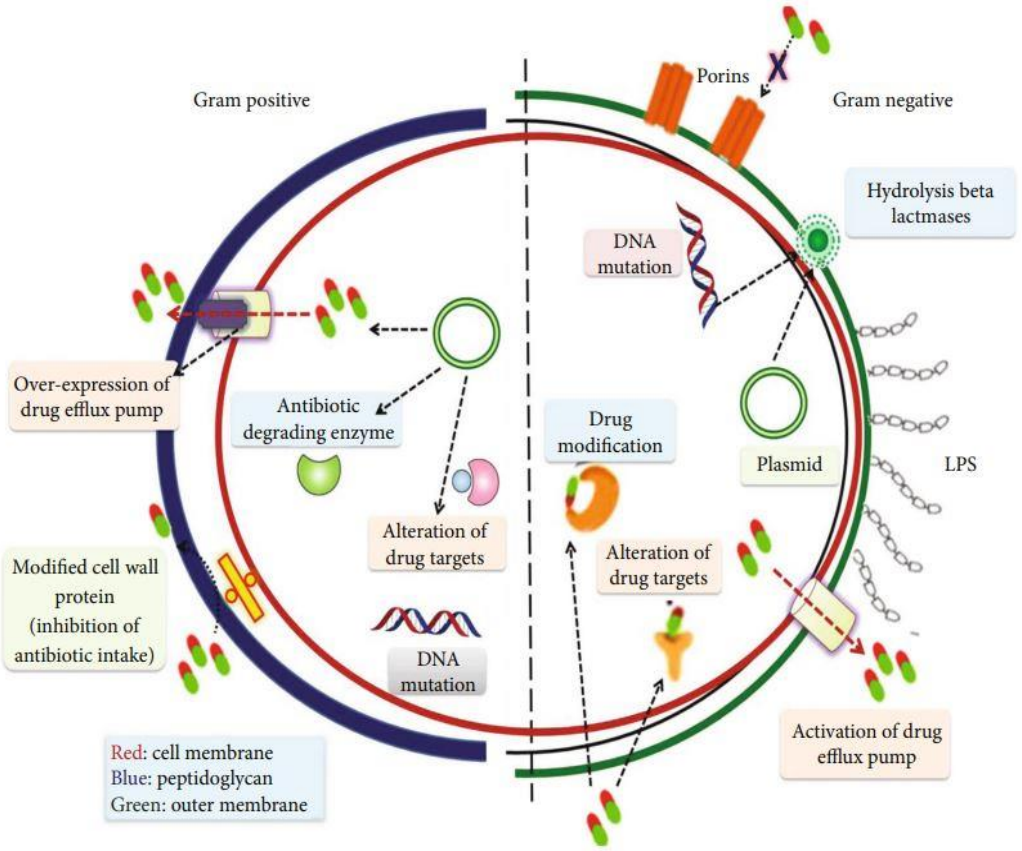

Figure 8: Emergence of antibacterial resistance in Gram-positive and Gram-negative bacteria

It has been suggested that the number of infections caused by resistant microbes is increasing, and that there is a need for a precise estimate of the burden of antibiotic resistance in developed countries in order to be able to introduce interventional strategies capable of limiting or preventing the spread of resistant infections.

2.7. Medicinal plants and their active components for wound healing applications

Herbal medicines (HM), which are known as complementary and alternative medicines, have been used over the decades to treat medical ailments and promote wellness through their bioactive ingredients. Over time, humans have discovered which plant species are more effective as treatments for specific illnesses. The use of herbal medicine is a standard practice in traditional

Chinese Medicine, Ayurveda, Unani, Russian herbalism, and other medical systems to apply botanicals topically to treat wounds and other dermatological problems. Moreover, the biological functions of botanicals' secondary metabolites are what give rise to their pharmacological effect (Albahri *et al*., 2023). Wound healing uses medicinal plants with a variety of phytoconstituents, with the main components having antibacterial and antifungal activities being Flavonoids, Tannins, Saponins, Terpenes, terpenoids *etc* (Figure 9). 1) Stimulation of Wound healing boosts homeostasis, contains hydroxyproline, increases tensile strength, and is an antioxidant. By the secondary metabolites of plants, such as Tannins, Flavonoids, β- carotene. 2) Plant glycosides decrease the wound closure time; these can increase epithelialization, homeostasis and stimulate granulation of tissues. 3) Vitamins and minerals of plants increase wound healing rate and wound contraction, and these reduce the infection. 4) Natural plant steroids and triterpenes increase epithelialization, increasing wound closure and collagenisation. Carbohydrates as energy sources are used in collagen synthesis. Thus, these compounds play an essential function in speeding up the recovery process by upregulating collagen synthesis during the maturation stage (Pathak and Mazumder, 2024).

Traditional knowledge of herbal medicine is disappearing which should be conserved and will give the baseline information for the chemist to discover new drugs. This is one of the steps taken towards documenting treasures of indigenous knowledge on the wound-healing property of medicinal plants. In ancient times, phytotherapy has been able to treat cutaneous wounds efficiently, reduce the onset of infections, and minimize the usage of antibiotics that cause critical antibiotic resistance. In diverse animal experimental models, secondary plant metabolites or active chemicals are the active agents that stimulate the process of wound repair. The most significant and specific examples include Asiatic acid, Madecassic acid, and Asiaticoside from *Centella asiatica*, curcumin from *Curcuma longa* and isatin, and indirubin from *Couroupita guianensis*. Aubl.

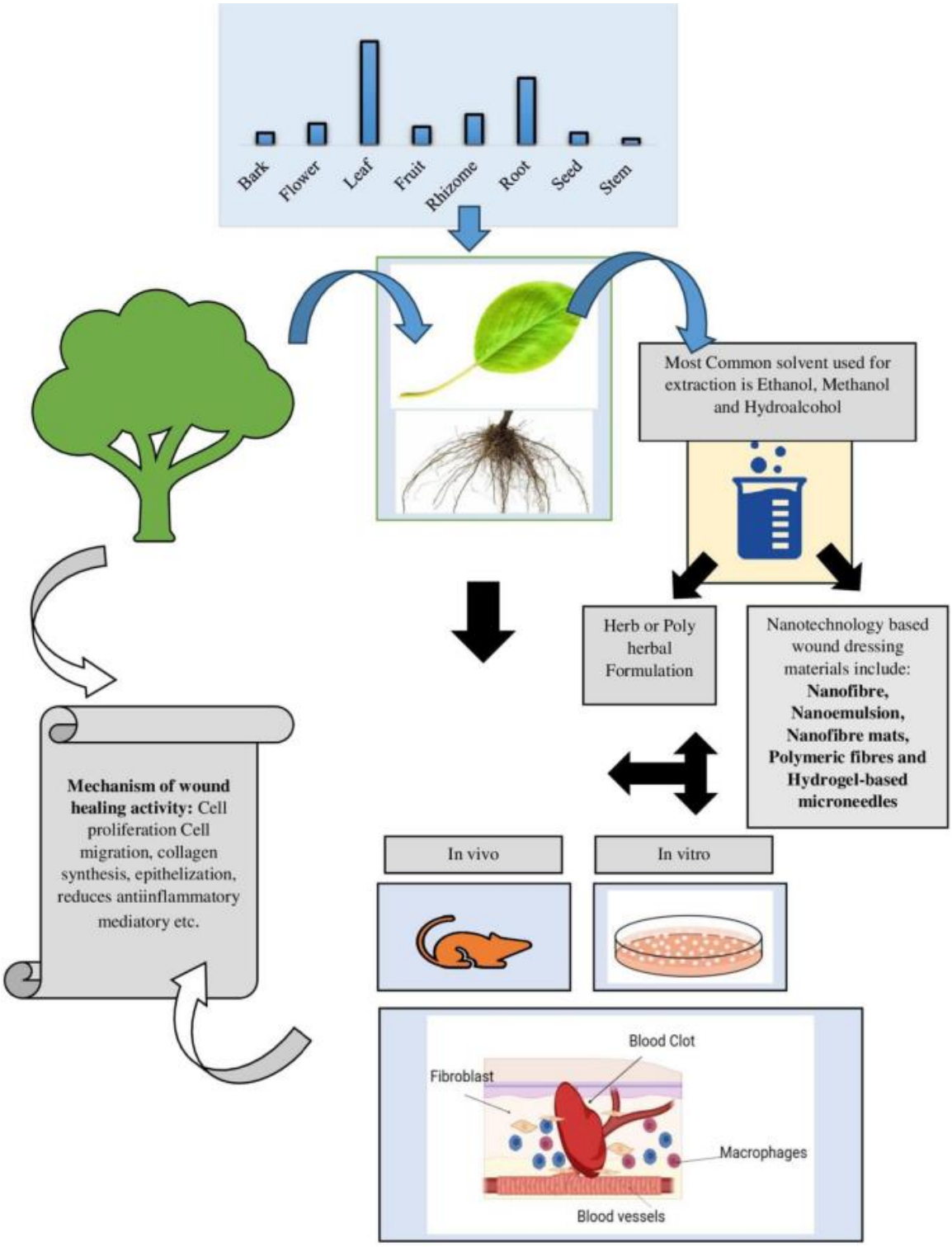

Figure 9: Medicinal plants in the treatment of wound infections

There are a remarkable number of wound-healing botanicals that are widely used in the Northern Hemisphere, including *Achiella millefolium, Aloe vera, Althaea officinalis, Calendula officinalis, Couroupita guianensis*. Aubl, *Matricaria chamomilla, Curcuma longa,* Eucalyptus, Jojoba, plantain, pine, green tea, pomegranate, and inula. Some studies have advocated for a combination of honey wound dressings alongside antibiotics in instances where sepsis is a concern. Combination therapy resulted in a synergistic response in scenarios where antibiotic resistance was previously observed (Coates *et al.*, 2020, Liu *et al.*, 2015).

Phytochemical content is to resolve their remedial features in wound repair, plant-derived substances were considered for their wound-healing activity as flavonols, flavanones, isoflavones, flavanols, flavonolignans, proanthocyanidins, cardiac glycosides, saponins, steroids, and tannins, β-glucans, bromelain, curcumin. Quercetin and rutin are flavonoids with strong antioxidant, antimicrobial, and anti-inflammatory effects but limited water solubility. It was revealed that incorporating quercetin and rutin into polycaprolactone and chitosan oligosaccharides to form a new bioactive electrospun nanofiber membrane exhibited superior efficacy among all nanofiber membranes for burn injuries. It was disclosed that different botanicals and medicinal plants are widely used as a topical treatment for wound repairing, such as *aloe vera,* banana leaves, turmeric*, Couroupita guianensis*, *Centella Asiatica, Rosmarinus officinalis*, and *Calendula officinalis* (Kasinathan *et al*., 2024).

Natural products such as plant extracts and other plant-derived products and their phytochemicals assist in managing inflammatory diseases, exert antimicrobial effects, and might aid skin tissue regeneration. The wound itself is a rupture of the epithelial integrity of the skin that might be caused by violence or trauma. The rupture of epithelial integrity is trailed by disruption of the structure and function of underlying normal tissue. They could remove oxidative stress and lower inflammation. The wound-repairing ability of different plant extracts and their actives is proven in wound-curing animal models. Such plants improved collagen deposition, the proliferation of epithelial cells, and angiogenesis in diabetic and nondiabetic animal models. Different types of plants are widely used

in managing wounds and injuries from previous scientific research (El-Sherbeni, and Negm, 2023). This process occurs through stimulating autolytic debridement, inducing an osmotic response, drawing water from the cells, and subsequently increasing the hydration at the wound site; this hydration needs to soften the slough at the wound site, and along with the denaturation of fibrin, it allows the slough to detach. Observing nature and perception of their traditional knowledge about medicinal properties pave the way for treating diseases. A combination of many parts of the same plant or parts from different plants or collective species of plants was used in wound healing, as cited. Many herbs and plants were utilized as medicine in dietary forms. There is an increased awareness of using traditional plants to cure ailments. Due to the cost and side effects of other drugs, there is an urge for documentation of the medicinal plants with indigenous knowledge. With the help of local communities with diverse knowledge of this data, the user-friendly database can be preserved and used for future generations (Kasinathan *et al*., 2024).

2.7.1. Traditional applications of *Couroupita guianensis*.Aubl

Traditional medicine remains the mainstay for promoting and maintaining good health in developing countries. Although the dependency varies between developed and developing countries, the majority (80%) of world's population depend on traditional medicine either as plant extracts or their active principles to meet their primary healthcare. Medicinal plants are reported to be rich in bioactive secondary metabolites, thereby act as a renowned supply of drugs being utilized in folklore to modern medicine for therapeutic purposes. Besides their therapeutic potencies, their holistic approach, self-contained nature, safety, and adequacy make them inevitable as a root for alternative medicine (Van Andel and Carvalheiro, 2013).

Couroupita guianensis Aubl belonging to Lecythidaceae family is well known for its medicinal and ornamental values. It is commonly called a Cannonball tree because of the cannonball appearance of its fruits. It is a large deciduous tropical evergreen tree widely cultivated as an ornamental plant for its

distinctive flower and fruit. It is more common among tribes and rural people (3) and widely used in traditional medicine. The trees were overexploited during the past for timber, settlement, and agriculture and so it is under the category of threatened medicinal plant and has been enrolled in International Union for Conservation of Nature (IUCN) red list. In India, it is regarded as a sacred tree. Its flower is proclaimed as the State flower by the government of Puducherry, Union territory of India (Sumathi and Anuradha, 2017).

Taxonomical classification

Kingdom:	Plantae – Plants
Subkingdom:	Tracheobionta
Superdivision:	Spermatophyta
Division:	Magnoliophyta
Class:	Magnoliopsida
Subclass:	Dilleniidae
Order:	Lecythidales
Family:	Lecythidaceae – Brazil-nut family
Genus:	Couroupita Aubl
Species:	*Couroupita guianensis Aubl*

Couroupita guianensis is popular among the tribal communities in the context of its medicinal values. Literature survey reveals that the cannonball tree is known for its cultural importance for many centuries. In India, the tree is considered as a sacred, widely seen in Lord Shiva temples. All of its parts have been utilized by natives to treat a wide spectrum of human illness such as hemorrhage, piles, scabies, dysentery, scorpion sting, hypertension, tumors, malaria, odontalgia, inflammatory processes, kidney and stomach problems, allergies, ulcers, toothache, and skin diseases. The rural people elsewhere in the world use various parts of the plant to treat microbial infections. Additionally, it is also widely used as a veterinarian plant. In the indigenous Ayurveda medicine,

Couroupita guianensis is used as a rubefacient, antiinflammatory and antirheumatic medicine (Sheba *et al*., 2023).

2.7.2. Phytochemistry and pharmacological activities of *Couroupita guianensis*

Physical factors like temperature, humidity, rainfall and sunlight and other factors like soil nutrients influence the synthesis of bioactive compounds in plants. Studies dedicated to *Couroupita guianensis* have reported the identification and isolation of various categories of phytochemicals from different parts of the tree. The terpenes, flavonoids, phytosterols, alkaloids and phenolic acids are considered the most dominant family of components occurring in the cannonball tree. The fruits of cannonball tree are apparently rich in alkaloid, isatin, tryptanthrin, indirubin, couroupitine A and couroupitine B. Cannonball tree has been widely screened for its various pharmacological activities. The reported pharmacological activities of the cannonball tree highlight the therapeutic potential of the tree (Juvekar *et al*., 2009).

The antibacterial activity of aqueous, chloroform and ethyl acetate extracts of leaf, flower and fruit against *Escherichia coli, Bacillus subtilis* and *Pseudomonas aeruginosa* and found that the chloroform and ethyl acetate extracts were predominant in phytochemicals and thus exhibiting higher zone of inhibition (ZI) comparable to that of streptomycin used as a positive control. Amongst the various extracts, the chloroform leaf, flower and fruit extracts exhibited significant antibacterial activity against *Escherichia coli* and *Bacillus subtilis*. Studies justify the use of *Couroupita guianensis* in wound healing in folklore medicine. In one such study, the ethanol extract of the whole plant was evaluated for its potential to heal the wound in rats by carrying out two methods: excision and incision models. Parameters such as wound contraction, epithelisation, tensile strength and hydroxyproline content were then determined and it was reported that there was a decrease in the surface area of the wound and increase in the tensile strength and hydroxyproline concentration. Furthermore, complete epithelisation was observed within 15 days. In another study, hydroethanolic leaf extract containing flavonoids such as 2′,4′-dihydroxy6′-methoxy-3′,5′-dimethylchalcone and

7-hydroxy-5- methoxy-6,8-dimethyl flavanone and the phenolic acid 4-hydroxybenzoic acid was reported to stimulate human skin fibroblast proliferation and promote UV absorption. Fibroblast plays an incredible role in wound healing by enhancing wound contraction (Figure 10) (Sheba *et al*., 2023).

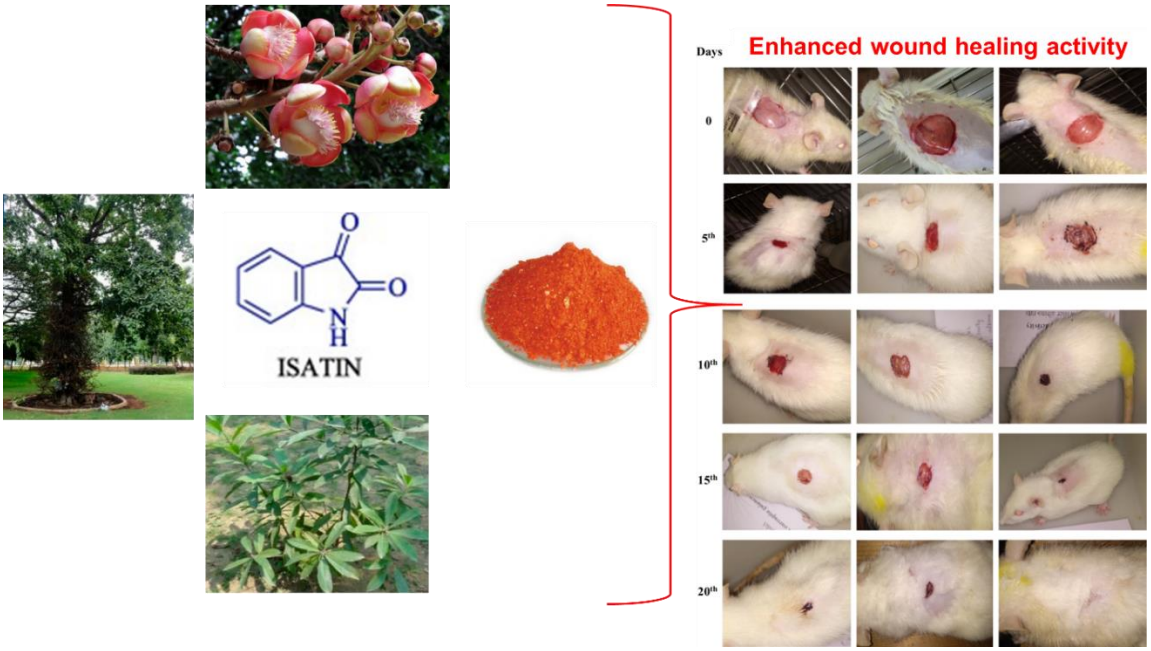

Figure 10: Wound healing potential of *Couroupita guianensis*.Aubl

2.7.3. Isatin: an ideal drug molecule

Isatin, a naturally occurring indole derivative, is recognized for its diverse pharmacological properties, particularly its potent antimicrobial activity. These compounds function as endogenous biological regulators and are present in various human tissues and body fluids. Their significance in synthetic chemistry lies in their straightforward synthesis and the wide range of biological activities exhibited by isatin and its derivatives. Its broad-spectrum efficacy against bacteria, fungi, and viruses makes it a lead compound in addressing wound infections, especially those caused by drug-resistant pathogens (Cheke *et al*., 2022).

Isatin (1H-indole-2, 3-dione) is a heterocyclic compound that includes an indole group.Initially synthesized by Erdman and Laurent in 1840, it was produced as a byproduct of theoxidation of indigo dye by nitric acid and chromium. For around a century, isatin was believed to be solely a synthetic

compound. However, it was later discovered to be naturally occurring and extracted from plants such as *Couroupita guianensis Aubl, Isatistinctoria, Melochiatomentosa,* and *Boronelakoniam boensis* (Barroso *et al.,* 2024). Isatin, a naturally occurring compound found in *Couroupita guianensis* and its derivatives, has garnered considerable attention due to its diverse pharmacological activities. These include anti-inflammatory, antioxidant, and antimicrobial properties. The broad spectrum of properties exhibited by these compounds has sparked considerable interest in heterocyclic chemistry in recent years. Numerous studies have been published focusing on the synthesis of heterocyclic molecules with potential anticancer and antimicrobial activities (Altamimi *et al.,* 2023).

The potential of isatin as a wound-healing agent is particularly promising, given its multifaceted mechanisms of action. Isatin is a versatile compound that has garnered significant interest in medicinal chemistry due to its broad spectrum of biological activities. Among its diverse pharmacological properties, its antimicrobial potential stands out, offering promising applications in combating various infectious diseases (Pakravan *et al*., 2013).

Since, isatin is a hydrophobic drug that shows poor solubility and bioavailability, it is limited to exert its targeted action at the disease sites. Due to these properties, it might be prone to premature degradation by various environmental conditions and cannot be released at the target sites in a controlled manner. Hence, there is a need for the appropriate drug carriers to encapsulate isatin to promote its bioavailability and controlled release at the target sites (Medvedev *et al*., 2007).

2.8. Supramolecular host-guest chemistry for controlled drug release

Supramolecular chemistry has significantly advanced drug delivery systems, offering new approaches to enhance drug stability, solubility, and targeted delivery. This review explores the supramolecular carriers used in drug delivery and host-guest systems (Figure 11). We discuss the mechanisms of drug encapsulation and release, highlight recent advancements, and address current challenges in the field. Supramolecular chemistry, defined by the study of

non-covalent interactions between molecules, combines forces such as hydrogen bonding, electrostatic interactions, *van der Waals* forces, and π-π stacking to create assemblies with unique properties like specificity, reversibility, and tunability. These properties are especially crucial in biological contexts, where molecular interactions must be both precise and adaptable to maintain the complexity and function of living systems. In biological environments, supramolecular interactions contribute to the formation of structured, hierarchical architectures essential for cellular processes, signaling pathways, and molecular recognition events. These interactions are not only selective but also transient, allowing for dynamic modulation in response to environmental or physiological changes. This delicate balance of supramolecular forces underpins a range of biological functions, from enzyme-substrate binding and protein folding to DNA replication and cellular signaling, making supramolecular chemistry fundamental to the molecular organization and functionality within living organisms (Jin *et al*., 2019; Chen *et al*., 2018).

Among various noncovalent interactions under the definition of supramolecular chemistry, host–guest interaction based on macrocyclic molecules is a very important phenomenon that has been extensively investigated. Through such host–guest inclusion, two or more chemical moieties can be integrated together in a facile and reversible manner, providing vast possibilities for the construction of novel supramolecular structures. During the past few decades, a series of macrocyclic molecules and their derivatives have been developed, including calixarenes (CAs), crown ethers, cyclodextrins (CDs), cyclophanes, cucurbit[*n*]urils (CBs), pillar[*n*]arenes, and so on. These macrocyclic molecules are regarded as the hosts, possessing the cavities to encapsulate the guests **(**Xing Ma and Yanli Zhao, 2015).

Supramolecular chemistry offers distinct advantages in biomaterial development by leveraging the properties inherent to its molecular building blocks. The predictable, reversible, and highly adaptable nature of supramolecular interactions enables the design of materials that can be finely tuned to meet specific biomedical requirements. Since these properties arise directly from non-covalent

interactions, materials developed through supramolecular chemistry can exhibit dynamic responses to environmental stimuli, which is invaluable for applications such as drug delivery, tissue engineering, and wound healing.

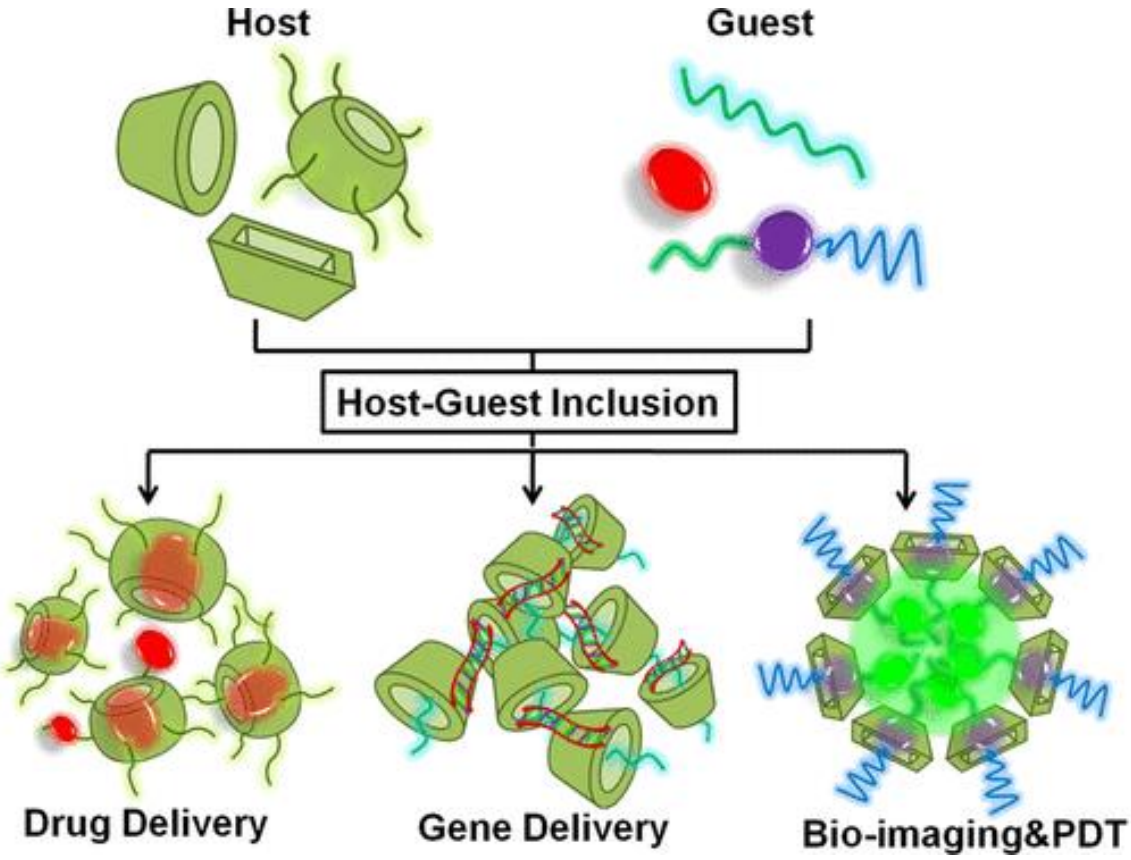

Figure 11: Supramolecular-based drug delivery systems by forming host-guest inclusion complexes

2.8.1. Host-guest recognition-mediated drug loading

The delivery and release of drugs, in either formulations or bodies, usually occur in an aqueous environment, where the hydrophobic domain on the drug structure can act as a good guest candidate for host–guest recognition in a drug-loading procedure. A typical guest drug has a highly hydrophobic structure, which acts as a proton-donating agent to form multiple hydrogen bonds with the proton-accepting structure of the host molecules. Such a supramolecular complex achieves molecular-level protection from drug degradation or deactivation (Hu *et al*., 2020).

A host–guest interaction with a high association constant provides many opportunities for hydrophobic drug loading. Macrocycles, such as cyclodextran (CD), cucurbituril (CB) and crown ether families of macrocycles, are the most popular host candidates to complex drug guests. Besides small hydrophobic drugs, a variety of therapeutics can act as recognition guests directly, including certain proteins with N-terminal aromatic amino acids such as insulin and human growth hormone. There is no doubt that, after complexation with macrocycle hosts, hydrophobic drugs could achieve enhanced solubility and stability. Some published literatures have further demonstrated that the host motif could also contribute a positive effect to permeability through biological membranes, and might be a promising platform for oral administration, topical cream, eye drops and nasal sprays (Yang *et al*., 2024b).

Thus, it is urgently required to enhance the solubility or dissolution of drugs in aqueous conditions. In the scope of supramolecular chemistry, a directive method is using the host–guest complexation between water-soluble macrocyclic molecules and hydrophobic drugs to enhance the water solubility of drugs. In addition, by forming such host–guest complexes, it is capable of protecting drug molecules from chemical reactions and photochemical/thermal degradation in biological environment. Chemical activity of delivered drugs might be altered by the host–guest inclusion as well. On account of the host–guest inclusion, the encapsulated drugs can be released sustainably from the cavity of macrocyclic molecules, achieving prolonged therapeutic effect. Upon external stimulus, such as thermal change, pH variation, or competitive binding, to disassociate the host–guest complexes, delivered drugs can be released in a controlled manner. Up to now, such host–guest complexation has been successfully demonstrated as a general approach to enhance the water solubility of drugs, aiming at better therapeutic efficacy (Ma and Zhao, 2015).

Supramolecular prodrug systems can be externally triggered to release the drug upon exposure to external stimuli, such as light, ultrasound, magnetic fields, or electric fields. External triggers induce conformational changes or disruption of the supramolecular assembly, leading to rapid drug release and

bioactivation at the desired location and time. Supramolecular prodrug systems enable targeted delivery of drugs to specific tissues or cells by functionalizing the carrier molecule with targeting ligands, such as antibodies, peptides, or aptamers. Targeted delivery enhances drug accumulation at the diseased site, minimizing off-target effects and systemic toxicity. Supramolecular prodrug systems offer precise control over drug release kinetics, allowing for sustained release, pulsatile release, or on-demand release of the drug. Controlled release profiles improve therapeutic efficacy, reduce dosing frequency, and enhance patient compliance in drug therapy. Supramolecular prodrug systems enable combination therapy by co-delivering multiple drugs or therapeutic agents within the same carrier molecule. Combination therapy enhances synergistic effects, overcomes drug resistance, and improves therapeutic outcomes in complex diseases, such as cancer and infectious diseases (Arthur, 2024).

2.8.2. Pillar[n]arenes and their therapeutic action as drug delivery vehicles

A key benefit of supramolecular systems lies in their combinatorial modularity, where interactions can be modified or enhanced without disrupting the core molecular assembly. This modularity, enabled by the robust affinity of specific supramolecular motifs, facilitates extensive customization, allowing scientists to tailor materials with multifunctional properties suited for targeted therapeutic applications. For instance, it becomes feasible to integrate various active agents, control release rates (Figure 12), or adjust degradation profiles, all while maintaining the integrity and functionality of the original supramolecular structure (Li *et al*., 2020; Webber and Langer, 2017).

Pillar[5]arene, a macrocyclic molecule known for its unique structural and chemical properties, serves as a versatile platform in drug delivery systems (Figure 13). Its symmetrical structure and hydrophobic cavities facilitate the encapsulation of bioactive molecules like isatin, enhancing their solubility, stability, and controlled release. The ability of pillar[5]arene to form host-guest complexes with drugs is particularly significant, as it allows for targeted delivery and improved therapeutic performance (Sathiyajith *et al*., 2017).

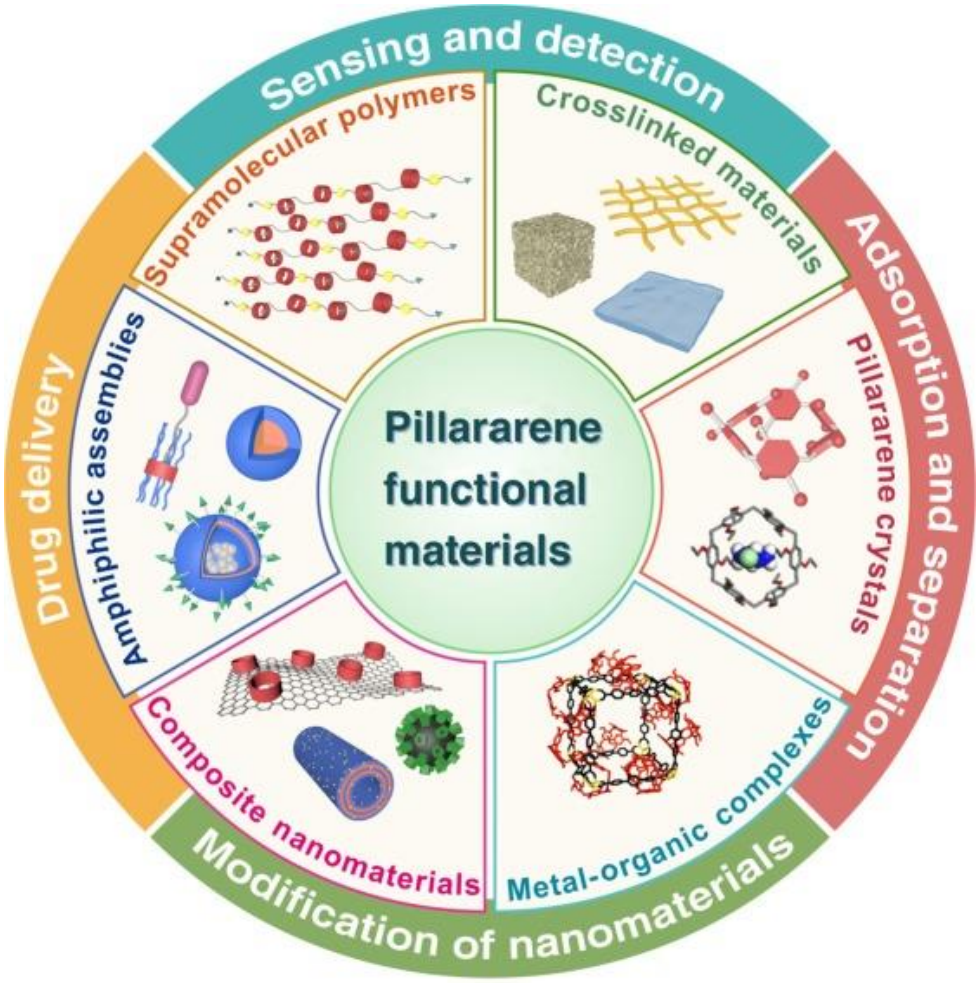

Figure 12: Functional materials of pillar[n]arenes and their applications

To date, a wide array of supramolecular polymeric delivery carriers has been documented, show casing diverse signs tailored to efficiently deliver chemotherapy drugs, therapeutic enzymes, and genetic materials. Among these carriers, pillar[5]arenes and their derivatives have garnered increasing attention due to the irrigid, symmetric, and tubular architecture. These compounds feature electron-rich interior cavities that facilitate the encapsulation of small molecules through supramolecular interactions. Recent studies have revealed the potential applications of pillar[n]arenes in various biological contexts and related fields. These applications include serving as artificial transmembrane transporters, celladhesives, DNAbinders, drugdelivery systems, and sensors for biologically relevant molecules (Boominathan *et al.,* 2019; Han *et al.,* 2019; Han *et al.,* 2018).

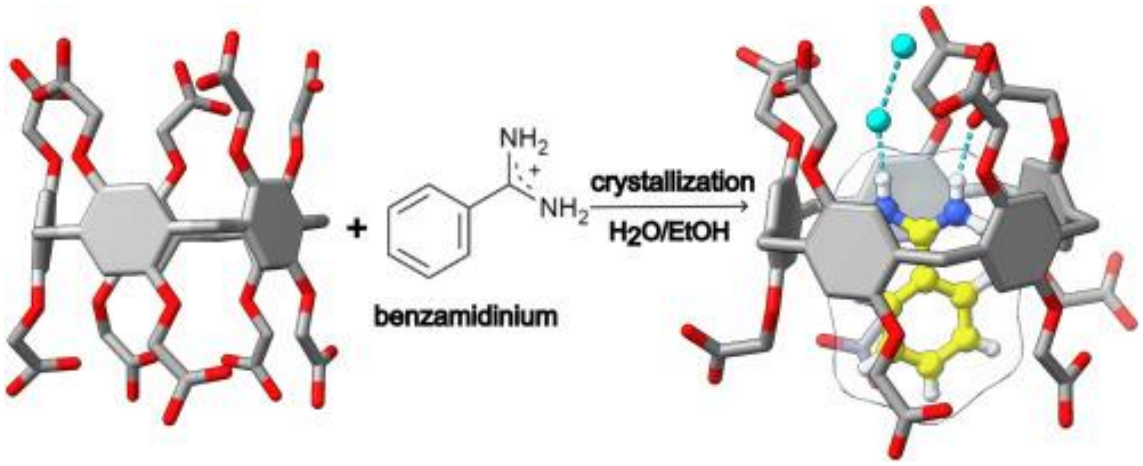

Figure 13: Electron-rich cavity to encapsulate drugs by pillar[5]arene

The field of supramolecular chemistry has increasingly highlighted the role of macrocyclic hosts in encapsulation and targeted, stimulus-responsive drug delivery. Among these hosts, pillar[5]arenes and their derivatives have attracted significant interest due to their unique structural characteristics. These macrocyclic molecules possess a rigid, symmetric, and tubular shape with electron-rich cavities that enable effective encapsulation of small molecules via non-covalent interactions. Such structural properties make pillar[5]arenes versatile and efficient hosts for various drug delivery applications, where controlled release is essential. Recent research highlights the wide-ranging potential of pillar[n]arenes in biomedical and related fields (Kiruthika *et al*., 2020; Sathiyajith *et al*., 2017).

Their architecture supports the development of systems that mimic biological functions, enabling applications as artificial transmembrane transporters, cell adhesives, and DNA binders. Furthermore, pillar[n]arenes have demonstrated utility in designing drug delivery platforms and biosensors for detecting biologically significant molecules. These applications leverage the ability of pillar[n]arenes to interact selectively with targeted molecules, providing a promising approach to enhance the efficacy and specificity of therapeutic and diagnostic tools (Boominathan and Arunachalam, 2020; Ogoshi *et al*., 2016).

Recent research highlights the promise of pillar[n]arenes as antibiofilm agents, a critical advancement in combating persistent infections associated with biofilms. Pillar[n]arenes are a class of macrocyclic molecules with a distinctive pillar-shaped structure that enables strong host-guest interactions, allowing them to complex with various guest molecules. This structural design provides these molecules with exceptional versatility, making them highly relevant in supramolecular chemistry and in applications requiring selective molecular interactions (Ping *et al*., 2016; Strutt *et al.,* 2011).

The inherent structural properties of pillar[n]arenes make them adaptable to diverse biological applications, especially as antibiofilm agents. Biofilms, formed by microbial communities on surfaces, often resist standard antibiotics, leading to chronic infections and treatment challenges. Pillar[n]arenes exhibit intrinsic antimicrobial activity against a range of planktonic bacteria, including both Gram-positive and Gram-negative strains. These antimicrobial properties are attributed to the ability of pillar[n]arenes to disrupt microbial adhesion and inhibit biofilm formation, suggesting their utility in clinical settings where biofilm inhibition is crucial (Ping *et al.,* 2017). Biocompatibility and safety are essential criteria for any antibiofilm agent intended for human use. Initial studies indicate that pillar[n]arenes and their derivatives exhibit low cytotoxicity, minimal adverse effects, and high biocompatibility, meeting essential safety standards for potential therapeutic use (Dai *et al.,* 2025). Their safety profile makes pillar[n]arenes strong candidates for further development as antibiofilm agents.

In addition to their antimicrobial capabilities, pillar[n]arenes offer functional versatility, including artificial transmembrane transport abilities. This feature allows specific molecules to traverse cell membranes, a significant capability for drug delivery applications. Pillar[n]arene derivatives can selectively facilitate the movement of therapeutic agents across biological barriers, enhancing the targeted delivery of drugs to infected or damaged tissues. Consequently, pillar[n]arenes are not only effective against biofilms but also serve as promising drug delivery vehicles, emphasizing their potential as multifunctional therapeutic agents in medical applications (Liu *et al*., 2024).

Overall, the literature review highlights the significant advancements in the understanding and application of various molecules and methodologies in combating microbial infections and enhancing wound healing. The literature underscores the potential applications of isatin as an effective wound-healing agent, citing its antimicrobial, anti-inflammatory, analgesic, antioxidant, and angiogenesis-promoting properties. The use of pillar[n]arenes as supramolecular hosts is another focal point. These macrocyclic compounds exhibit remarkable capabilities in forming host-guest complexes, offering a robust platform for targeted drug delivery and antibiofilm applications. Functional modifications of pillar[n]arenes enhance the biocompatibility and efficacy of isatin, making them promising candidates for combating biofilm-associated bacterial infections. The review emphasizes the importance of novel therapeutic approaches, including supramolecular systems and plant-derived metabolites, in overcoming these challenges.