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A Comprehensive Review of Synthetic compound and Conventional Antibiotics in Antibacterial Resistance:

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Abstract:
Antibiotic resistance poses a formidable challenge in contemporary healthcare, necessitating innovative strategies to combat resistant pathogens. One promising approach involves the development of synthesized chemical compounds tailored to overcome resistance mechanisms and enhance antimicrobial efficacy. This review synthesizes current research on the design, synthesis, and evaluation of such compounds as potential therapeutics against antibiotic-resistant bacteria. The design of synthesized compounds involves a rational approach, leveraging structural insights into bacterial resistance mechanisms and targeting essential cellular processes. Chemical synthesis techniques enable the creation of diverse compound libraries with varied structural scaffolds and functional groups, optimizing antimicrobial activity and pharmacokinetic properties. Evaluation of synthesized compounds encompasses in vitro and in vivo studies to assess efficacy, toxicity, and mechanisms of action. These studies reveal promising candidates with potent antimicrobial activity against multidrug-resistant pathogens, including Gram-positive and Gram-negative bacteria, as well as emerging threats such as carbapenem-resistant Enterobacteriaceae (CRE) and methicillin-resistant Staphylococcus aureus (MRSA). Moreover, synthesized compounds exhibit synergistic effects when combined with existing antibiotics, overcoming resistance mechanisms, and restoring their efficacy. Combinatorial approaches also mitigate the development of resistance and broaden the spectrum of antimicrobial activity. Overall, the development of synthesized chemical compounds represents a valuable strategy in addressing antibiotic resistance and revitalizing the antimicrobial armamentarium. Future research directions include further optimization of compound properties, elucidation of resistance mechanisms, and clinical trials to assess safety and efficacy in human populations. With continued innovation and collaboration across disciplines, synthesized compounds hold promise as a vital tool in the ongoing battle against antibiotic-resistant infections.

Keywords: Antimicrobial, methicillin-resistant Staphylococcus aureus, scaffolds

Introduction

Infections and diseases may be caused by different types of organisms like bacteria, fungi, and viruses, etc., in humans and animals. The science dealing with the study of the prevention and treatment of diseases caused by micro-organisms is known as medical microbiology. Its sub disciplines are virology (study of viruses), bacteriology (study of bacteria), mycology (study of fungi), phycology (study of algae) and protozoology (study of protozoa). The bacteria are microscopic organisms with relatively simple and primitive forms of prokaryotic type. Danish Physician Christian Grams discovered the differential staining technique known as Gram staining, which differentiates the bacteria into two groups “Gram positive” and “Gram negative”, Gram positive bacteria retain the crystal violet and resist decolorization with acetone or alcohol and hence appear deep violet in colour; while Gram negative bacteria, which loose the crystal violet, are counter-stained by saffranin and hence appear red in colour. Some important bacteria which cause infections in humans are as follow: *S. Aureus, M. tetragenus, S. lutea, Str. Pygenes, N.gonorrhoeae, N. meningitidi, N. catarrhalis, C. dipthheriae, L. monocytogene, L. rhusiopathiae, K. pneumoniae, K. pneumoniae, K. aerogenes, Sal. typhosa, Sh. dysenterise, Pr. vulgaris, P. pestis, F. tularensis, H. influenzae, H. duoreyi, M. lacunata, A. mallei, B. anthracis, B. subtilis, Cl. tetani, Ps. aeruginosa, M. pneumoniae, M. tuberculosis, M. laprae, A. bovis, Strepto. griseus, Bor. duttoni, Bor. vincenti,*

Tr. pallidum, Tr. pertenue. A fungus is any member of the group of eukaryotic organisms that includes microorganisms such as yeasts and molds, as well as the more familiar mushrooms. These organisms are classified as a kingdom, which is separate from the other eukaryotic life kingdoms of plants and animals [5]. Some fungi are single-celled, while others are multicellular. Single-celled fungi are called yeast [9]. Some fungi alternate between single-celled yeast and multicellular forms depending on what stage of the life cycle they are in. Unlike plants, they don't perform photosynthesis and they have chitin, a derivative of glucose, in their cell walls. Like animals, fungi are heterotrophs, which means they get their nutrients by absorbing them. Fungi reproduce both sexually and asexually, and they also have symbiotic associations with plants and bacteria. However, they are also responsible for some diseases in plants and animals. There are five phyla of fungi: Chytridiomycota, Zygomycota, Glomeromycota, Ascomycota, and Basidiomycota [11]. Fungi may cause benign but unsightly infection of the skin, nail, or hair (dermatophytosis), relatively trivial infection of mucous membranes (thrush), or systemic infection causing progressive, often fatal disease. Some important fungi which cause infections in humans are as follow: *Candida Albicans, Aspergillus Niger, Penicillium, Cryptococcus neoformans, Histoplasma capsulatum, Ustilago maydis, Batrachochytrium dendobatidis, Allomyces macrogynus*, *Blastocladiella emersonii*, *Physoderma maydis, Rhizopus stolonifer, Fibillanosema crangonysis, and Neocallimastix frontalis* [15]. The drug used to prevent the pathogenicity of microorganisms is called an antimicrobial agent [21]. Antimicrobials are one of the most successful forms of chemotherapy and have been used to save the human population from the threat of infectious diseases. A**ntimicrobial** is an agent that kills microorganisms or stops their growth. Antimicrobial medicines can be grouped according to the microorganisms they act primarily against. For example, antibiotics are used against bacteria and antifungals are used against fungi. They can also be classified according to their function. Agents that kill microbes are called microbicidal, while those that merely inhibit their growth are called biostatic. The use of antimicrobial medicines to treat infection is known as antimicrobial chemotherapy, while the use of antimicrobial medicines to prevent infection is known as antimicrobial prophylaxis [38].

1. Major types of antimicrobial drugs are commonly available.

Antibacterial drugs: drugs that are used to inhibit the pathogenic activity of bacteria are called as antibacterial drugs. Antibacterials are among the most used drugs and among the drugs commonly misused by physicians. Because of widespread and injudicious use of Antibacterials, there has been an accelerated emergence of antibiotic-resistant pathogens, resulting in a serious threat to global public health [21]. The resistance problem demands that a renewed effort be made to seek antibacterial agents effective against pathogenic bacteria resistant to current antibacterials. Prolonged use of certain antibacterials can decrease the number of enteric bacteria, which may have a negative impact on health. The discovery, development, and use of antibacterials during the 20th century have reduced mortality from bacterial infections. Their classifications within these categories depend on their antimicrobial spectra, pharmacodynamics, and chemical composition [18]. Example: Quinolones, Cephalosporins, Penicillins, Aminoglycosides, Chloramphenicol, Macrolides antibiotic, Tetracyclines, Clindamycin [23].

1.1. β-Lactam antibiotics:

Penicillins, Cephalosporins, and certain other antibiotics belong to a family of compounds collectively known as β-lactam antibiotics, which all possess a β-lactam ring. In penicillins the β-lactam ring is fused to a thiazolidine ring, whereas cephalosporins have a fused β-lactam/dihydrothiazine ring structure [22]. Cephalosporins generally exhibit a somewhat broader spectrum than penicillins, though, idiosyncratically, they lack activity against enterococci [16]. They are mostly stable to staphylococcal β-lactamase and often lack cross allergenicity with penicillins. The original cephalosporin, cephalosporin C, was never marketed but has given rise to a large family of compounds that continues to expand. Cephalosporins display diverse properties that tend to be grouped according to their relative activity against Gram-positive and Gram-negative bacteria. Cephalosporins are commonly described as first, second, third, fourth and, most recently, fifth generation compounds [34].

1.2. Aminoglycosides:

The aminoglycosides are potent, broad-spectrum bactericidal agents that are very poorly absorbed when given orally and are therefore administered by injection for systemic infection or topically. Their spectrum includes most Gram-negative bacilli and staphylococci but not streptococci and anaerobes [46]. Activity against

streptococci can often be improved via use in conjunction with penicillins, with which aminoglycosides interact synergically. Aminoglycosides penetrate poorly into mammalian cells and thus are of limited value in infections caused by intracellular bacteria. Some members of the group display important activity against Mycobacterium tuberculosis or Pseudomonas aeruginosa [33].

1.3. Chloramphenicol:
Chloramphenicol was one of the first therapeutically useful antibiotics to appear from systematic screening of Streptomyces strains in the wake of the discovery of streptomycin in the 1940s.Although it is a naturally occurring compound, it is a relatively simple molecule and can readily be synthesized [57]. Chloramphenicol acts by inhibiting the peptidyl transferase reaction—the step at which the peptide bond is formed—on bacterial ribosomes. The spectrum of activity embraces most Gram- positive and Gram-negative bacteria and also extends to chlamydiae and rickettsiae, strictly intracellular bacteria that cause a variety of infections, including trachoma, psittacosis, and typhus [42].

1.4. Tetracyclines:
The tetracyclines exhibit a very broad spectrum, displaying good activity against most Gram-positive and Gram-negative bacteria (excluding Proteus spp., Providencia spp., Morganella spp., and *Ps. aeruginosa*), rickettsia, chlamydia, mycoplasmas, and spirochaetes. They generally have similar antibacterial activity and are distinguished more by their pharmacokinetic behavior [25]. The older tetracyclines, doxycycline and minocycline are the most widely used. These derivatives are more completely absorbed when given orally and, unlike the others, they do not aggravate renal failure, so they can be used in patients suffering renal impairment; they also exhibit marginally better antibacterial activity and display sufficiently long serum half-lives to allow them to be given only once or twice daily. Susceptible bacteria concentrate tetracyclines by an active transport process [31]. In the cell they interfere with the binding of aminoacyl tRNA to the A-site on the ribosome. The therapeutic importance of tetracyclines has declined over the years with the upsurge of resistant strains, particularly among enterobacteria and streptococci [32]. The tetracyclines are still widely used for the treatment of respiratory infections, particularly chronic bronchitis and mycoplasma pneumonia, and in selected skin infections [47]. Traditionally, they are the drugs of choice for rickettsial and chlamydial infections of all types, although use for the latter indication has been eroded by the newer macrolides [61].

1.5. Fusidic acid:
Fusidic acid is the only therapeutically useful member of a group of naturally occurring antibiotics that display a steroid-like structure. The antibiotic prevents the translocation step in bacterial protein synthesis by inhibiting one of the substances (factor G) essential for this reaction [23]. Fusidic acid is active in vitro against Gram-positive and Gram-negative cocci, *M. tuberculosis*, *Nocardia asteroides*, and many anaerobes; the ribosomes of Gram-negative bacilli are susceptible to the action of the drug, but access is denied by the Gram-negative cell wall. Staphylococcus aureus is particularly susceptible to fusidic acid, and the compound is usually regarded simply as an anti staphylococcal agent [60].

1.6. Macrolides:
Erythromycin, Azithromycin, Clarithromycin, Dirithromycin, Roxithromycin. The earliest macrolide, erythromycin, was discovered in 1952 as a product of *Streptomyces erythreus*. This and related antibiotics share a similar molecular structure characterized by a 14-, 15-, or 16-membered macrocyclic lactone ring substituted with some unusual sugars. All members of the group are thought to act by causing the growing peptide chain to dissociate from the ribosome during the translocation step in bacterial protein synthesis. Macrolides are most notable for their antistaphylococcal and antistreptococcal activity, though the spectrum encompasses other important pathogens, including chlamydiae, *Mycoplasma pneumoniae*, *legionellae*, and some mycobacteria; macrolides lack useful activity against enterobacteria and *Ps. Aeruginosa*. Macrolides have many attractive properties as well-tolerated oral compounds that display good tissue penetration [22]. Their spectrum of activity makes them particularly suitable for the treatment of respiratory and soft-tissue disease and for infections caused by susceptible intracellular bacteria [38].

1.7. Ketolides:
A new class of erythromycin derivatives, the ketolides, has been obtained by introducing a keto function into the macrolactone ring of erythromycin after removal of one of the sugars. These compounds share the Gram-positive spectrum of the earlier macrolides but retain activity against macrolide-resistant strains [62].

1.8. Mupirocin:
Mupirocin (formerly known as pseudomonic acid) is a component of the antibiotic complex produced by the bacterium *Ps. fluorescens*, and the novel structure of this inhibitor consists of monic acid with a short fatty acid sidechain. The terminal portion of the molecule distal to the fatty acid resembles isoleucine, and mupirocin inhibits protein synthesis by blocking the incorporation of this amino acid into polypeptides. The analogous process in mammalian cells is unaffected. The spectrum of activity embraces staphylococci and streptococci but excludes most enteric Gram-negative bacilli [56].

1.9 **Streptogramin**:
Each member of the streptogramin family is not one antibiotic but two: they are produced as synergic mixtures by various species of Streptomyces. One of these compounds, virginiamycin, has been extensively used as a growth promoter in animal husbandry. Another streptogramin, pristinamycin is sometimes used as an antistaphylococcal agent [10].

2.0. Lincosamide:
The original Lincosamide, lincomycin, a naturally occurring product of *S. lincolnensis*, has been superseded by Clindamycin, which exhibits improved antibacterial activity. Lincosamides interfere with the process of peptide elongation in a way that has not been precisely defined. The ribosomal binding site is probably like that of erythromycin, since resistance to erythromycin caused by methylation of the ribosomal binding site also affects lincosamides. Lincomycin and Clindamycin possess good antistaphylococcal and antistreptococcal activity, and in vitro studies demonstrate reduced toxin release by producer strains even in the presence of low concentrations of Clindamycin [20].

2.1. Oxazolidinones:
Several Oxazolidinones have attracted attention over the years owing to their activity against Gram-positive organisms, including staphylococci, pneumococci, and enterococci. They are very well absorbed by the oral route and exhibit bacteriostatic activity. They act at an early stage in protein synthesis by blocking the formation of the 70S initiation complex [57].

2.2. Polymyxins:
The polymyxins are a family of compounds produced by Bacillus polymyxa and related bacteria. Only polymyxins B and E are used therapeutically. Polymyxin E is usually known by its alternative name, colistin. Structurally, the polymyxins are cyclic polypeptides with a long hydrophobic tail .They act like cationic detergents by binding to the cell membrane and causing the leakage of essential cytoplasmic contents. The effect is not entirely selective, and both polymyxin B and colistin exhibit considerable toxicity and so are not used for systemic therapy. They have a limited role in topical therapy such as in selective decontamination regimens and ‘Hospital-acquired pneumonia and in cystic fibrosis. Daptomycin, a semi-synthetic lipopeptide antibiotic not unlike the polymyxins in structure has various effects on bacteria but the primary mode of action is thought to lie in the disruption of the cell membrane [59].

2.3. Sulphonamides:
Sulphonamides have a broad antibacterial spectrum, although the activity against enterococci, Pseudomonas aeruginosa, and anaerobes is poor. These agents are relatively slow to act: several generations of bacterial growth are needed to deplete the folate pool before inhibition of growth occurs. Resistance emerges readily, and bacteria resistant to one sulphonamide are cross-resistant to the others [25].

2.4. Trimethoprim:
Trimethoprim is the most important antibacterial agent and used for is in urinary tract infection [5].

2.5. Quinolones:
Nalidixic acid was the first representative to appear of a family of compounds that share close similarities of structure. During the 1980s a new series of quinolones were synthesized, known collectively as fluoroquinolones. These compounds, of which ciprofloxacin is a typical example exhibit considerably enhanced activity. All antibacterial quinolones act against the remarkable enzymes that are involved in maintaining the integrity of the supercoiled DNA helix during replication and transcription (piddok). Two enzymes are affected, DNA gyrase and topoisomerase IV, so that these drugs have a dual site of action. These compounds are characterized by enhanced activity against Gram-positive cocci, including *Staph. aureus* and *Streptococcus pneumoniae* as well as chlamydiae and mycoplasmas; clinafloxacin, gatifloxacin, moxifloxacin, and trovafloxacin also have sufficient activity against anaerobes of the bacteroides fragilis group to make treatment of infections with those organisms feasible. They are not reliably active against *Ps. aeruginosa*. Ciprofloxacin is the most widely used fluoroquinolones [8].

2.6. Rifamycins:
The clinically useful Rifamycins, of which rifampicin is the most important, are semi-synthetic derivatives of rifamycin B, one of a group of structurally complex antibiotics produced by *Streptomyces mediterranei*. These compounds interfere with mRNA formation by binding to the β-subunit of DNA-dependent RNA polymerase. Resistance readily arises by muta-tions in the subunit. For this reason, the drugs are normally used in combination with other agents. Rifampicin is one of the most effective weapons against two major mycobacterial scourges of mankind: tuberculosis and leprosy [19].

3.0. Antifungal drugs:
Drugs that are used to prevent the fungal activity in the host are called antifungal drugs. Antifungal medicines are used to treat fungal infections, which most commonly affect your skin, hair and nails. Fungal infections like ringworm, athlete's foot, candiasis, vaginal thrush, fungal meningitis, and aspergillosis. Human fungal infections have increased dramatically in incidence and severity in recent years, owing mainly to advances in surgery, cancer treatment, and treatment of patients with solid organ and bone marrow transplantation, the HIV epidemic, and increasing use of broad-spectrum antimicrobial therapy in critically ill patients. These changes have resulted in increased numbers of patients at risk for fungal infections. The major groups of antifungals are the polyenes, azoles, and allyamines. Example: Miconazole, Clotrimazole, Econazole, Terbinafine, Fluconazole, Itraconazole, Ketoconazole, Amphotericin B, Nystatin, Grisiofulvin [26].

3.1.Polyenes:
The polyenes are naturally occurring compounds exhibiting a complex macrocyclic structure. All act by binding to sterols in the fungal cell membrane, thereby interfering with membrane integrity and causing leakage of essential metabolites. The only one that can be administered parenterally is Amphotericin. Among related polyenes available for topical treatment in some countries are Nystatin, Natamycin (pimaricin), and trichomycin (hachimycin).The activity of the polyenes embraces a variety of pathogenic fungi; yeasts are particularly susceptible. Nystatin has been extensively used for treating Candida infections of the mucous membranes but has largely been replaced by imidazoles and triazoles. Most polyenes are restricted to topical use but intravenous Amphotericin remains an important agent for the treatment of systemic fungal infections, including disseminated candidiasis, cryptococcosis, aspergillosis, and deep mycoses caused by dimorphic fungi. Amphotericin can also be administered orally for the treatment of oral, oesophageal, and intestinal candidiasis but azole derivatives are now preferred [32].

3.2. Flucytosine:
Flucytosine is a pyrimidine analogue originally developed as an anticancer drug but found to have considerable activity against yeasts; it has no useful activity against filamentous fungi. The activity depends on its being converted intracellularly to 5-fluorouracil, which is incorporated into fungal RNA. The drug can be given orally or parenterally but resistance develops readily and some times emerges during treatment. For this reason, Flucytosine is normally administered in combination with Amphotericin, especially for the treatment of HIV-associated cryptococcal meningitis, for which it enhances fungal clearance from the cerebrospinal fluid and thus improves the clinical outcome.

3.4. Griseofulvin:
Griseofulvin was the first antifungal antibiotic to be described. It is well absorbed when administered orally, particularly if a fine-particle formulation is used, and serious side effects are uncommon. It is ineffective topically. The mode of action has not been definitively established but activity appears to be directed against the process of mitosis, perhaps by interfering with the microtubules of the mitotic spindle. Use of Griseofulvin is confined to the treatment of dermatophyte infections of the skin, nail, or hair. In the case of nail infections, treatment is prolonged. The failure rate is high, so alternative drugs, especially Terbinafine are usually preferred. It induces the hepatic metabolism of some drugs and should not be taken with alcohol because it can cause flushing and vomiting (antabuse-type reaction).

3.5. Azoles:
Many imidazole and triazole derivatives display antifungal activity and, in fact, these compounds offer the nearest approximation to broad-spectrum antifungal agents. They act selectively against fungi (and some protozoa) by interfering with the demethylation of lanosterol during the synthe sis of ergosterol, which is the principal sterol in the fungal cell membrane. Antifungal imidazoles are most widely used for topical application in superficial fungal infections and vaginal candidiasis. Indeed, these are virtually the only useful roles for bifonazole, butoconazole, Clotrimazole, Econazole, Fenticonazole, Isoconazole, Miconazole, Oxiconazole, Sulconazole, and Terconazole, all of which have very similar properties and indications. One antifungal imidazole, Tioconazole, is also available in a formulation that is painted on infected nails, but is unlikely to be effective alone in severe nail infections, for which better treatment is available. The triazoles: Fluconazole, Itraconazole, Voriconazole, and Posaconazole are well absorbed after oral administration. Triazoles are used in many forms of systemic mycosis. Fluconazole is widely used in the treatment of systemic Candida infections and, because of its ability to penetrate into cerebrospinal fluid, cryptococcal meningitis.

3.6.Allylamines:
Allylamines, like the antifungal azoles, interfere with ergosterol synthesis but act at an earlier stage by inhibiting the formation of squalene epoxide, a precursor of lanosterol. The most important compound of this type, Terbinafine, exhibits broad-spectrum antifungal activity and is almost completely absorbed when given orally. It accumulates in keratin, where it persists after treatment is stopped. This is particularly important in dermatophyte infections of the toenails, which are notoriously refractory to therapy.

3.7.Amphotericin B:
Amphotericin B is a macrocyclic, polyene antifungal antibiotic produced by *Streptomyces nodosus*. Its primary role is in the treatment of severe fungal infections, and it is thought to act by binding to sterols in the fungal cell membrane, with a resulting change in membrane permeability, allowing leakage of a variety of small molecules from the fungal cell.

4.0. **Antiviral agents:**
Drugs which are used to stop the pathogenic action of a virus are called as antiviral agents. Antiviral agents are used to inhibit production of viruses that cause disease. Most antiviral agents are only effective while the virus is replicating. Example: Amantadine, Acyclovir, Ganciclovir, Famciclovir, Cidofovir, Valacyclovir, Peramivir, Valganciclovir, Penciclovir, Adefovir, Vidarabine, Idoxuridine, Trifluridine, Telbivudine, Foscarnet, Ribavirin, Fomivirsen, Amantadine, Rimantadine, Docosanol, Zanamivir, Oseltamivir, Peramivir, Interferons, Palivizumab, Imiquimod.

5.0. **Antiparasitic drugs:**
Pathogenic protozoa and helminths are among the most important causes of morbidity and mortality in the world an estimated 700 million people suffer from malaria, filariasis, and schistosomiasis alone, and two-thirds of the world's population live in conditions in which parasitic diseases are unavoidable. Drugs that are used to prevent the growth of pathogenic parasites are called antiparasitic drugs. Parasites can live on or in a host. Parasites include helminths: nematodes, cestodes, trematodes and etc, Protozoa, Amoeba and ectoparasites includes fleas, lice etc. They cause diseases such as malaria, trichomoniasis and leishmaniasis. Parasitic diseases affect hundreds of millions of people worldwide. Example: Praziquantel, Chloroquine, Quinine, Primaquine, Mefloquine,

Tinidazole, Diloxanide Furoate, Albendazole, Metronidazole, Niclosamide, Furazolidone, Nifurtimox, Pentamidine, Metrifonate, Oxamniquine, Diethylcarbamazine, Artemisinins [36].

5.1.Nitroimidazoles:
Metronidazole was originally used for the treatment of trichomoniasis and subsequently for two other protozoal infections—amoebiasis and giardiasis. The antibacterial activity of the compound was first recognized when a patient suffering from acute ulcerative gingivitis responded spontaneously while receiving metronidazole for a Trichomonas vaginalis infection [56].

Nitrofurans: Several nitrofuran derivatives have attracted attention over the years, among which nitrofurantoin is much the most important. Others have very limited roles; for example, Nifurtimox is only used in Chagas disease (Davey P, 2015).

6.0. Mechanism of Antimicrobial Agents
Antimicrobial agents disrupt the vital life processes of microorganisms, eliminating microbial growth and preventing their reproduction. These antimicrobial agents typically work through five mechanisms to disrupt the vital life processes of microbes and help prevent the formation of drug-resistant bacteria:

- **Inhibitors of cell wall synthesis-**

The essence of antimicrobial chemotherapy is selective toxicity—to kill or inhibit the microbe without harming the host (patient). In bacteria, a prime target for attack is the cell wall, since practically all bacteria (with the exception of mycoplasmas) have a cell wall, whereas mammalian cells lack this feature. In both Gram-positive and Gram-negative bacteria, the cell wall is formed from a cross-linked chain of alternating units of N-acetylglucosamine and N-acetylmuramic acid, known as peptidoglycan or mucopeptide. In Gram-positive organisms, the cell wall structure is thick (about 30 nm), tightly cross-linked, and interspersed with polysugarphosphates (teichoic acids), some of which have a lipophilic tail buried in the cell membrane (lipoteichoic acids). Gram-negative bacteria, in contrast, have a relatively thin (2–3 nm), loosely cross-linked peptidoglycan layer and no teichoic acid. Several types of antibiotics, notably β-lactam agents (penicillins, cephalosporins, and their relatives) and glycopeptides (vancomycin and teicoplanin) take advantage of this difference (Fig.1). Some compounds used in the treatment of tuberculosis and leprosy act on the specialized mycobacterial cell wall. Examples: Penicllins, Cephalosporins, Carbapenems, Sulbactam, Tazobactam, Clavulanic acid, Bacitracin, Fosfomycin, Cycloserine and Vancomycin (Davey P, 2015).

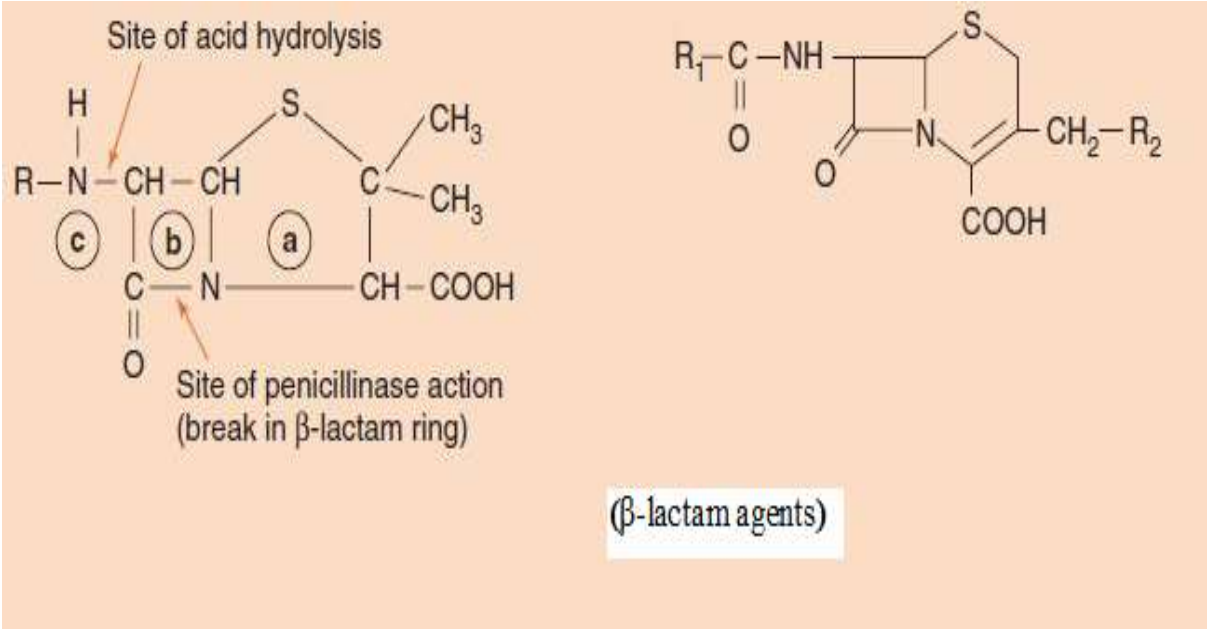


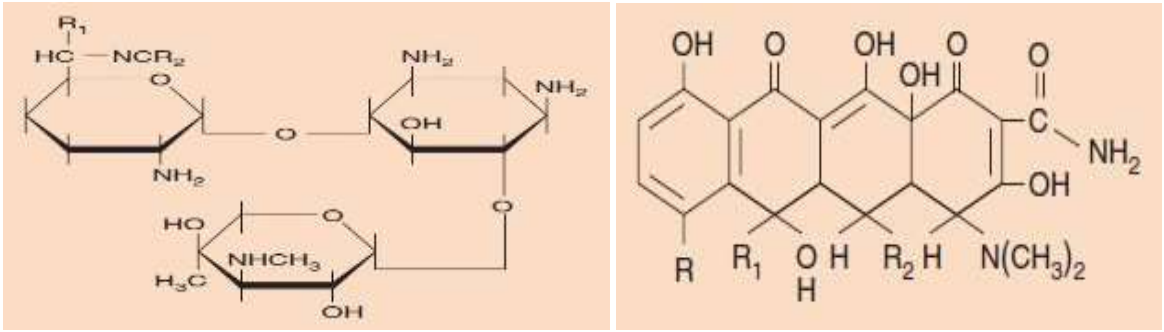
Fig 1. Beta lactam agents

- **Inhibitors of cell membrane function-**

Cell membranes are important barriers that segregate and regulate the intra- and extracellular flow of substances. A disruption or damage to this structure could result in leakage of important solutes essential for the cell's survival. Because this structure is found in both eukaryotic and prokaryotic cells, the action of this class of antibiotic are often poorly selective and can often be toxic for systemic use in the mammalian host. Most clinical usage is therefore limited to topical applications. Examples: polymyxins,

- **Inhibitors of protein synthesis-**

The remarkable process by which proteins are manufactured on the ribosomal conveyor belt according to a blueprint provided by the cell nucleus is of fundamental importance to cell life. Although the general mechanism is thought to be universal, the process as it occurs in bacterial cells is sufficiently different from mammalian protein synthesis to offer scope for the selective toxicity required of therapeutically useful antimicrobial agents. Enzymes and cellular structures are primarily made of proteins. Protein synthesis is an essential process necessary for the multiplication and survival of all bacterial cells. Several types of antibacterial agents target bacterial protein synthesis by binding to either the 30S or 50S subunits of the intracellular ribosomes. This activity then results in the disruption of the normal cellular metabolism of the bacteria, and consequently leads to the death of the organism or the inhibition of its growth and multiplication. Examples: Aminoglycosides, Tetracyclines (Fig.2), Chloramphenicol, Macrolides, Fusidic acid, Ketolides, Mupirocin. Lincosamides, Clindamycin, Oxazolidinones.



(Aminoglycosides) (Tetracyclines)

Fig 2. Aminoglycosides and Tetracyclines

- **Inhibitors of nucleic acid synthesis-**

DNA and RNA are keys to the replication of all living forms, including bacteria. Some antibiotics work by binding to components involved in the process of DNA or RNA synthesis, which causes interference of the normal cellular processes which will ultimately compromise bacterial multiplication and survival. Examples: Sulphonamides, Trimethoprim, Quinolones.

- **Inhibitors of other metabolic processes-**

Other antibiotics act on selected cellular processes essential for the survival of the bacterial pathogens. For example, both sulfonamides and trimethoprim disrupt the folic acid pathway, which is a necessary step for bacteria to produce precursors important for DNA synthesis. Sulfonamides target and bind to dihydropteroate synthase, trimethophrim inhibit dihydrofolate reductase; both of these enzymes are essential for the production of folic acid, a vitamin synthesized by bacteria, but not humans (Tab. 1).

Mechanism of Action	Drugs
Inhibition of cell wall synthesis	
1. (a) Antibacterial activity inhibition of cross-linking (transpeptidation) of peptidoglycan	Penicillins, cephalosporins, imipenem, aztreonam, vancomycin
(b) Inhibition of other steps in peptidoglycan synthesis	Cycloserine, bacitracin
2. Antifungal activity inhibition of β-glucan synthesis	Caspofungin
Inhibition of protein synthesis	
Action on 50S ribosomal subunit	Chloramphenicol, erythromycin, clindamycin, linezolid
Action on 30S ribosomal subunit	Tetracyclines and aminoglycosides
Inhibition of nucleic acid synthesis	
Inhibition of nucleotide synthesis	Sulfonamides, trimethoprim
Inhibition of DNA synthesis	Quinolones (e.g., ciprofloxacin)
Inhibition of mRNA synthesis	Rifampin
Alteration of cell membrane function	
Antibacterial activity	Polymyxin, daptomycin
Antifungal activity	Amphotericin B, nystatin, terbinafine, azoles (e.g., itraconazole)
Other mechanisms of action	
1. Antibacterial activity	Isoniazid, metronidazole, ethambutol, pyrazinamide
2. Antifungal activity	Griseofulvin, pentamidine

Tab 1. Mechanism of action of common antimicrobials agents

7.0 Antimicrobial resistance

Antimicrobial resistance (AMR or AR) is the ability of a microbe to resist the effects of medication that once could successfully treat the microbe. Drug resistance is an ever-increasing worldwide health threat that involves all major microbial pathogens and antimicrobial drugs. Antimicrobial drugs resistance has increased substantially in recent years and considered as fast-growing therapeutic problem. The development of antimicrobial drugs resistance can be natural or intrinsic and acquired which can be transmitted within same or different species of bacteria. Microbes, such as bacteria, viruses, fungi, and parasites, are living organisms that evolve over time. Their primary function is to reproduce, thrive, and spread quickly and efficiently. Therefore, microbes adapt to their environments and change in ways that ensure their survival. If something stops their ability to grow, such as an antimicrobial, genetic changes can occur that enable the microbe to survive. There are several ways this happens [55].

- **Intrinsic resistance:**

If whole bacterial species are considered, rather than individual isolates, it is apparent immediately that they are not all intrinsically susceptible to all antibiotics for example, a coliform infection would not be treated with erythromycin, or a streptococcal infection with an aminoglycoside, since the organisms are intrinsically resistant to these antibiotics. Similarly, Pseudomonas aeruginosa and Mycobacterium tuberculosis are intrinsically resistant to most of the agents used to treat more tractable infections. Such intrinsically resistant organisms are some-times termed non-susceptible, with the term resistant reserved for variants of normally susceptible species that acquire mechanism(s) of resistance [66]. Actually, the terms resistant and non-susceptible are often used interchangeably. A microbe will be intrinsically resistant to an antibiotic if it either does not possess a target for the drug's action or is impermeable to the drug. Thus, bacteria are intrinsically resistant to polyene antibiotics such as amphotericin B as sterols that are present in the fungal but not bacterial cell membrane are the target for these drugs. The lipopolysaccharide outer envelope of Gram-negative bacteria is important in determining susceptibility patterns, since many antibiotics cannot penetrate this barrier to reach their intracellular target. Fortunately, intrinsic resistance is therefore often predictable and should not pose problems, provided that informed and judicious choices of antibiotics are made for the treatment of infection. Of greater concern is the primarily unpredictable acquisition or emergence of resistance in previously susceptible microbes, sometimes during the course of therapy itself [42].

- **Acquired resistance:**

Introduction of clinically effective antibiotics has been followed invariably by the emergence of resistant strains of bacteria among species that would normally be considered to be susceptible. Acquisition of resistance has

seriously reduced the therapeutic value of many important antibiotics but is also a major stimulus to the constant search for new and more effective antimicrobial drugs [21]. However, while the emergence of resistance to new antibiotics is inevitable, the rate of development and spread of resistance is not predictable. The first systematic observations of acquired drug resistance were made by Paul Ehrlich between 1902 and 1909 while using dyes and organic arsenicals to treat mice infected experimentally with trypanosomes. Within a very few years of the introduction of sulphonamides and penicillin (in 1935 and 1941, respectively), microorganisms originally susceptible to these drugs were found to have acquired resistance. When penicillin came into use, less than 1 per cent of all Staphylococcus aureus strains were resistant to its action. By 1946, however, under the selective pressure of this antibiotic, the proportion of penicillin-resistant strains found in hospitals had risen to 14 per cent [27]. A year later, 38 per cent were resistant, and today, resistance is found in more than 90 per cent of all *Staph. aureus* strains. In contrast, over the same period, an equally import-ant pathogen, *Streptococcus pyogenes*, has remained uniformly susceptible to penicillin, although there is no guarantee that resistance will not spread to *Str. pyogenes* in future years. It is possible that some such examples of limited or no resistance emergence are because resistant mutant cells cannot survive and/or proliferate. There is no clear explanation for the marked differences in rate or extent of acquisition of resistance between different species. Possession of the genetic capacity for resistance does not always explain its prevalence in a particular species. Even when selection pressures are similar, the end result may not be the same [31]. Thus, although about 90 per cent of all strains of Staph.aureus are now resistant to penicillin, the same has not happened to ampicillin resistance in E. coli under similar selection pressure. At present, apart from localized outbreaks involving epidemic strains, about 50 per cent of E. coli strains are resistant to ampicillin and this level have remained more or less steady for a number of years. However, since an increasing incidence of resistance is at least partly a consequence of selective pressure, it is not surprising that the withdrawal of an antibiotic from clinical use may often result in a slow reduction in the number of resistant strains encountered in a particular environment. For example, fluoroquinolone resistant strains of P. aeruginosa that emerged in some hospitals as ciprofloxacin or levofloxacin were used more frequently were replaced by more susceptible strains following the restriction or removal of these drugs [23]. Conversely, sulphonamide resistant E. coli strains that became commonplace when the sulphonamide containing combination drug co-trimoxazole was widely used are still prevalent. This is probably because the selection pressure still exists for other antibiotics, such as ampicillin, and the genes coding for sulphonamide and ampicillin resistance are often intricately linked on plasmids; hence, use of one antibiotic can select or maintain resistance to another. The introduction of new antibiotics has also resulted in changes to the predominant spectrum of organisms responsible for infections. In the 1960s semi-synthetic 'β-lactamase stable' penicillins and cephalosporins were introduced which, temporarily, solved the problem of staphylococcal infections. Unfortunately, Gram-negative bacteria then became the major pathogens found in hospitals and rapidly acquired resistance to multiple antibiotics in the succeeding years. In the 1970s the pendulum swung the other way, with the first outbreaks of hospital infection with multi resistant staphylococci that were resistant to nearly all antistaphylococcal agents [15]. Outbreaks of infection caused by such organisms have occurred subsequently all over the world. Gram-negative bacteria are once again assuming greater importance, particularly in hospitals. Resistance to newer cephalosporins—mediated by extended-spectrum β-lactamases and fluoroquinolones in E. coli and other enterobacteria has increased or is continuing to increase, depending on geographical locale, rendering these commonly used antibiotics less effective. Multiresistant Gram-negative bacteria (such as Acinetobacter spp.) have emerged that are resistant to most and, occasionally, all approved antibiotics. The recent emergence of carbapenemase producing enterobacteria is a most worrying development given the 'last line of defence' status of the carbapenemclass of antibiotics. Some Gram-negative bacilli may produce both drug-inactivating enzymes and altered porins and thus become resistant to carbapenems because of a combination of antibiotic cleavage and reduced cell penetration**.**

- **Types of acquired resistance:**

Two main types of acquired resistance may be encountered in bacterial species that would normally be considered susceptible to a particular antibacterial agent: mutational resistance and transmissible resistance**.**

- **Mutational resistance**

In any large population of bacterial cells, a very few individual cells may spontaneously become Resistant. Such resistant cells have no particular survival advantage in the absenceof antibiotic but, after the introduction of

antibiotic treatment, susceptible bacterial cells will be killed, so that the (initially) very few resistant cells can proliferate until they eventually form a wholly resistant population. Many antimicrobial agents select for this type of acquired resistance in many different bacterial species, both in vitro and in vivo. The problem has been recognized as being of particular importance in the long-term treatment of tuberculosis (TB) with anti-TB drugs [25].

- **Transmissible resistance**

A more spectacular type of acquired resistance occurs when genes conferring antibiotic resistance transfer from a resistant bacterial cell to a sensitive one. The simultaneous transfer of resistance to several unrelated antimicrobial agents can be demonstrated readily, both in the laboratory and the patient [11]. Exponential transfer and spread of existing resistance genes through a previously susceptible bacterial population is a much more efficient mechanism of acquiring resistance than the development of resistance by mutation of individual susceptible cells. Mechanisms by which transfer of resistance genes takes place are discussed. Notably, however resistance appears in a hitherto susceptible bacterial cell or population, it will only become widespread under the selective pressures produced by the presence of appropriate antibiotics. In addition, the development of resistant cells does not have to happen often or on a large scale. A single mutation or transfer event can, if the appropriate selective pressures are operating, lead to the replacement of a susceptible population by a resistant one. Without selective pressure, antibiotic resistance may be a handicap rather than an asset to a bacterium.

Cross-resistance and multiple resistances

These terms are often confused. Cross-resistance involves resistance to several different members of a group of (usually) chemically related agents that are affected alike by the same resistance mechanism. For example, there is almost complete cross-resistance between the different tetracyclines because tetracycline resistance results largely from an efflux mechanism that affects all members of the group. The situation is more complex among other antibiotic families. Thus, resistance to aminoglycosides may be mediated by any one of a few different drug-inactivating enzymes with different substrate specificities, and the range of aminoglycosides to which the organism is resistant will depend on which enzyme it produces. Cross-resistance can also beobserved occasionally between unrelated antibiotics. For example, a change in the outer membrane structure of Gram-negative bacilli may concomitantly deny access of unrelated compounds to their target sites. In contrast, multiple drug (multidrug) resistance involves a bacterium becoming resistant to several unrelated antibiotics by different resistance mechanisms. For example, if a staphylococcus is resistant to penicillin, gentamicin, and tetracycline, the resistances must have originated independently, since the strain destroys the penicillin with a β-lactamase, inactivates gentamicin with an aminoglycoside-modifying enzyme, and excludes tetracycline from the cell by an active efflux mechanism. It is, however, not always clear whether cross-resistance or multiple resistances is being observed. Genes conferring resistance to several unrelated agents can be transferred en bloc from one bacterial cell to another on plasmids thereby giving the appearance of cross-resistance. In such cases, detailed biochemical and genetic analysis may be required to prove that the resistance mechanisms are distinct (multiple resistance), although the genes conferring resistance are linked and transferred together on one plasmid. The end result may be the same (i.e. resistance to multiple agents) but the risk of the spread is greater for plasmid mediated resistance (Davey P 2015). **Natural (Biological) Causes:** Selective pressure, mutation, gene transfer, societal pressures inappropriate use of drugs, inadequate diagnostics and hospital use (Fig 3).

- **The clinical problem of drug resistance**

Concerns about resistance have been raised at regular intervals since the first introduction of anti-microbial chemotherapy but awareness of the antibiotic resistance problem has probably never been greater than it is today. For example, a 2013 report estimated that in the United States alone at least two million people acquire serious infections with bacteria that are resistant to one or more antibiotics of potential use in such cases. Furthermore, there are at least 23,000 deaths each year as a direct result of these antibiotic-resistant infections, with many other deaths indirectly related to resistance. Indeed, some have suggested that antibiotic resistance threatens to return some settings to a ‘pre-antibiotic era’. It is important not to understate or overstate the problem; the situation is presently becoming serious but is not yet desperate, since most infections are still treatable with several currently available agents. This may, however, mean that the only antibiotics that are still active are more toxic or less effective (or both) than those to which bacteria have acquired resistance [55]. For example, it is

generally accepted that glycopeptide antibiotics are less effective in the treatment of *Staph. aureus* infection than are antistaphylococcal penicillins (e.g. flucloxacillin); since the latter cannot be used against methicillin-resistant *Staph. aureus* (MRSA), this may partly explain the poorer outcome, including increased risk of death that is seen in such cases in comparison with infection caused by methicillin-susceptible strains. There is good evidence that if the antibiotic regimen chosen is subsequently shown to be inactive against the pathogens causing infection, then patient outcome is worse this means that clinicians are likely to opt for unnecessarily broad-spectrum therapy, particularly in critically ill patients. Unfortunately, repeated use of such regimens against bacteria that harbor resistance genes intensifies the selective pressure for further resistance development, notably in hospitals, where the most vulnerable patients are managed. In many less-developed countries of the world, the therapeutic options may be severely restricted for economic reasons[17]. There is no doubt that the problem of antibiotic resistance is a global issue, and in future years there is a real possibility that physicians will be faced increasingly with infections for which effective treatment is not available. There are many examples of the intercontinental spread of resistant pathogens, and so the judicious use of antibiotics has global as well as local relevance. Some of the organisms in which resistance is a particular problem are summarized below [9].

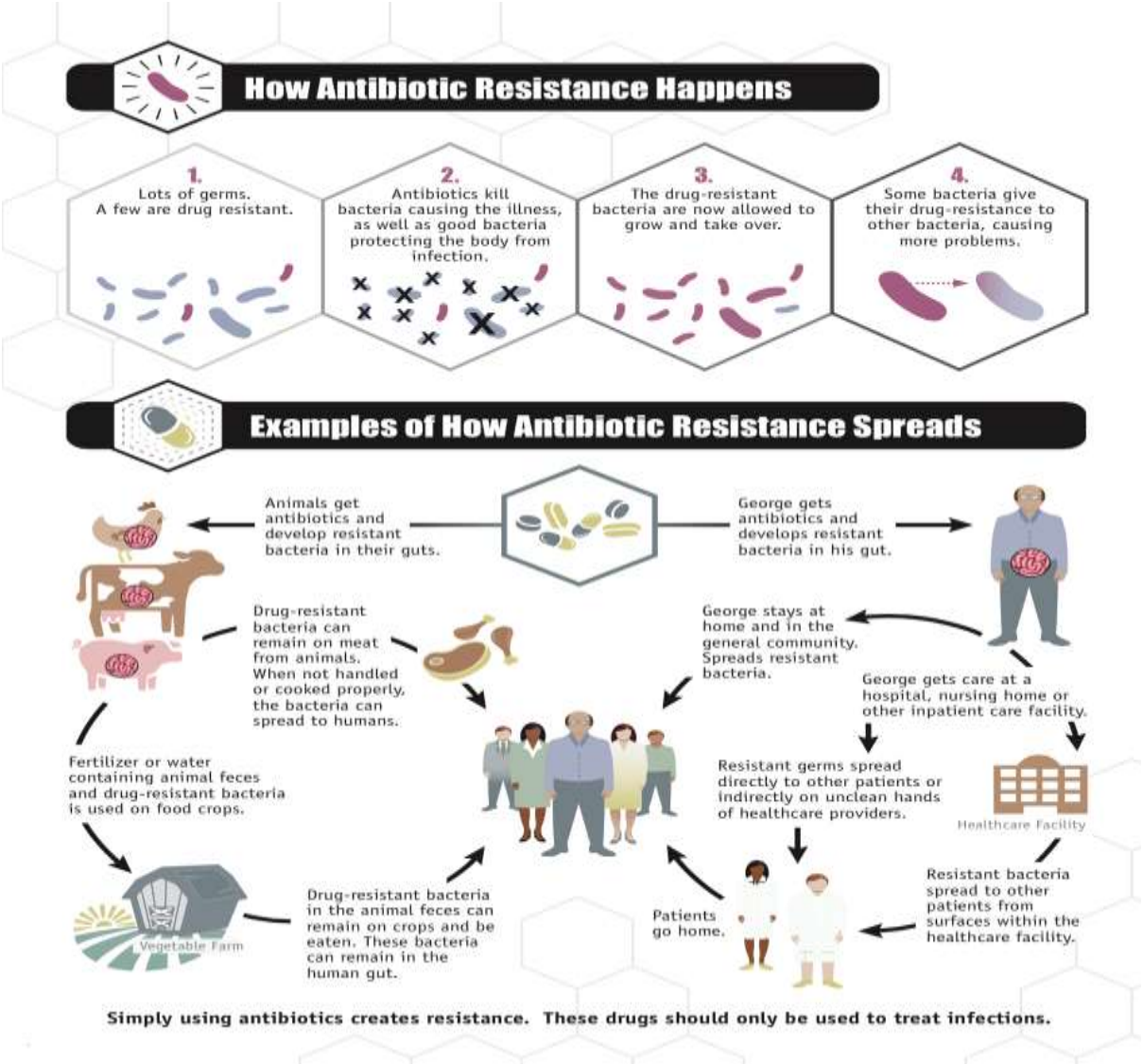


Fig 3. How antibiotics resistance evolves and spreads

- **Therapeutic uses of Antimicrobials:**

Antimicrobials are referring to prevent the setting of infections or suppressing contacted infections before it becomes clinically manifest. They are used as prophylactically or to treat the microbial infections.

Antimicrobials are used in Respiratory infections are caused by viruses, or bacteria, or both. If the illness is entirely viral in origin, an antibiotic will not help. If there is a bacterial component, antibiotic treatment will sometimes help and may be vital. It is often difficult to recognize when bacteria may be involved in respiratory infection, as secondary bacterial infection may complicate viral respiratory infections. Antimicrobial chemotherapy is just one component of an overall strategy to prevent and treat infections. Respiratory infections are: Sore throat, acute otitis media, acute sinusitis, acute cough, community-acquired pneumonia, chronic obstructive pulmonary disease, acute bronchitis, cystic fibrosis, pertusis, and tuberculosis [34].
Urinary tract infection is the second most common clinical indication for empirical antimicrobial treatment in primary and secondary care; respiratory tract infections are the commonest clinical indication in both settings. Sexually transmitted infections: Gonorrhoea, Non-specific urethritis, Thrush, Trichomoniasis, Non-specific vaginosis, Syphilis, Chancroid, Herpes, Lymphogranuloma venereum, Herpes and Warts [18].
Gastrointestinal infections: Gastrointestinal disease caused by bacteria, viruses, protozoa, and helminths are among the commonest infections suffered by mankind. Cholera, Campylobacter infection, amoebiasis Salmonellosis, Enteric (typhoid and paratyphoid) fever, Shigellosis, etc. are major gastrointestinal infections [15].
Bacterial bloodstream infections: Bacteraemia, Sepsis, are the common bloodstream infections. Endocarditis is inflammation of the endocardial surface of the heart and usually involves the heart valves. When caused by microorganisms it is known as ‘infective’ endocarditis and may be caused by bacteria, including rickettsiae and chlamydiae, and fungi. Bone and joint infections: septic arthritis, Osteomyelitis is common bone and joint infections [51].

Infections of the central nervous system: include meningitis, encephalitis, and brain abscess. These can be caused by viruses, bacteria, fungi, and protozoa; however, bacterial and viral causes predominate. Bacterial infection is generally acquired from an exogenous source and spreads to the central nervous system via the bloodstream. Penetrating injuries and trauma, including neurological procedures, can be complicated by infection. In the case of brain abscess, bloodstream or spread from adjacent infected sites (middle ear, sinuses) are also important. All infections of the central nervous system are serious. Many infections, notably, meningitis, encephalitis, and brain abscess, will prove fatal unless diagnosed and treated promptly. Skin and soft-tissue infections: Many different microorganisms, including bacteria, fungi, and some viruses, may be involved in skin and soft-tissue infections. However, by far the commonest bacterial causes are *Staph.aureus* and *Str. pyogenes*. Thrush is usually caused by the yeast *Candida albicans* and cold sores by the virus herpes simplex. Skin and soft-tissue infections are common and frequently severe. Cellulitis and erysipelas, Pustules, Impetigo, Pustular lesions, Gas gangrene are skin and soft tisuue infections [23]

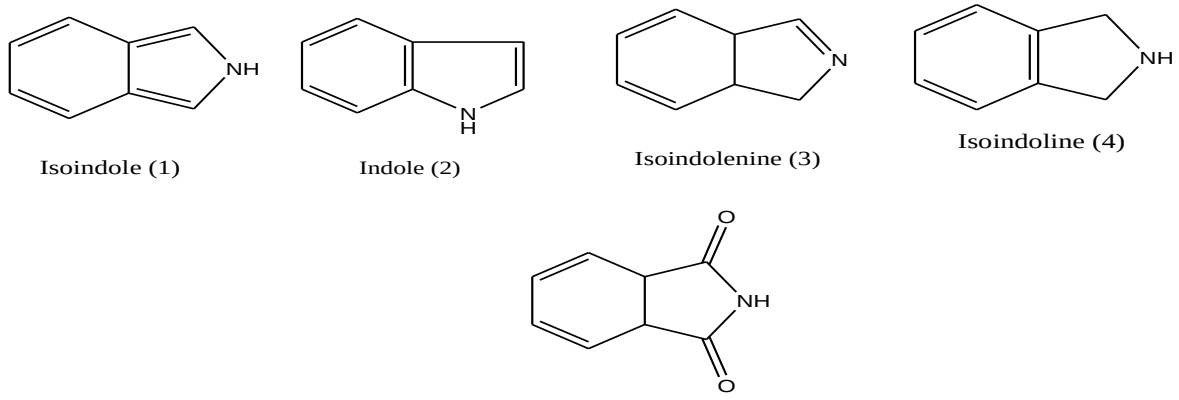
1.6 Introduction to the development and marketing of antimicrobial drugs:
Moreover, nearly all new antibacterial agents are chemically modified variants of existing compounds, although entirely new classes of antiviral and antifungal agents have emerged. Fourteen classes of antibiotics were introduced for human use between 1935 and 1968. There is a particular lack of new agents with novel targets or mechanisms of action against multi drug resistant Gram-negative bacteria. The cost of development of a new antimicrobial, risk of failure to gain regulatory approval (especially considering the number of current agents), and perceived profit margin (unlike drugs prescribed for chronic diseases, antibiotics are typically given for only a few days to each patient) has led to many pharmaceutical companies ceasing development of antibiotics. Only five major pharmaceutical companies (GlaxoSmithKline, Novartis, AstraZeneca, Merck, and Pfizer) still had active antibacterial discovery programmes in 2008. In the same year an investigation of the development pipeline of both small and large pharmaceutical companies found that only 15 of 167 antimicrobial agents had a new mechanism of action with the potential to meet the challenge of multidrug resistance. Most of those were in the early phases of development and thus the chance of these successfully navigating the clinical investigation pathway required for new drugs is slim. In vitro screening offers an extremely simple and generally effective way of detecting antimicrobial activity and has yielded a rich harvest of therapeutically useful compounds over the years [34]. In contrast, the rational design of antimicrobial agents that can disable vulnerable stages of microbial development has not been very fruitful so far, although the use of newer approaches such as genomics, molecular modelling, and combinatorial chemistry offer the prospect that this might change in the future. Compounds that pass the initial screening tests must be made available in sufficient quantities and in sufficiently

pure form to enable preliminary tests of toxicity and efficacy to be carried out in laboratory animals, and more extensive and precise in vitro tests to be performed. Animal tests of toxicity, pharmacology, and efficacy are an indispensable part of the development of any new drug but they also have certain limitations. Idiosyncratic reactions may suggest toxicity in a compound that would be safe for human use or, more importantly [44], adverse reactions peculiar to the human subject may go undetected. The pharmacological handling of the drug may be vastly different from that encountered in the human subject. As regards efficacy testing, animals have important limitations in that experimental infections seldom correspond to the supposedly analogous human condition, either anatomically or in the relationship of treatment to the natural history of the disease process. If preliminary tests of toxicity and efficacy indicate that the compound is worth advancing further, full-scale acute and chronic toxicity tests are carried out in animals. These include long-term tests of mutagenic or carcinogenic potential, effects on fertility, and teratogenicity. Mutagenicity tests may also be performed in microbial systems (Ames test). Provided the animal toxicity studies reveal no serious toxicity problems, the first tentative (Phase 1) trials are undertaken in healthy human volunteers to investigate the pharmacokinetic properties and safety of the new drug in man. Although animal data provide only a crude estimate of how the drug may be handled in human beings, if properly interpreted, they allow an estimate to be made for the first human dose-ranging studies. Once these tests have been successfully completed, application may be made to the drug-licensing authority for permission to undertake (Phase 2 and 3) clinical trials [26].

1.7 **Phthalimide (Isoindoline-1, 3-dione) as antimicrobials**

In recent years, microbial infections are associated with high rates of attributable morbidity and mortality. Infections caused by microbial species are common in immune compromised patients and have significant treatment costs and mortality [14]. The increasing rate of bacterial resistance to clinical antimicrobial agents and its impact on the treatment of infectious diseases have begun to present a unique problem throughout the world. Drug resistant, multiple drug resistant (MDR), and extensively drug resistant (XDR) to infectious bacterial pathogens put a greater risk on the population at large due to the risk of pandemic illness [24]. Nowadays, the most serious public health problems in the world are infectious diseases. The evidence of multi-drug resistant microbial pathogens due to extensive use of antibiotics has been appeared and stimulated the search for discovery of new safer, potent, and resistance-free antimicrobial agents [48]. Moreover, the research for novel, selective and more potent antimicrobial agents is still a vital challenge for biologists and medicinal chemists. Heterocyclic compounds have been found to possess important physiological and pharmaceutical properties [Jones, 2002; Alexandre 2005]. Major fractions of organic compounds isolated from nature are comprised of nitrogen heterocycles. The structural diversity and biological importance of nitrogen containing heterocycles have made them attractive targets for synthesis over many years [12]. Phthalimide (isoindoline1, 3-dione) has usually been employed in the design of potential anti-microbial drug candidates [17]. There are a number of studies showing that compounds bearing a phthalimide core may be a scaffold for designing new anti-microbial agents [33]. Isoindoline is a heterocyclic organic compound with the molecular formula C_8H_9N. The parent compound has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing ring. Isoindoline-1, 3-dione commonly known as phthalimide, a key heterocyclic compound [43] used for variety of biological applications. Phthalimides have served as starting materials and intermediates for the synthesis of many types of alkaloids and pharmacophores [38]. Phthalimide is an imido derivative of phthalic acid. It can be synthesized by the reaction between phthalic anhydride and substituted amino compounds in presence of base. In organic chemistry, imide is a functional group consisting of two carbonyl groups bound to nitrogen. These compounds are structurally related to acid anhydrides [Kushwaha N, 2016]. N-1, 3-disubstituted isoindolines are heterocyclic compounds constituents of some pharmaceuticals and natural products and possess important physiological and pharmaceutical properties.

Isoindole (1) is isomeric with indole (2) which comprises a benzene ring fused with a pyrrole nucleus. The parent compound and the 2-unsubstituted derivatives can tautomerize with the 1H isomer, i.e. isoindolenine or (1H-isoindole) (3). Isoindole is much more unstable compared with indole and undergoes rapid oxidation in air to form polymers. Isoindole is thermodynamically more stable than its isoindolenine isomer at room temperature [19]. The next stable reduction state of isoindole is isoindoline (4). Phthalimide is isoindoline-1, 3-dione (5) (Fig. 4).



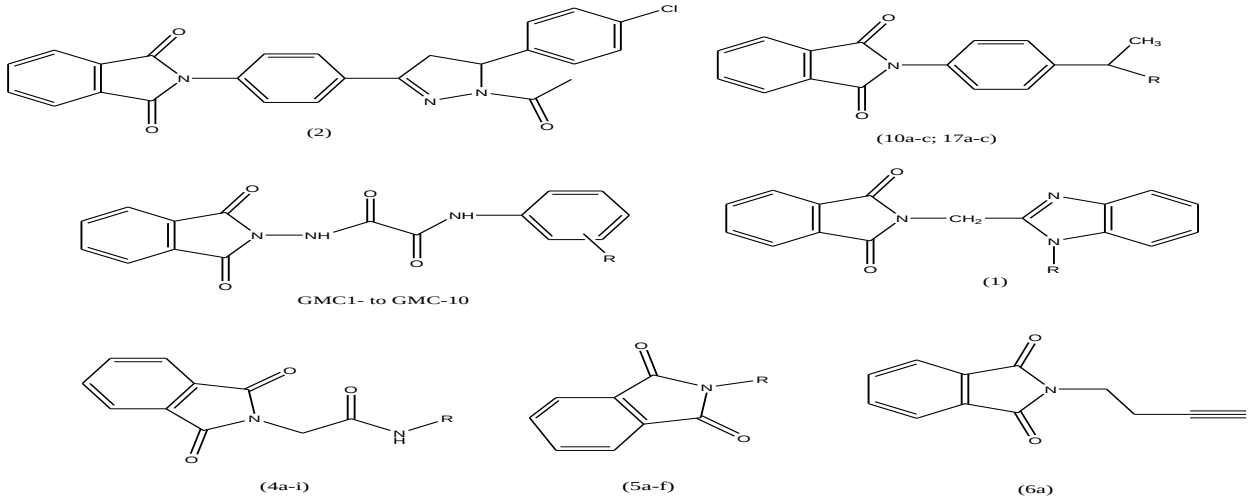
Isoindole (1) Indole (2) Isoindolenine (3) Isoindoline (4)

Phthalimide or 2*H*-isoindole-1,3(3a*H*,7a*H*)-dione (5)

Fig 4. General structures of Isoindole

Substituted phthalimides are used predominantly as chiral building blocks in organic synthesis and can be used as key intermediates in the preparation of bio-active compounds i.e. antibacterial, analgesic, antifungal, virucidal, plant growth regulator and also in dye industry.

Phthalimides and their N-substituted derivatives belong to the imide ring containing heterocyclic class of compounds which possess extensive biological activities [47]. The most important biological activity properties that have been reported for phthalimide (isoindoline-1, 3-dione) derivatives area anti-microbial [49]. According to the World Health Organization (WHO), infectious and parasitic diseases are still the second cause of death worldwide. This is assumed to be due to resistance to the anti-microbial agents used. There are several studies showing that compounds bearing a phthalimide core may be a scaffold for designing new anti-microbial agents [41]. A literature search of suitable nuclei of use as antimicrobial agents, revealed phthalimide was one of these heterocyclic compounds [36]. The chemical core of phthalimide (-CO-N(R)-CO-) shows they are hydrophobic, and this increases their potential to cross biological membranes in vivo [42]. To increase the biological activity of phthalimide derivatives, a molecular hybridization approach was used for antimicrobial and biological activities. Phthalimides have served as starting materials and intermediates for the synthesis of many types of therapeutic synthons, alkaloids, and pharmacophores has been used as herbicides to control bacterial contamination [49]. Following are representative examples of isoindoline derivatives for antimicrobial potentials (Fig.5).



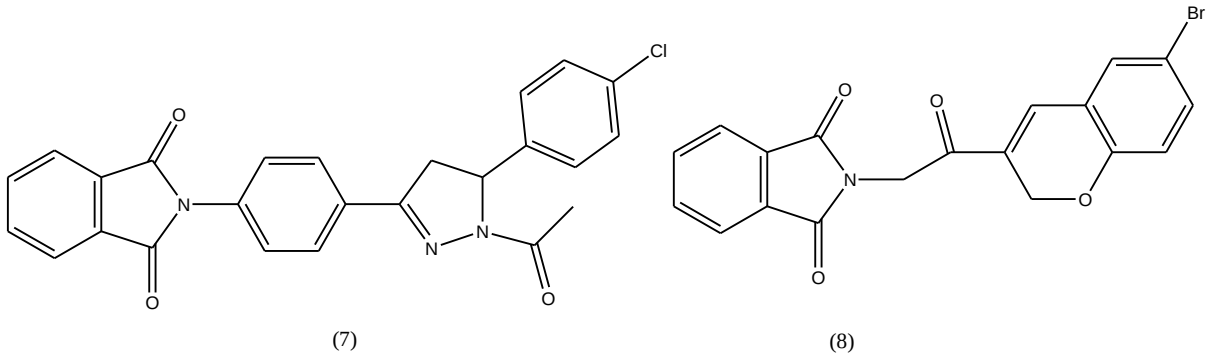


Fig 5. Examples of isoindoline derivatives for antimicrobial potentials.

Due to wide range of applications in medicinal chemistry, interest is increasing in the synthesis and biological activities of phthalimide and its derivatives. Herein, we report the synthesis and biological evaluation of some new compounds containing mainly a phthalimide pharmacophore and enhanced by certain modifications for finding with antimicrobial potentials (Fig 6).

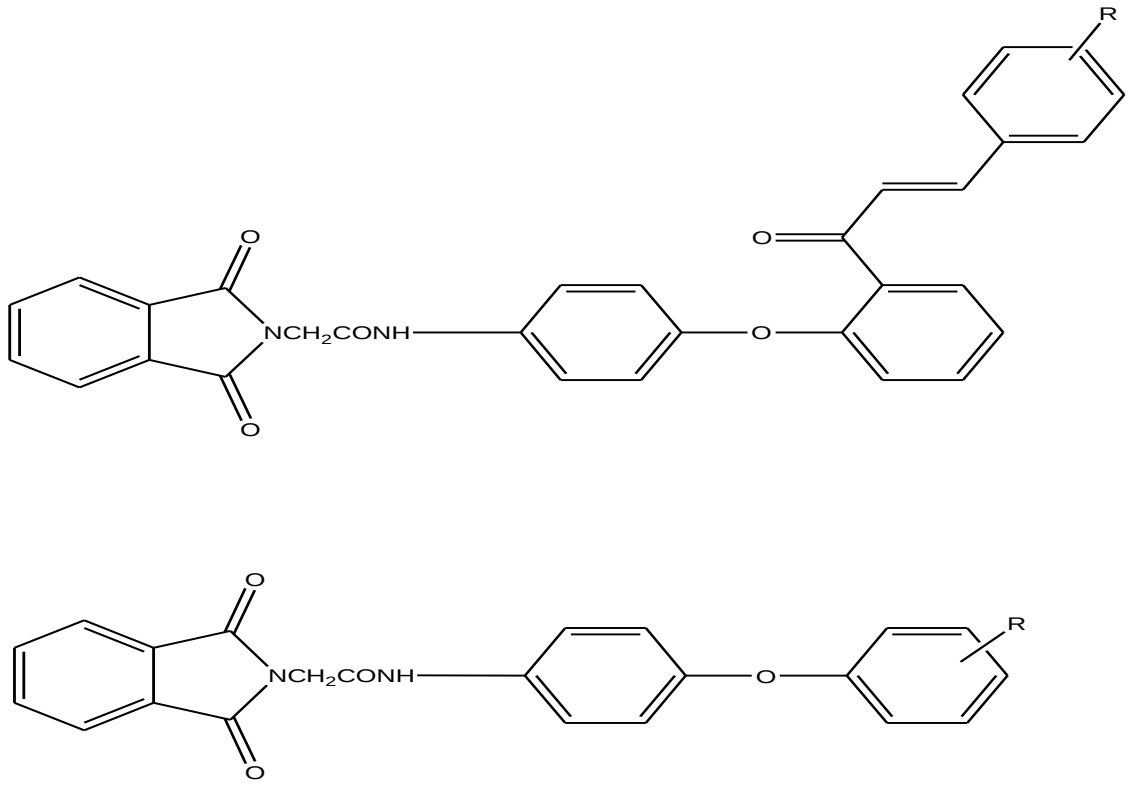


Fig 6. Designing of isoindoline derivatives

Mechanisms of Antibacterial Resistance:

Antibacterial resistance can arise through various mechanisms, including:

Genetic Mutation: Bacteria can acquire resistance to antibiotics through spontaneous mutations in their genetic material, leading to alterations in the target sites of antibiotics or the expression of enzymes that inactivate antibiotics [25], Horizontal Gene Transfer: Bacteria can exchange genetic material through mechanisms such as conjugation, transformation, and transduction, facilitating the spread of resistance genes among bacterial populations [35]. Efflux Pumps: Bacteria can develop efflux pumps that actively extrude antibiotics from the bacterial cell, reducing their intracellular concentration and rendering them ineffective [61]. Biofilm Formation:

Bacteria embedded in biofilms exhibit increased resistance to antibiotics due to the limited penetration of antibiotics into the biofilm matrix and the presence of persister cells with reduced metabolic activity.

Contributing Factors to Antibacterial Resistance:
Several factors contribute to the emergence and spread of antibacterial resistance, including:

- **Overuse and Misuse of Antibiotics**: The inappropriate use of antibiotics in human and animal healthcare, including unnecessary prescriptions, incomplete treatment courses, and agricultural use, accelerates the development of resistance.
- **Poor Infection Control Practices**: Inadequate infection prevention and control measures in healthcare settings facilitate the transmission of antibiotic-resistant bacteria among patients.
- **Globalization and Travel**: The interconnectedness of modern society facilitates the global spread of antibiotic-resistant bacteria through travel, trade, and migration.
- **Lack of New Antibiotics**: The pipeline for new antibiotic development has dwindled in recent years, leading to a scarcity of effective treatment options for resistant infections.

Challenges in Addressing Antibacterial Resistance:
Addressing antibacterial resistance poses several challenges, including:

- **Complexity of Resistance Mechanisms**: Antibacterial resistance mechanisms are diverse and complex, requiring a multifaceted approach for effective control and prevention.
- **Economic Considerations**: The development of new antibiotics is costly and time-consuming, making it challenging for pharmaceutical companies to invest in antibiotic research and development.
- **Global Coordination**: Antibacterial resistance is a global problem that requires coordinated efforts across countries and regions to implement effective surveillance, infection control, and antimicrobial stewardship measures.
- **One Health Approach**: Antibacterial resistance is interconnected with human, animal, and environmental health, necessitating a One Health approach that addresses antimicrobial use and resistance in all sectors.

Strategies to Combat Antibacterial Resistance:
Several strategies can be employed to combat antibacterial resistance, including:

- **Antimicrobial Stewardship Programs**: Implementing antimicrobial stewardship programs in healthcare settings to promote judicious antibiotic use, improve prescribing practices, and prevent the emergence of resistance.
- **Development of Novel Antibiotics**: Investing in research and development for the discovery of new antibiotics and alternative therapies that target resistant bacteria.
- **Surveillance and Monitoring**: Enhancing surveillance systems to monitor antibiotic resistance patterns, identify emerging threats, and track the spread of resistant bacteria.
- **Public Awareness and Education**: Increasing public awareness about the appropriate use of antibiotics, the importance of infection prevention, and the consequences of antibacterial resistance.

Conclusion:
Antibacterial resistance is a complex and multifaceted problem that requires concerted efforts from healthcare providers, policymakers, researchers, and the public to address effectively. By understanding the mechanisms of resistance, identifying contributing factors, and implementing targeted strategies, it is possible to mitigate the impact of antibacterial resistance and preserve the effectiveness of antibiotics for future generations. Continued investment in research, surveillance, and global collaboration is essential to combat this urgent public health threat. antimicrobial resistance (AMR) stands as an imminent threat to global health, demanding urgent and coordinated action. The rise of resistant pathogens poses a grave challenge, jeopardizing our ability to combat infectious diseases effectively. This phenomenon not only undermines medical advancements but also endangers countless lives worldwide. Addressing AMR requires a multifaceted approach involving collaboration among healthcare professionals, policymakers, researchers, and the public. Implementing robust surveillance systems to monitor resistance patterns, promoting judicious antimicrobial use through education and guidelines, and investing in research for new antimicrobial agents and alternative therapies are paramount. Furthermore,

fostering international cooperation and strengthening health systems, particularly in low- and middle-income countries, is essential to curb the spread of resistant infections globally. Sustainable funding mechanisms, innovative incentives for research and development, and regulatory frameworks to ensure responsible antimicrobial use are integral components of this endeavor. Individuals also play a pivotal role in combating AMR by adhering to prescribed treatments, practicing good hygiene, and advocating for antimicrobial stewardship in their communities. Ultimately, addressing antimicrobial resistance demands a concerted effort at all levels of society. The role of the synthesized derivative s of the **isoindoline has been illustrated, b**y prioritizing this issue and implementing comprehensive strategies, we can mitigate the threat posed by resistant pathogens, safeguarding the efficacy of antimicrobials for future generations and ensuring a healthier and more resilient world.

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