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ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF ANTIMICROBIAL FORMULATIONS - A REVIEW

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ABSTRACT: Microbes are widespread and have been studied widely in recent years. Disease-causing microbes can also be called pathogens, germs, or bugs. These microbes are responsible for causing infectious diseases. Microbes are mediators in almost all ecosystem processes and act as a global pivotal game changer in various ecological activities. The therapeutic outcome with antimicrobial drugs depends totally on the selection of antimicrobial drugs. The choice of antimicrobial drugs depends on causative agents, patient factors, and clinical pharmacology of antimicrobial agents. The current review discusses how microbes can enter the human body through different sites and how antimicrobial drugs help cure various infectious diseases. Along with the same, the current review also represents how antimicrobial drugs affect the viability of microorganisms. The article also incorporates the prophylactic use of antimicrobial drugs. The main objective of the current review article is to give detailed knowledge about single, binary and tertiary combinations of antimicrobial drugs, analytical methods, and patent search of these drugs.

INTRODUCTION: The primary cause of death and dysfunction is an infectious illness. Bacteria are becoming increasingly difficult to handle because of their resistance to the drugs (antibiotics) used to treat infections. Of the six main types of microorganisms, mainly bacteria, viruses, protozoa, fungi, algae and archaea have been associated with human disease [1]. Pathogens can be considered as all those microbes that have the potential to cause illness [2]. Less than 1% of bacteria are hazardous germs that can enter our bodies (the host) and cause illness.

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Germs bring on infectious diseases like the flu and measles. Additionally, there is compelling evidence that bacteria may be the root of various chronic non-infectious disorders, including coronary heart disease and a few types of cancer. Microbes must enter our bodies in the proper chronological order to trigger an illness. They enter through a location called a portal of entry [3].

The four locations indicated below from which microbes can enter the body:

- ✓ The mouth and nose, e.g., the respiratory tract (where the influenza virus that causes the flu lives).
- ✓ Gastrointestinal tract, such as Vibrio cholera, which causes cholera, in the mouth or oral cavity.

- ✓ Infections of the urogenital tract, such as cystitis-causing Escherichia coli.
- ✓ Skin surface breaks that allow bacteria like Clostridium tetani, which causes tetanus, to enter.

Microbes need to do the following to infect us and cause illness [3]:

- ✓ Reach their target site in the body.
- ✓ Connect with the target they are trying to infect to prevent them from being released.
- ✓ Multiply instantly
- ✓ Take nutrients from the host.
- ✓ Prevent and sustain the attack of the host immune system.

For some of the most common infectious diseases, there are vaccines and therapies available. Many are very cost-effective and reasonably priced, but due to prices and access issues brought on by underperforming healthcare systems, many are underutilized. The creation of new drugs and vaccines will continue to be vital tools for treating and preventing infections, but reducing the burden of infection will depend on how well these interventions are delivered [4].

Classification of Antimicrobial Drugs: Bacteria, viruses, fungi, and parasites are the four main microorganisms used in medicine.

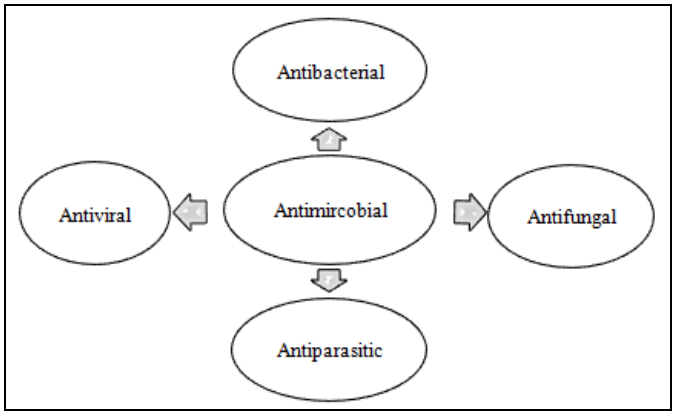

FIG. 1: CLASSIFICATION OF ANTIMICROBIAL DRUGS [5]

Antibacterial: An antibacterial agent prevents bacteria from proliferating and growing. Antibacterial agents are currently most frequently defined as substances that clean surfaces, eliminate potentially hazardous germs, and neutralize household cleansers. They should only be used if clinical or lab results indicate bacterial infection.

Based on their effectiveness and the amount of residue they leave behind, antibacterial agents can be categorized into two categories: Those in the first category function swiftly to eliminate bacteria, but they also vanish (*via* evaporation or disintegration) and leave no active residue behind (referred to as non-residue-producing). Aldehydes, alcohols, chlorine, and peroxides are a few examples of this category.

The second group is primarily made up of more recent substances that have a sustained action by leaving long-lasting residues on the surface to be cleaned (referred to as residue-producing). Benzalkonium chloride, triclosan and triclocarban are typical members of this group [5].

Antiviral agents: Medications in the antiviral medicine class are used to treat viral infections. Specific viruses enter our bodies and cause a variety of ailments. At the same time, the majority of antivirals focus on specific viruses, a broad-spectrum antiviral works against a range of viruses. Available antiviral drugs are primarily used to treat hepatitis b and c, influenza a and b, HIV and herpes viruses [6].

Antiparasitic agent: Antiparasitic drugs are treatments used to control and cure infections caused by parasites such as protozoa, helminths and ectoparasites. Various classes of antiparasitic medications treat a wide range of diseases brought on by parasites. This activity describes the uses, modes of action, side effects and contraindications of major antiparasitic drug classes as effective treatments for illnesses like malaria, pneumocystis, trypanosomiasis and scabies[7].

Antifungal agent: Fungal infections are treated by antifungal drugs. Ringworm, yeast infections, and skin and nail infections are a few examples. Respiratory ailments can result from breathing in fungus spores. Immune deficiencies make people more vulnerable to fungal infections that call for antifungal medication. Antifungals are drugs that either eradicate or inhibit the development of the

fungi that cause infections. They are also termed as antimycotic agents [8].

Different types of drugs and antifungal treatments come in many classes.

- ✓ Fluconazole and other azoles are fabricated, synthetic antifungals that stop the growth of fungi.
- ✓ Echinocandins, are more recent semi-synthetic antifungals that target and harm the fungus wall, including micafungin [8].

Pathophysiology of Antimicrobials: There are five basic ways that antimicrobials might alter the viability of microorganisms [9].

- ❖ Inhibition of cell wall synthesis
- ❖ Inhibition of microbial protein synthesis
- ❖ Interference with nucleic acid synthesis
- ❖ Inhibition of metabolic pathways
- ❖ Disruption and increased permeability of the cytoplasmic membrane

The following **Table 1** represents the classification of antimicrobial agents and their mode of action.

TABLE 1: CLASSIFICATION OF SOME ANTIMICROBIAL AGENTS AND THEIR MODE OF ACTION [9]

Drug target (Mode of action)	Antimicrobial agent
Inhibition of cell wall synthesis	B-lactam: penicillin, cephalosporin, carbapenems, monobactam Glycopeptide: vancomycin
Inhibition of protein synthesis	Aminoglycoside, tetracycline and macrolides.
Interference with nucleic acid	Inhibit DNA synthesis: fluoroquinolones. Inhibit RNA synthesis: rifamycin
Inhibition of metabolic pathway	Sulphonamide and trimethoprim
Disruption of increased permeability of the cytoplasmic membrane	Polymyxin

Antimicrobial agents have different sites and mechanisms of action. **Fig. 2** represents the Mechanism and Site of Action of Antimicrobial Agents.

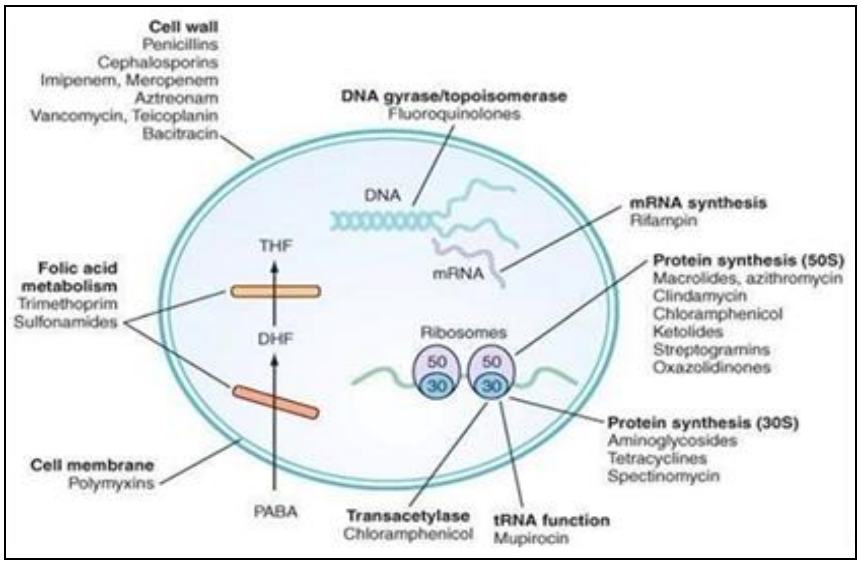

FIG. 2: MECHANISM AND SITE OF ACTION OF ANTIMICROBIAL AGENTS [9]

Inhibition of Cell wall Synthesis [9]: Interfere with peptidoglycan synthesis. Low toxicity causes cell lysis and includes penicillin and vancomycin as examples Ampicillin, methicillin and oxacillin are further antibiotics in the penicillin family (B-lactam). B-lactam antibiotics like penicillin and cephalosporins are the most frequently utilized antimicrobial medicines that prevent cell wall production. Direct inhibition of bacterial transpeptidases by B-lactam antibiotics is highly effective. B-lactam transpeptidase inhibitors prevent the maturation of peptidoglycan from its immature state; as a result, these enzymes are known as penicillin-binding proteins (PBPs).

Glycopeptides are a different class of antibacterial drugs that prevent the production of cell walls. When compared to B-lactams, vancomycin's inhibition of peptidoglycan production results in a relatively slow inhibition. Vancomycin transfers the disaccharide of the peptidoglycan precursor to the developing glycan polymer of the cell wall by forming a stoichiometric 1:1 complex with the trans glycosylase enzyme and the peptidoglycan precursor. The glycopeptides prevent the transglucosylase and transpeptidase enzyme processes from completing the formation of the stiff cell wall peptidoglycan.

Microbial Protein Synthesis Inhibition [9]: A variety of antimicrobial agents function by blocking the development of bacterial proteins (ribosome function). Some of these include aminoglycosides, macrolides and tetracyclines. In the initiation, elongation and termination phases, cytoplasmic components connect to particles with the help of ribosomes, to control the synthesis of proteins in microbes.

Interfere with mitochondrial prokaryotic (the 70s) ribosomes. While erythromycins, chloramphenicol, and clindamycin work at the level of 50S ribosomal subunits, tetracyclines, aminoglycosides and chloramphenicol act at 30S ribosomal subunits.Aminoglycosides kill bacteria by preventing protein synthesis. They achieve this by attaching to the 30S subunit ribosome, which prevents the initiation complex from functioning and prevents the creation of peptide bonds.

Most of the time, they target Gram-negative bacteria. Tetracyclines prevent aminoacyl t-RNA from attaching to the 30S ribosomal subunits, preventing bacteria from producing protein. They stop new amino acids from being added to the peptide chain. They are inconsistently effective against infections brought on by bacilli and cocci. By preventing the release of t-RNA after the transfer of its amino acids to the growing polypeptide, clindamycin prevents the creation of bacterial proteins.

Interference with Nucleic Acid Synthesis [9]: Disrupt the transcription and replication of DNA. Some substances, such as rifamycin and quinolones, may be harmful to human cells. Synthetic nalidixic acids are quinolones. They belong to the same class of medications as levofloxacin, ofloxacin, and ciprofloxacin. They are antibacterial and work by preventing DNA gyrase from causing bacteria to synthesize DNA. It takes the enzyme DNA gyrase to unwind DNA strands so that they can be duplicated. Both Gram-positive and Gram-negative organisms are susceptible to quinolones antimicrobial effects. Rifampin inhibits the development of bacteria by tightly binding to their DNA-dependent RNA polymerase. This prevents the synthesis of RNA in bacteria. Rifampin works against viruses using a different way. It prevents a crucial step in the formation of polioviruses.

Inhibition of Metabolic Pathways [9]: Sulphonamides and trimethoprim prevent the synthesis of nucleotides, which prevents the production of nucleic acids. Sulphonamides compete for the enzyme's active center and replace PABA. Overuse of PABA can negate the sulphonamides inhibitory effects on bacterial growth. Sulphonamides are bacteriostatic medications that work well against both Gram-positive and Gram-negative bacteria.

Both Gram-positive and Gram-negative organisms are susceptible to the drug trimethoprim. The substance prevents dihydro folic acid reductase from functioning. This enzyme reduces tetrahydro folic acid from dihydro folic acid, inhibiting DNA and purine synthesis.

Disruption and Increased Permeability of Cytoplasmic Membrane [9]: Influence modifications in membrane permeability.

1. Cause cell lysis and/or metabolite loss.
2. Several antibiotics are found in polypeptides.
3. Polymyxin, for instance (antibacterial)

By attaching to the cell membrane, polymyxin increases its permeability. Cell death results from water uptake. They act as detergents because they are cationic, basic proteins (surfactants). Acute renal tubular necrosis and neurotoxicity are two possible side effects. It is commonly used in topical first-aid preparation.

Management of Antimicrobial Therapy:

Introduction of Antimicrobial Therapy: The urgency of the condition should determine when to begin initial therapy. In severely ill patients, such as those in septic shock, febrile neutropenic patients and patients with bacterial meningitis, empiric therapy should be initiated right after or concurrently with the collection of diagnostic specimens. Two important examples of this idea are subacute bacterial endocarditis and vertebral osteomyelitis/diskitis.

Antibiotic therapy should be delayed until numerous blood cultures, disc space aspirate specimens and/or bone biopsy specimens have been collected (in the case of endocarditis). Antibiotic medication should be delayed until the patient has symptoms, which frequently take days to weeks to manifest in patients with these illnesses. In these circumstances, if antimicrobial medication is initiated too soon, it may inhibit bacterial growth and render a microbiological diagnosis which is crucial for monitoring these patients care impossible. To recover, these individuals must receive directed antimicrobial therapy for several weeks to months [10].

Antimicrobial agents:

Combination Therapy [10-11]: A combination of two or more antimicrobial medicines is advised in a few circumstances, even though single-agent antimicrobial therapy is normally favoured.

Treatment of Microbial disease using More than one Antimicrobial agent: Certain lactams and aminoglycosides work in synergy to combat a wide range of gram-positive and gram-negative bacteria. They are used to treat serious infections where quick killing is crucial (e.g., treatment of endocarditis caused by Enterococcus species with a combination of penicillin and gentamicin). Gentamicin is bactericidal when combined with penicillin; penicillin alone is simply bacteriostatic, while gentamicin alone has no discernible effect. A comparable synergistic combination of penicillin or ceftriaxone with gentamicin for two weeks can be beneficial as penicillin or ceftriaxone alone in treating endocarditis brought on by some streptococci. Similar synergistic combinations can also be used to shorten the period of antimicrobial therapy.

To Treat Polymicrobial Diseases by Broadening the Antimicrobial Spectrum Beyond what can be achieved with a Single Agent: A combined regimen may be chosen when illnesses are suspected to be brought on by multiple organisms since it would broaden the antimicrobial range beyond what can be attained by a single drug. For instance, most intra-abdominal infections are frequently caused by multiple organisms with gram-positive cocci, gram-negative bacilli, and anaerobes. These situations may benefit from using antimicrobial combinations such as fluoroquinolone plus metronidazole or a third-generation cephalosporin which are sometimes more inexpensive than an equivalent single agent (e.g., a carbapenem).

To Inhibit Resistance from Developing: Antimicrobial medication typically exerts selective pressure on bacteria, leading to resistant variants. Suppose the mechanisms of resistance to the two antimicrobial agents are dissimilar. In that case, a mutant strain's likelihood of being resistant to both antimicrobial agents is significantly lower than its likelihood.

Combining therapy would improve the possibility that at least one drug will be effective, preventing the resistant mutant population from becoming the dominant strain and resulting in therapeutic failure. Because of this, combination drug therapy is accepted as the gold standard for treating disorders, including tuberculosis and the human immunodeficiency virus (HIV) when treatment duration is likely to be protracted.

Prophylactic use of Antimicrobial Drugs [11]: This refers to using antimicrobial drugs for prevention rather than the treatment of infections.

To preserve against certain microorganisms:

A. Long-acting penicillin G is used to prevent group A streptococci infections in patients with a history of rheumatic heart disease.

B. Procaine penicillin is advised for the prevention of gonorrhoea or syphilis after contact with an infected person.

C. Prevention of recurrent urinary tract infections caused by *E. coli*, trimethoprim-sulphamethoxazole is used.

Prevention of Infections among Patients at High Risk:

A. Preventing endocarditis by pre-treating individuals with valvular abnormalities who are getting dental work done, having tonsils removed, or having endoscopies with a high risk of bacteremia.

B. Patients enduring cancer chemotherapy or organ transplant.

C. To prevent wound infections following a variety of surgical procedures.

D. Dirty, filthy surgical procedures (e.g., resection of the colon). In clean surgical procedures, chemotherapy should not be performed consistently.

The use of antimicrobials in this way is the most widespread and prolonged. A wound infection occurs when several germs are present in the wound at the time of closure. Antibiotics must be used wisely and effectively in this case. They should be given immediately before and shortly after the procedure.

Antimicrobial therapy should not be continued for longer than 24 hours to prevent the development of resistant strains. The effectiveness of the antibacterial medication should successfully reduce the risk of surgical site infection. First-generation cephalosporins are now being used for chemoprophylaxis.

Patent Search for Antimicrobial Drugs: Over the past couple of years, much research has been done on antimicrobial drugs and many patents that can be beneficial for research purposes. **Table 2** Represents a list of the patent search for antimicrobial drugs.

TABLE 2: PATENTS OF ANTIMICROBIAL DRUGS

Sr. no.	Publication number	Patent title	Summary
1	US7470786B2	Method for manufacture of ceftriaxone sodium[12]	The most used intravenous cephalosporin antibiotic worldwide, ceftriaxone sodium has been safely prescribed for adults and children for more than 15 years [12]
2	CN101756897B	Clindamycin hydrochloride injection and preparation method[13]	The clindamycin hydrochloride injection has the advantages: firstly, the formula is simple, the species of excipients are few and the excipients belong to the medicinal injection grade, are commonly used medicinal excipients meet the requirements of intravenous injection[13]
3	US6663890B2	Metronidazole antibiotic product, use and formulation [14]	The use and composition of an antibiotic product are discussed in this. The invention also relates to an antibiotic product containing metronidazole and its salts, esters, metabolites etc [14.]
4	US4086332A	Doxycycline compositions [15]	It must deal with 2-pyrrolidone-containing aqueous doxycycline solutions. This is especially crucial when administering veterinary parenteral formulations to large animals [15]
5	US5710280A	Preparation of fluconazole and pharmaceutically acceptable salts[16]	The drug is effective in treating a variety of fungal infections, including mycosis, which affects the digestive and respiratory systems and fungal meningitis, which is brought on by, among other things, different species of Candida, Coccidioides and Trichophyton [16]
6	US6413537B1	Nystatin formulation has reduced toxicity[17]	To treat systemic fungal infections, the current invention offers a unique formulation of nystatin for parenteral administration. The formulation does not contain the toxicity and solubility issues that existed in nystatin formulations before it [17.]
7	US2985534A	Bacitracin products and processes [18]	Bacitracin may be prepared by the cultivation of microorganisms, such as Bacillus subtilis and particularly Bacillus licheniformis. This antibiotic has recently found considerable application in the preparation of feeds for poultry and livestock [18]
8	CN101537009A	The production process of compound preparation of ceftriaxone sodium and	The invention adopts evenly mixing of the liquid phase, can achieve good mixing uniformity, effectively increase the purity of the preparations simultaneously and further guarantees the advantage of high safety of clinic use[19]

		tazobactam sodium for injection [19]	
9	WO2013151516A1	Film tablet formulations comprising cefuroxime acetyl and clavulanic acid [20]	The current invention is directed to pharmaceutical formulations containing cefuroxime acetyl and clavulanic acid for use in the treatment and prophylaxis of upper respiratory tract infections caused by gram-positive and gram-negative bacteria, such as otitis media and otorhinolaryngological infections[20]
10	CN1839872A	Preparation method of clindamycin phosphate solution formulation [21]	The present invention relates to the solution of antibiotics clindamycin external preparation and put tablet field, particularly a kind of clindamycin phosphate topical solution agent and the preparation method of putting a sheet on the skin thereof on the skin [21]
11	DE19737348C2	Pharmaceutical composition containing clindamycin and clotrimazole [22]	The invention relates to a new pharmaceutical composition containing a combination of clindamycin and clotrimazole for vaginal use in bacterial Infections and fungal or mixed infections of the vagina [22]
12	WO2012017349A3	A topical pharmaceutical composition comprising nanosized silver sulfadiazine and chlorhexidine gluconate [23]	An improved topical pharmaceutical formulation for the treatment of microbiological infections in humans and animals is the core of the invention [23]
13	US7217430B2	Compositions and methods of treatment comprising amoxicillin and potassium clavulanate with xanthan [24]	Amoxicillin and potassium clavulanate may be used in a high dosage regimen to treat bacterial infections. Preferably, a bilayer pill is used to deliver the dosage[24]
14	US9682093B2	Compositions and methods for treating or preventing metabolic syndrome disorders [25]	The utility model discloses procedures, substances, applications for substances, assays and kits for modifying brown adipose tissue (BAT) in obese, insulin-resistant and disturbed glucose homeostasis individuals and animals [25]
15	CN102266326B	Imipenem and Cilastatin sodium pharmaceutical composition liposome injection [26]	The imipenem and cilastatin sodium injection prepared by using the method provided by the invention improves the quality of the preparation product, reduces toxic and adverse effects, increases the bioavailability of medicinal components and has good preparation stability [26]
16	US2799620A	Neomycin and process of preparation [27]	This invention is directed to antibiotic compounds and their production process and is more specifically concerned with a new and potent antibiotic material that has recently been created by the artificial microorganism growing process[27]
17	CN103127509A	Medicine composition and preparation method and purpose [28]	The medicine composition is composed of a gastric acid secretion inhibitor, the medicine composition can be used for producing the medicine for curing the peptic ulcer by combining the pylorus helicobacter infection. antibiotics and vitamin U [28]
18	WO2002094179A2	Novel topical microbicidal compositions [29]	Metronidazole and Povidone-Iodine are present in an effective amount in a pharmaceutical topical composition for the treatment of microbial and mycotic diseases brought on by aerobic and anaerobic microorganisms[29.]
19	BRPI0719454A2	Method of maintenance therapy of melasma and use of a mixture of fluocinolone acetonide, tretinoin hydroquinone[30]	The method of treatment for melasma maintenance proposed by the present invention further includes producing a melasma medication by combining fluocinolone acetonide, hydroquinone and tretinoin[30]
20	ES2784307T3	Besifloxacin for the treatment of resistant	The current disclosure is especially concerned with the development of novel compounds, compositions and

		acne [31]	formulations for the treatment of bacterial infections caused by pathogens that are resistant to antibiotics [31]
21	US20190256557A1	Polymyxin b sulfate crystal and preparation method [32]	The proposed invention pertains to a polymyxin B sulphate crystal or a preparation in the technical area of pharmacy [32]

List of Validated Analytical Methods of Antimicrobial Drugs: Analytical methods need to be validated or revalidated before their introduction into routine analyses [33]. This review article's primary goal was to examine how the drug was developed and validated from the beginning of the formulation process to the final commercial batch of the product.

Validation is crucial to the efficient operation of pharmaceutical companies. Validation was done at every level, from the raw materials to the finished product. The technique was appropriately established, and validation parameters are described in terms of precision, accuracy, the limit of detection (LOD), the limit of quantitation (LOQ), ruggedness and system suitability testing with the use of specific drugs as examples [34].

ICH Q2(R1) guidelines also mention that analyses must adhere to GMP and GLP practices; protocols and acceptance criteria must be followed when developing analytical methods in the routine and stability analysis, and all validation parameters are utilized.

However, UV spectrophotometry, RP-HPLC, and HPTLC stability indicate the RP-HPLC method. **Table 3** represents reported methods for assessment of combinations of antibacterial drugs. **Table 4** shows reported methods for assessment of a combination of antifungal drugs. **Table 5** depicts reported methods for assessment of combinations of anti-viral drugs. **Table 6** illustrates reported methods for assessing combinations of anti-parasitic drugs are shown below.

TABLE 3: REPORTED METHOD FOR ASSESSMENT OF COMBINATIONS OF ANTIBACTERIAL DRUGS

Sr. no.	Drug name/ combination available	Therapeutic category	Reported Method
1	Ceftriaxone sodium Combination is available- Ceftriaxone + Sulbactam sodium (injection)	Antibacterial agent- Ceftriaxone Effective in treating a variety of dangerous illnesses, such as complex urinary tract infections, multi-resistant typhoid fever and bacterial meningitis [35.]	Simultaneous Estimation of Ceftriaxone Using the RP-HPLC-UV Method [36.] QbD technique for sodium ceftriaxone HPLC method development and validation [37.] Dosage form: (Injection) Mobile phase: acetonitrile to water (0.01% triethylamine Detector wavelength: 270 nm Flow rate: 1 ml/minute [37.]
2	Clindamycin hydrochloride Combination is available-Clindamycin + clotrimazole (capsule)	Antibacterial agent For the treatment of bacterial vaginosis, clindamycin can be administered intravaginally as a vaginal cream or suppository or orally. Infections of the bones and joints are treated with clindamycin parenterally[38.]	Development and use of a validated Hplc method for clindamycin hydrochloride determination in marketed drug products [39.] Development of a UV spectrophotometric method for estimating clindamycin in bulk and dose form [40.] Dosage form- Capsule Mobile phase: 10 mM carbonate buffer and acetonitrile pH 10.5 Detector wavelength: 214 nm Flow rate: 1 mL/min [39]
3	Metronidazole Combination is available- Bismuth sub-citrate potassium, Metronidazole and tetracycline hydrochloride (Tablet).	Antibacterial agent Metronidazole is recommended for those who have been diagnosed with trichomoniasis. Treatment of Bacteroides species infections, clostridium infections and fusobacterium infections [41.]	- Method development and UV spectrophotometricmethod validation for metronidazole in solid dose form [42.] - Development and validation of an RP-HPLC method for metronidazole quantification studies in tablet and powder dosage forms [43.] Dosage form- Tablet Mobile phase A: methanol/ 0.1% phosphoric acid aq. (20/ 80 v/ v) Flow rate: 1 ml/ minDetector wavelength: 317 nm [43]
4	Doxycycline Combination is available- Doxycycline and ambroxol (capsule)	Antibacterial agent- Doxycycline is indicated for both protozoal & bacterial infections. Respiratory tract infections caused by Mycoplasma pneumoniae.	The invention of an HPLC method for the detection of doxycycline in human seminal fluid [45] HPLC-UV Quantification of Doxycycline Hyclate in Tablets[46] Dosage form- Tablet Mobile phase:acetonitrile (A) and water buffered at

		Cholera caused by Vibrio cholerae [44.]	pH 2.5 with a concentrated orthophosphoric acid (B) in the volume ratio of 20:80 (v/v). Absorbance: 350nm [45]
5	Bacitracin Combination is available- Bacitracin + neomycin sulfate and polymyxin B sulfate (ointment)	Antibacterial agent. Used for Corticosteroid responsive dermatoses. Prevention of superficial bacterial skin infections associated with minor cuts, scrapes or burns [47.]	- Optimization of the HPLC method for bacitracin stability testing [48.] Development and Validation of a UV Spectroscopic Bacitracin Estimation Method [49.] Dosage form- Ointment
6	Ceftriaxone + Tazobactam (injection)	Antibacterial agents used for serious infections including. Bacterial meningitis Urinary tract infections Post-operative infections [50.]	Development and validation of a stability-indicating technique for RP-UPLC-based simultaneous estimation of ceftriaxone and tazobactam injection [51.] Ceftriaxone and Tazobactam were measured simultaneously in injectables using the UHPLC technique [52.] Dosage form: Parenteral Mobile phase: containing methanol, phosphate and triethylamine in the ratio of 14:86:0.2 v/v/v flow rate: 1.55 mL/min Absorbance: 220 nm [51]
7	Cefuroxime Acetyl and Potassium Clavulanate (oral suspension)	Antibacterial agent used for the treatment of Infections caused by bacteria and parasitic diseases. Eye Illnesses Infection after tooth extraction, Endophthalmitis after eye surgery [53.]	Cefuroxime Acetyl with Potassium Clavulanate in Pharmaceutical Dosage Form Simultaneous Determination by RP- HPLC [54.] Dosage form: Oral suspension Mobile phase: methanol: water in the ratio of 90:10 (v/v) Absorbance:230 nm Flowrate: 1.0 mL/min [54]
8	Clindamycin Phosphate + Adapalene(Cream)	Antibacterial agent It minimizes oil production and helps to reduce inflammation. It also kills acne-causing microorganisms and prevents infection. It helps to prevent pimples, blackheads and whiteheads on the skin.55	A New RP-HPLC method for estimation of clindamycin and adapalene in gel formulation Development and validation consideration.56Dosage form- Cream Mobile phase:acetonitrile: phosphate buffer pH 3.0 (60:40, v/v) Absorbance:278 nm Flowrate: 1.0 mL/min [56]
9	Potassium Clavulanate + Amoxicillin Trihydrate(Tablet)	Antibacterial agent Used to treat infections of the Lower Respiratory Tract Skin and Skin Structure Infections - Sinusitis [57.]	Potassium Clavulanate and Amoxicillin Trihydrat Simultaneous Determination by UV Spectrophotometry Method [58.] Dosage form- Tablet Linearity - 0.2-8.5 µg/ml for PC and 6.4-33.6 µg/ml for AT Absorbance - 271 nm [58]
10	Clindamycin phosphate and Tretinoin	Antibacterial agents It indicated for the topical treatment of acne vulgaris when papules and pustules are present in patients 12 years or older [59.]	Residue Determination of Clindamycin phosphate and Tretinoin on the Surface of Manufacturing Equipment by (RP-HPLC) [60.] Dosage form- Topical preparation Mobile phase- Tetrahydrofuran, 95:05 %v/v and mobile phase B as Acetonitrile. Absorbance- 210 nm Flow rate- 1.5mL/min [60]
11	Imipenem + Cilastatin	Antibacterial agents - Effective monotherapy for septicemia, neutropenia, lower respiratory tract infections, genitourinary, gynaecological, skin and soft tissue, bone and joint infections is provided by imipenem and cilastatin [61.]	The simultaneous quantification of imipenem and cilastatin using the stability-indicating RP-HPLC method in injection formulations [62.] Imipenem-cilastatin formulations' first-order derivative ultraviolet spectrophotometry [63.] The development and validation of an analytical method for the simultaneous quantification of imipenem and cilastatin using RP-HPLC [64.] Dosage form- Parenteral Mobile phase- (70:30 v/v) methanol: phosphate Absorbance-258nm Flow rate- 1mL/min [64]
12	Amoxicillin, Clarithromycin and Esomeprazole	Antibacterial agents used to treat peptic ulcer disease caused by Helicobacter pylori infection. Symptoms include. Stomach pain	Simultaneous Determination of Amoxicillin, Clarithromycin and Esomeprazole in Mice Plasma after Oral Administration by Reverse Phase HPLC Method [66.] Drug interaction studies of esomeprazole

		Discomfort, Loss of appetite Weight loss Difficulty Swallowing bloating [65.]	with amoxicillin and clarithromycin [67.] Dosage form- Tablet Mobile phase-Potassium di hydrogen phosphate (KH2PO4) 0.05 and methanol (60:40 v/v) Absorbance- 205nm Flow rate- 1mL/min [66]
13	Sucralfate + Metronidazole + Povidone Iodine	Antiseptic and antibacterial agents. It effectively treats lacerations (deep cuts in the skin) Abrasions (the	Sucralfate in bulk and commercial formulation: stability indicating technique development and validation by RP-HPLC [69.]

TABLE 4: REPORTED METHOD FOR ASSESSMENT OF COMBINATION OF ANTIFUNGAL DRUGS

Sr. no.	Drug name/ combination available	Therapeutic category	Reported Method
1	Fluconazole Combination is available-Fluconazole + azithromycin and secnidazole (tablet)	An anti-fungal agent used to treat. Vaginal yeast infections caused by Candida. oesophageal and or pharyngeal candidiasis [70.]	Drug Fluconazole and Related Impurities HPLC Analysis [71.] Dosage form-Tablet Mobile phase- 35% ACN with 0.1% H3PO4 Detector - UV 235 nm Flow rate - 1 mL/min [71]
2	Nystatin Combination is available-Nystatin and triamcinolone acetonide (ointment)	An antifungal agent used to treat. Oral candidiasis Intestinal candidiasis Anal candidiasis [72]	HPLC technique for nystatin measurement in saliva for use in clinical trials [73.] Spectrophotometric technique for the quantitative assessment of pharmaceutical formulations containing nystatin [74.] Dosage form- Ointment Mobile phase: MeOH, $H_2O$and DMF (70:20:10, v/v/v) Flow rate: 0.8 ml/min detector: UV and fluorescence detection[73]
3	Clindamycin phosphate and Clotrimazole (tablet)	Anti-fungal agent used to cure vaginal diseases such as Bacterial vaginosis Candidiasis Trichomoniasis [75]	Development and validation of an RP-HPLC technique for the measurement of Clindamycin Phosphate and Clotrimazole in pharmaceutical dosage forms [76.] Development of a UV spectrophotometric method for clindamycin phosphate quantification in bulk and dose form [77.] Dosage form- Tablet Mobile phase- 13.6 g Potassium dihydro orthophosphate in 1000 ml of water acetonitrile: l in the ratio of 70:30 v/v as eluent. Absorbance- 210 nm Flow rate- 1.0 ml / min [76]
4	Mometasone furoate + Terbinafine HCL	Anti-fungal agents Relief of corticosteroid responsive dermatoses [78]	Creation and approval of an HPTLC method for the simultaneous measurement of mometasone furoate and terbinafine hydrochloride in combination dosage forms [79.] Dosage form – Cream
5	Miconazole Nitrate + Fluocinolone Acetonide	Anti-fungal agents Effective in treating fungus infections [80.]	The development and validation of a stability indicating HPTLC method for the simultaneous measurement of Fluocinolone Acetonide and Miconazole Nitrate in Ointment [81.] Dosage form – Cream

TABLE 5: REPORTED METHOD FOR ASSESSMENT OF COMBINATIONS OF ANTI-VIRAL DRUGS

Sr. no.	Drug name/	Therapeutic category	Reported Method
1	Famciclovir	Anti-viral agents It can cure shingles, as well as early and recurrent oral and genital herpes flare-ups [82.]	- Development and Validation of an Experimental Design-Based LC Method for the Determination of Famciclovir in Pharmaceutical Formulation [83]. The development and validation of an RP-HPLC famciclovir technique [84]. Dosage form- Tablets Mobile phase- methanol and water (75: 25 v/v) Absorbance- 221nm Flow rate – 1mL/min
2	Daclatasvir and sofosbuvir	Anti-viral agents. For the treatment of individuals with chronic genotype 3 hepatitis C virus infection [85.]	Effective HPTLC-dual-wavelength Spectro densitometric technique for simultaneous sofosbuvir and daclatasvir determination: Biological and pharmaceutical analysis [86.] Development of a reliable UPLC method to measure a novel

			combination of sofosbuvir and daclatasvir in human plasma simultaneously [87]. Dosage form –Tablet
3	Darunavir + Ritonavir	Anti-viral agents. To treat Human Immunodeficiency Virus (HIV-1) infection in adults and adolescents who have received treatment [88.]	Atazanavir, Darunavir and Ritonavir Simultaneous Quantitative Method of HIV Protease Inhibitors in Human Plasma by UPLC-MS/MS [89]. Creation and approval of a new analytical technique for the simultaneous measurement of darunavir and ritonavir in pharmaceutical dosage forms [90]. Dosage form – Tablet
4	Simeprevir and sofosbuvir	Anti-viral agents. To cure chronic hepatitis C [91]	Application to Combined Pharmaceutical Dosage Forms and Human Plasma: Feasible TLC-Spectro-Densitometry Technique for Simultaneous Determination of Two Hepatitis C Antiviral Drugs, Sofosbuvir and Simeprevir [92]. Simeprevir and sofosbuvir, two direct-acting antiviral medications, have been quantitatively analysed using a variety of spectrophotometric techniques [93]. Dosage form –Tablet
5	Tenofovir Disoproxil Fumarate and Emtricitabine	Anti-viral agents. Pre-exposure prophylaxis (PREP) is recommended in conjunction with safer sex practises to lower the risk of sexually transmitting HIV-1 in persons at high risk [94].	Emtricitabine and Tenofovir Disoproxil Fumarate Simultaneous Estimation in a Tablet Dosage Form: A Validated RP-HPLC Method [95]. Emtricitabine and Tenofovir Disoproxil Fumarate Assay Using Stability Indicating RP-UPLC Method in Bulk Forms [96]. Dosage form –Tablet
6	Dolutegravir + Emtricitabine + Tenofovir Alafenamide Fumarate	Anti-viral agents. Used to treat adult cases of Human Immunodeficiency Virus (HIV) infections [97].	The simultaneous determination of related chemicals presents in the pharmaceutical dosage form of emtricitabine, tenofovir alafenamide and dolutegravir was developed and validated using an RP-HPLC method [98]. Dosage form –Tablet
7	Lamivudine + Stavudine	Anti-viral agents. For HIV infection[99].	High throughput LC-MS/MS approach for lamivudine, stavudine and nevirapine simultaneous analysis in human plasma [100]. Dosage form- Tablet
8	Elbasvir + grazoprevir	Anti-viral agents. Hepatitis C virus (HCV) genotype 1 or genotype 4 infected people who have received treatment [101].	Elbasvir and grazoprevir were determined simultaneously in their pharmaceutical formulation using synchronous fluorescence spectroscopy and the dual-wavelength technique [102]. Dosage form – Tablet

TABLE 6: REPORTED METHOD FOR ASSESSMENT OF COMBINATIONS OF ANTI-PARASITIC DRUGS

Sr. no.	Drug name/	Therapeutic category	Reported Method
1	Albendazole	Anti-parasitic agents. Employed to treat parasitic worm infestations. It functions by eradicating the infection-causing worms and halting the spread of the ailment [103.]	Determination of albendazole sulfoxide and albendazole sulfone in plasma using simultaneous liquid chromatography and mass spectrometry [104]. Dosage form- Tablet
2	Ivermectin + Praziquantel	Anti-parasitic agents. Used to diagnose and treat internal parasites in dogs, including nematodes and cestodes [105]	Stability Indicating RP-HPLC Method for Chromatographic Quantification of Ivermectin and Praziquantel in the Tablets [106]. Dosage form- Tablet Mobile phase- 0.1M disodium hydrogen phosphate (pH 4.5) and acetonitrile (55:45, v/v) Absorbance- 242 nm Flow rate- 1.0ml/min
3	Ivermectin And Clorsulon	Anti-parasitic agents. Effectively used to treat and manage external parasites as well as inside parasites, such as adult liver flukes [107]	Determination of Ivermectin, Clorsulon Their Related Substances in an Injectable Finished Product [107]. Dosage form – Tablet Mobile phase- acetonitrile/methanol (65:35, v/v). Absorbance- 251 nm. Dosage form – Tablet

CONCLUSION: The present review depicts how antimicrobial drugs affect the viability of microorganisms and their management and initiation therapy antimicrobials. This review work also sheds light on the prophylactic use of antimicrobial drugs. The present review gives information about the various analytical methods reported for determining all combinations of

antimicrobial drugs along with the patents and therapeutic effects. The current review will be a reference for further development and validation of the analytical methods of antimicrobial combinations and provides detailed knowledge about the characteristics of all antimicrobial drugs.

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