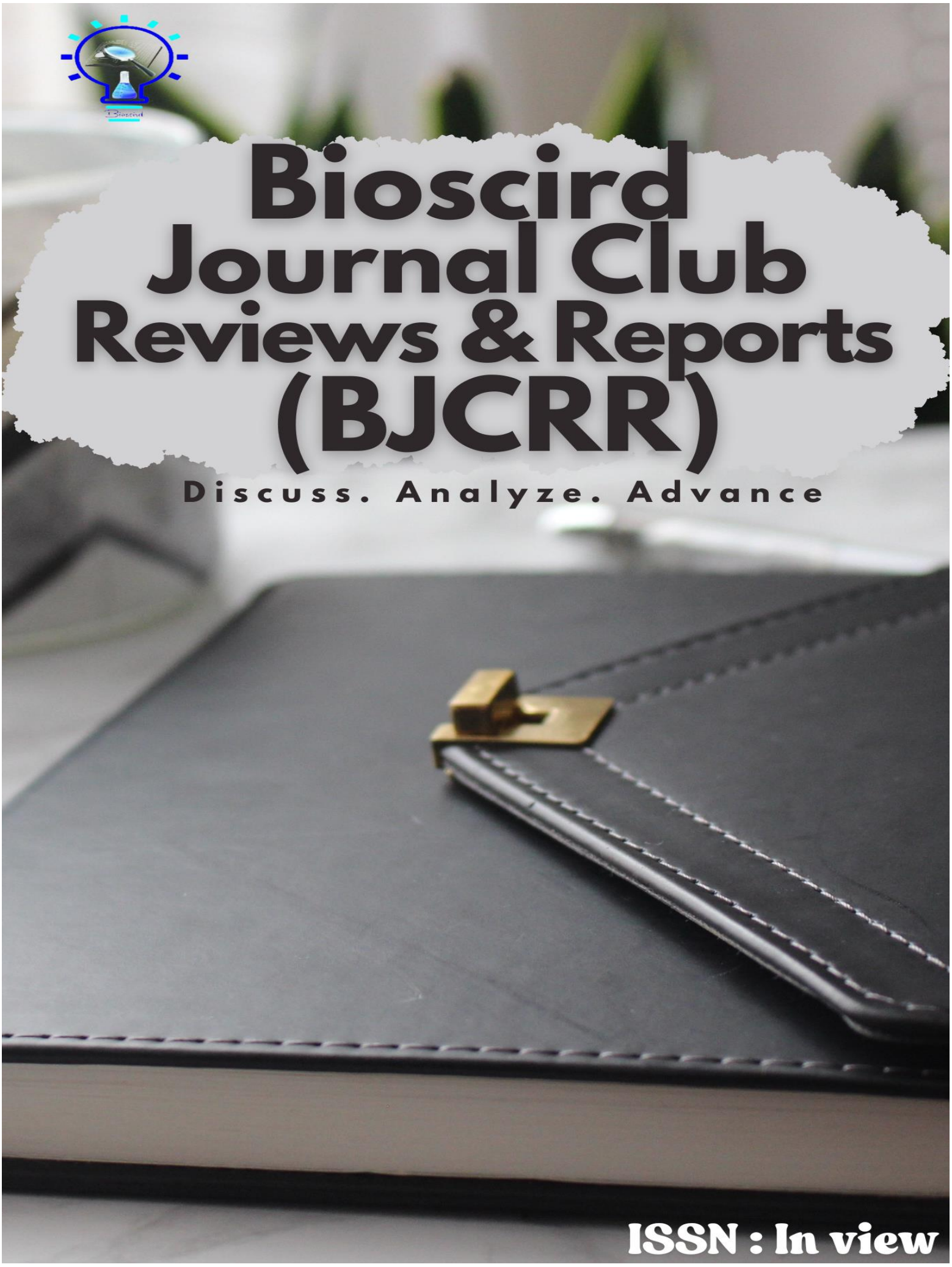

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GUIDE TO AUTHORS

Chemotherapy of antibiotics, antivirals, antifungals and anticancer agents

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ABSTRACT

Chemotherapy comprises a wide array of pharmacological agents used to treat infectious diseases and cancer. This review offers an overview of four primary chemotherapeutic classes: antibiotics, antivirals, antifungals, and anticancer drugs. Sources were identified through databases such as PubMed, Scopus, Web of Science, and Google Scholar using keywords "chemotherapy," "anticancer drugs," and "chemotherapeutic strategies." Antibiotics combat bacterial infections by targeting cell wall synthesis, protein synthesis, or DNA replication; however, antimicrobial resistance poses a critical global threat. Antiviral agents, essential in managing infections such as HIV, hepatitis, and SARS-CoV-2, function by disrupting viral replication but face challenges due to resistance and limited drug targets. Antifungal therapies, though fewer in number, are vital in treating invasive fungal infections, especially in immunocompromised patients, by affecting membrane integrity or cell wall synthesis. Resistance in this domain is also rising. In oncology, anticancer drugs encompass cytotoxic agents and targeted therapies that disrupt cell division and signaling pathways. Innovations such as personalized medicine and immunotherapy have enhanced treatment precision, yet toxicity and drug resistance persist as major limitations. Across all categories, resistance, adverse effects, and lack of specificity remain significant barriers. This review discusses therapeutic strategies, mechanisms of action, clinical applications, resistance development, and future directions. A comprehensive understanding of these chemotherapeutic agents is critical for improving outcomes, informing research, and advancing novel therapies amid the growing complexity of disease and drug resistance.

KEYWORDS: Chemotherapy, Anticancer drugs, and Chemotherapeutic strategies, Antifungal, Molecular effects, Infection

INTRODUCTION

Chemotherapy, a cornerstone of modern cancer treatment, refers to the use of chemical substances particularly cytotoxic drugs used to destroy or inhibit the growth of malignant cells [1]. While its primary association is with oncology, the scope of chemotherapy extends beyond cancer to include the treatment of various infectious and autoimmune diseases. This broad application underscores its critical role in contemporary medicine [2].

The origins of chemotherapy can be traced back to the early 20th century, with significant milestones emerging during and after World War II, notably with the use of nitrogen mustards. These early developments laid the foundation for a wave of pharmaceutical innovations that transformed once-fatal diagnoses into manageable or even curable conditions. Over the decades, advances in pharmacology, molecular biology, and clinical protocols have expanded the chemotherapy arsenal, improving efficacy and reducing toxicity [3].

Today, chemotherapy remains a vital component of multi-modal treatment strategies, often used in combination with surgery, radiation therapy, immunotherapy, and targeted therapies. Its relevance persists amid the evolving landscape of precision medicine, where personalized regimens are tailored to individual patient profiles. Given its enduring significance and the ongoing quest to enhance therapeutic outcomes while minimizing adverse effects, a comprehensive review of chemotherapy's definition, history, and current role is both timely and essential [4].

Methods

This review was conducted through a comprehensive and structured analysis of existing literature on chemotherapy, with the aim of synthesizing current knowledge and tracing the evolution of its applications. Relevant peer-reviewed journal articles, clinical guidelines, historical records, and authoritative textbooks were identified using electronic databases such as PubMed, Scopus, Web of Science, and Google Scholar. Keywords employed in the search included "chemotherapy," "history of chemotherapy," "anticancer drugs," "cytotoxic agents," and "chemotherapeutic strategies."

Inclusion and exclusion protocols

To ensure the inclusion of both foundational and recent advancements, sources published from the early 20th century to 2025 were considered. Priority was given to high-impact studies, systematic reviews, meta-analyses, and landmark clinical trials that have significantly influenced the understanding and practice of chemotherapy. In addition, historical texts and archival documents were reviewed to establish the chronological development of chemotherapy and its expanding role in medical treatment.

Data extraction

Data extraction focused on key themes such as the definition and scope of chemotherapy, historical breakthroughs, and classification of chemotherapeutic agents, mechanisms of action, clinical applications, and evolving therapeutic trends. The findings were organized thematically to provide a coherent narrative that integrates historical context with current practice and emerging directions. This qualitative approach allows for a broad yet detailed overview, making the review a valuable resource for healthcare professionals, researchers, and students seeking to understand the multifaceted nature of chemotherapy.

Results and Discussion

B-lactam antibiotics and their mechanisms of actions

B-lactam antibiotics can be broadly classified based on their chemical structure and mechanism of action. This diverse group includes penicillins, cephalosporins, monobactams, and carbapenems. They share a common β-lactam ring and exert their bactericidal activity by inhibiting penicillin-binding proteins (PBPs), essential for peptidoglycan synthesis in bacterial cell walls [5]. Another class is the aminoglycosides. These antibiotics, such as gentamicin and streptomycin, bind irreversibly to the 30S ribosomal subunit, disrupting protein synthesis and leading to misreading of mRNA. They are primarily effective against aerobic Gram-negative bacteria. The third prominent class is the tetracyclines. This class, including doxycycline and tetracycline, binds to the 30S ribosomal subunit and inhibits the attachment of aminoacyl-tRNA, thus blocking protein synthesis. They are broad-spectrum agents effective against many Gram-positive and Gram-negative organisms.

The macrolides are a peculiar group of antibiotics with examples like erythromycin and azithromycin which bind to the 50S ribosomal subunit, inhibiting translocation during protein elongation. Macrolides are commonly used against Gram-positive cocci and atypical respiratory pathogens [6].

Nitroimidazole

Nitroimidazoles are a class of antimicrobial agents primarily effective against anaerobic bacteria and certain protozoa. Their molecular mode of action hinges on the selective reduction of the nitro group ($-NO_2$) under anaerobic or hypoxic conditions, which triggers a series of biochemical events leading to microbial cell death [7]. Inside susceptible microorganisms, nitroimidazoles undergo enzymatic reduction of their nitro group via electron transport proteins such as ferredoxins or other low-redox-potential redox enzymes that are abundant in anaerobic environments. This process converts the nitro group into reactive nitro radical anions and other reduced intermediates

The reactive intermediates formed are highly unstable and interact with critical biomolecules, primarily DNA. These nitro radical anions cause DNA strand breaks, base modifications and inhibition of nucleic acid synthesis. The DNA damage is lethal to the microorganism, preventing replication and transcripttion, ultimately causing cell death [8].

The selective toxicity of nitroimidazoles is largely due to their requirement for reductive activation, which predominantly occurs in anaerobic or microaerophilic environments where electron transport proteins reduce the drug. Aerobic cells generally lack the reducing conditions needed to activate nitroimidazoles, rendering these drugs selectively toxic to anaerobic pathogens. In summary, nitroimidazoles act as prodrugs that, once reduced in anaerobic microorganisms, generate reactive species that damage DNA and inhibit replication, leading to microbial death [9].

Chemical nature and overview of sulphonamides

Sulphonamides (also called sulfa drugs) are a group of synthetic antimicrobial agents characterized by the presence of a sulfonamide functional group ($–SO_2NH_2$). They were among the first effective antibacterial agents discovered and have been widely used since the 1930s [10]. Sulphonamides act as competitive inhibitors of dihydropteroate synthase (DHPS), an enzyme involved in the bacterial synthesis of folic acid, which is essential for nucleic acid and protein synthesis. Bacteria synthesize folic acid de novo, starting from para-aminobenzoic acid (PABA).

Sulphonamides are structural analogues of PABA and competitively bind to DHPS. This prevents incorporation of PABA into dihydropteroate, leading to inhibition of dihydrofolic acid synthesis [11]. Without folic acid, bacteria cannot synthesize purines, thymidine, and certain amino acids, ultimately inhibiting DNA replication and cell division. Humans do not synthesize folic acid and instead rely on dietary intake, which explains the selective toxicity of sulphonamides toward bacteria. Sulphonamides are primarily bacteriostatic and effective against a broad range of Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus*, *Streptococcus* species, *Escherichia coli* and *Proteus* species. However, resistance has reduced their use as monotherapy in many infections [12].

Sulphonamides are often used in combination with trimethoprim, which inhibits a subsequent step in folic acid synthesis (dihydrofolate reductase), producing a synergistic bactericidal effect. The combination is widely known as co-trimoxazole [12].

Chemical nature and overview of chloramphenicol

Chloramphenicol is a broad-spectrum antibiotic originally derived from *Streptomyces venezuelae*. It is effective against a wide range of Gram-positive and Gram-negative bacteria, as well as some atypical organisms [13]. Chloramphenicol exerts its antibacterial effect by inhibiting bacterial protein synthesis. Specifically, it binds reversibly to the 50S ribosomal subunit of bacterial ribosomes. This binding blocks the peptidyl transferase enzyme, which catalyzes the formation of peptide bonds during translation. As a result, the elongation of the polypeptide chain is halted, leading to inhibition of protein synthesis. The drug is bacteriostatic against most susceptible organisms but can be bactericidal against certain bacteria at higher concentrations.

Chloramphenicol has a broad spectrum and is active against many Gram-positive bacteria (e.g., *Staphylococcus*, *Streptococcus*), Gram-negative

bacteria (e.g., *Haemophilus influenzae*, *Neisseria meningitidis*), anaerobes, Rickettsiae and some protozoa.

Due to its toxicity, chloramphenicol use is generally reserved for serious infections where alternatives are unavailable or contraindicated, such as Typhoid fever caused by *Salmonella typhi*, bacterial meningitis (especially in resource-limited settings) and Rickettsial infections [14-16]. The use of chloramphenicol is limited by potentially severe toxicities, not limited to aplastic anemia (a rare but often fatal bone marrow suppression unrelated to dose or duration), Gray baby syndrome (which occurs in neonates due to immature liver enzymes leading to accumulation and toxicity), dose-related bone marrow suppression (usually reversible upon drug discontinuation) and other side effects including gastrointestinal disturbances and hypersensitivity reactions [17].

Resistance to chloramphenicol arises mainly via chloramphenicol acetyltransferase (CAT) enzymes, which inactivate the drug by acetylation and efflux pumps that reduce intracellular drug concentration. Chloramphenicol remains an important antibiotic in specific clinical scenarios, but its use requires careful consideration of risks versus benefits [18].

Resistance mechanisms to antibacterial agents

The rise of antibiotic resistance poses a major challenge in clinical therapy. One of bacterial resistance mechanisms include enzymatic degradation or modification. β-lactamases are enzymes that hydrolyze the β-lactam ring, rendering β-lactam antibiotics ineffective [19]. Extended-spectrum β-lactamases (ESBLs) and carbapenemases represent major clinical concerns [20].

Another mechanism is alteration of target sites. Mutations in Penicillin-Binding Proteins (PBPs) (e.g., PBP2a in MRSA) or ribosomal subunits (as seen in macrolide resistance) reduce antibiotic binding and efficacy [21]. Another reported resistance mechanism involves the efflux pumps in bacteria. Some bacteria express transport proteins that actively expel antibiotics, such as tetracyclines and fluoroquinolones, from the cell [22]. Bacteria also presents reduced permeability to antibiotics by changing the membrane porins thus decreasing antibiotic uptake, especially in Gram-negative bacteria [23]. Furthermore, bacteria may develop alternative metabolic routes (bypass pathway) to circumvent the inhibitory action of certain drugs, such as sulfonamides and trimethoprim.

Clinical applications

Antibiotics are indispensable in modern medicine and are used for both treatment and prophylaxis: β-lactams are first-line treatments for a range of infections, including streptococcal pharyngitis, pneumonia, urinary tract infections, and bacterial meningitis. Aminoglycosides are reserved for serious Gram-negative infections and are often used in combination with β-lactams for synergistic effects [24]. Tetracyclines are employed in the treatment of acne, atypical pneumonia, Lyme disease, and certain sexually transmitted infections. Macrolides are commonly prescribed for community-acquired pneumonia, pertussis, and Helicobacter pylori eradication regimens [25].

Recent advances and challenges

In recent years, significant advances have been made in the field of antibiotics, driven largely by the urgent need to combat rising antimicrobial resistance (AMR). One of the most notable developments has been the discovery of novel antibiotic compounds, particularly from previously unexplored natural sources such as soil microbes, marine organisms, and even the human microbiome. For example, the identification of *teixobactin*, a new class of antibiotic discovered through innovative culturing techniques, has offered hope due to its ability to target bacterial cell wall synthesis without detectable resistance. In addition to new molecules, researchers have been employing advanced technologies such as artificial intelligence (AI) and machine learning to accelerate the discovery process and predict antimicrobial properties, significantly reducing the time and cost traditionally associated with

antibiotic development.

Another promising area of advancement is the development of antibiotic adjuvants compounds that enhance the efficacy of existing antibiotics or help overcome resistance mechanisms [26]. These adjuvants can inhibit bacterial enzymes that inactivate antibiotics or disrupt biofilms that protect bacterial colonies. Furthermore, progress in nanotechnology has led to the creation of nanoparticle-based drug delivery systems that can target infections more precisely, minimizing side effects and reducing the likelihood of resistance development.

Despite these advances, the field faces numerous challenges. Perhaps the most pressing is the rapid evolution of bacterial resistance, which often outpaces the development of new drugs. Multidrug-resistant organisms, such as *Klebsiella pneumoniae* and *Acinetobacter baumannii*, are becoming increasingly prevalent in healthcare settings, leading to infections that are difficult or even impossible to treat with existing antibiotics [27]. Additionally, there is a significant decline in pharmaceutical investment in antibiotic research due to the high cost and low return on investment, as antibiotics are typically short-course treatments and are increasingly reserved for use only when absolutely necessary.

Regulatory hurdles and the complexity of conducting clinical trials for new antibiotics also pose barriers to progress. Moreover, the misuse and overuse of antibiotics in both human medicine and agriculture continue to drive resistance, highlighting the need for better stewardship programs and public education.

Furthermore, it is noted that remarkable strides have been made in antibiotic discovery and delivery, the growing threat of resistance and systemic challenges in drug development and distribution require a multifaceted response. Collaboration between governments, researchers, healthcare providers, and the pharmaceutical industry is essential to ensure the continued effectiveness of antibiotics and to safeguard public health [28].

Plasmid-mediated resistance

The emergence and rapid dissemination of antibiotic resistance remains one of the greatest challenges to global public health. Among the various mechanisms by which bacteria acquire resistance, plasmid-mediated resistance is particularly concerning due to its efficiency in spreading resistance genes across different bacterial species. Plasmids are extrachromosomal DNA molecules capable of autonomous replication and horizontal gene transfer, making them ideal vectors for the propagation of resistance traits.

Plasmid-mediated resistance has been identified in a wide range of clinically significant pathogens, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. These plasmids often carry multiple resistance genes, rendering bacteria multidrug-resistant (MDR) and limiting therapeutic options. Resistance mechanisms facilitated by plasmids include the production of extended-spectrum beta-lactamases (ESBLs), carbapenemases, and enzymes that modify aminoglycosides or inactivate fluoroquinolones. The rapid transfer of such plasmids through conjugation significantly contributes to the epidemiology of resistance, especially in hospital and community settings. [29]. What makes plasmid-mediated resistance particularly alarming is its resilience and adaptability. Plasmids not only evolve to maintain their stability within host cells but also can recombine and accumulate new resistance determinants over time. This dynamic nature challenges conventional infection control strategies and underscores the need for rigorous surveillance programs and molecular typing methods to track plasmid lineages.

The clinical implications are profound. Infections caused by plasmid-bearing MDR bacteria are often associated with prolonged hospital stays, increased mortality, and higher healthcare costs. Moreover, the presence of such resistance elements in commensal or environmental bacteria creates reservoirs that facilitate the resurgence of resistance even after successful treatment or disinfection.

Efforts to counteract plasmid-mediated resistance include the development of novel antimicrobials, plasmid-curing agents, and phage

therapies targeting resistance elements. However, these are still in various stages of research and development. Equally important is the implementation of stringent antibiotic stewardship programs, better diagnostic tools for rapid resistance detection, and policies that regulate antibiotic usage in agriculture and medicine [29].

In conclusion, plasmid-mediated resistance represents a formidable barrier to effective antimicrobial therapy. Understanding the molecular mechanisms of plasmid biology and their role in gene transfer is critical for designing innovative strategies to curb the spread of resistance. A multidisciplinary approach that combines molecular microbiology, epidemiology, clinical medicine, and public health is essential to confront this escalating threat.

Antiviral agents in chemotherapy

Antiviral agents function by targeting specific stages of the viral life cycle, aiming to inhibit replication and reduce viral load. Common mechanisms include inhibition of viral entry into host cells, interference with viral genome replication, blockage of protein processing, and prevention of viral assembly or release. These interventions exploit the dependence of viruses on host cellular machinery, striving for selectivity to minimize cytotoxicity. Notably, most antivirals act on virus-specific enzymes, such as polymerases and proteases, or interfere with viral genome integration and transcription [29].

Antivirals can be categorized into several mechanistic and structural classes (Table 1). These include Nucleoside and Nucleotide Analogs (NNA) which mimic natural nucleosides and are incorporated into viral DNA or RNA during replication, leading to chain termination or faulty genome synthesis. Examples include acyclovir (HSV), tenofovir (HIV, HBV), and remdesivir (COVID-19). Another class is the Protease Inhibitors (PI) which is agents that inhibit viral proteases that are necessary for processing polyprotein precursors into functional viral proteins. They are a cornerstone in HIV therapy (e.g., lopinavir, darunavir) and have also been used for hepatitis C virus (HCV) [30].

Table 1: Classes of antivirals, examples and srug targets

Drug Class	Drug target	Example	Viral disease
Entry inhibitors	Blocks attachment/fusion to host	Maraviroc, Enfuvirtide	HIV
Uncoating inhibitors	RNA/DNA release	Rimantadine, Amantadine	Influenza
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs/NtRTIs)	Inhibit reverse transcriptase, halt viral DNA synthesis	Zidovudine, Tenofovir	HIV, HBV
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Bind allosteric site of reverse transcriptase	Efavirenz, Nevirapine	HIV
DNA Polymerase Inhibitors	Inhibit viral DNA synthesis	Acyclovir, Ganciclovir	HSV, VZV, CMV
RNA-Dependent RNA Polymerase (RdRp) inhibitors	Inhibit viral RNA replication	Sofosbuvir, Remdesivir, Favipiravir	HCV, SARS-CoV-2, Ebola
Integrase inhibitors	Block viral DNA integration into host genome	Raltegravir, Dolutegravir	HIV
Protease inhibitors	Prevent viral protein processing	Ritonavir, Lopinavir, Glecaprevir	HIV, HCV
Neuraminidase Inhibitors	Prevent release of new virions	Oseltamivir, Zanamivir	Influenza A & B
Capsid inhibitors	Disrupt viral capsid formation	Letermovir (CMV)	CMV
Immune modulators	Enhance host immune response	Interferon-α, Imiquimod	HBV, HCV, HPV
Monoclonal antibodies	Neutralize virus or block entry	Palivizumab, Bebtelovimab	RSV, SARS-CoV-2

**HAV, HBV, HCV are hepatitis A, B and C respectively; HSV, VZV, CMV are Herpes*

Simplex Virus, Varicella-Zoster Virus, Cytomegalovirus respectively; RSV, SARS-CoV-2, HPV are Respiratory Syncytial Virus, Severe Acute Respiratory Syndrome Coronavirus 2 and Human Papillomavirus, respectively.

Integrase Inhibitors (II) are drugs, such as raltegravir and dolutegravir, prevent the integration of viral DNA into the host genome, a critical step in the life cycle of retroviruses like HIV. Entry and Fusion Inhibitors (EFI) is another class of antivirals that prevent viruses from attaching to or fusing with host cell membranes. Enfuvirtide (HIV) and maraviroc (a CCR5

antagonist) exemplify this class. Neuraminidase Inhibitors (NI) are antiviral agents used primarily for influenza. Drugs like oseltamivir inhibit the neuraminidase enzyme, reducing the release of progeny virions [31]. Lastly, Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) bind directly to reverse transcriptase and inhibit its activity through non-competitive mechanisms, as observed mainly in HIV treatment [32].

Resistance mechanisms to antiviral agents

Resistance to antiviral drugs emerges via mutations in viral genes encoding the target proteins, often under selective pressure from long-term therapy. For example, point mutations in HIV reverse transcriptase or protease genes can confer resistance to respective inhibitors. Similarly, HBV and HCV can develop polymerase mutations that reduce drug susceptibility. Resistance is a significant mhallenge in antiviral therapy, particularly for chronic infections like HIV and HBV, necessitating the use of combination regimens to limit viral evolution [32].

Emerging therapies and research directions

The antiviral field continues to evolve, with ongoing research focusing on broad-spectrum agents, host-targeted therapies, and RNA-based interventions. CRISPR-Cas systems are being explored for viral genome editing, while RNA interference (RNAi) holds promise for silencing viral genes. Long-acting formulations and implantable devices aim to improve adherence and reduce dosing frequency, especially in chronic infections like HIV. Additionally, pan-coronavirus inhibitors and antivirals targeting conserved viral proteins are under development to prepare for future pandemics. The integration of artificial intelligence and structural biology accelerates drug discovery by predicting drug-target interactions and resistance profiles [33].

RNA polymerase transcribes RNA from DNA or RNA templates

RNA dependent RNA polymerase (RdRp) catalyzes the synthesis of RNA from a RNA template. RdRp are found in hepatitis C virus (HCV), SARS-CoV-2, Ebola virus, respiratory syncytial virus (RSV), and influenza. Table 2 presents nucleoside/nucleotide analogs that mimic RNA building blocks, get incorporated into viral RNA, and inhibit or corrupt RNA synthesis.

Table 2: Mode of action of some drugs nucleoside/nucleotide analogs that mimic RNA building blocks

Drug	Virus	Mechanism
Sofosbuvir	Hepatitis C (HCV)	Uridine analog; inhibits NS5B RdRp, causes chain termination [34, 35]
Remdesivir	SARS-CoV-2, Ebola	Adenosine analog; causes delayed RNA chain termination [36, 37]
Favipiravir	Influenza, SARS-CoV-2	Guanine analog; inhibits RdRp and causes lethal mutagenesis [38, 39]
Molnupiravir	SARS-CoV-2	Cytidine analog; incorporates into viral RNA and causes mutagenesis [40, 42]

*Hepatitis C Virus (HCV), SARS-CoV-2; RdRp represents, NS5B

Antifungal agents

Antifungal drugs target key components of fungal cell structure or metabolic pathways that are distinct from human cells. The main mechanisms include inhibition of cell membrane function by Polyenes (e.g., amphotericin B, nystatin), binding to ergosterol, a key component of fungal membranes, causing membrane leakage and cell death by Azoles (e.g., fluconazole, itraconazole)

and the subsequent inhibition of lanosterol 14α-demethylase with blockage of ergosterol synthesis, resulting in defective membranes [43]. Table 3 represents some commonly employed antiviral agents.

Table 3: Classes of antifungals, examples and mechanism of action

Drug classes	Examples	Mechanism/Targets
Azoles	Fluconazole, Itraconazole	Targets Ergosterol synthesis by inhibit 14-α-demethylase [44]
Allylamines	Terbinafine	Inhibit squalene epoxidase [45]
Nucleoside analogue Antimetabolites	Flucytosine	Converted to 5-FU, blocks synthesis of DNA/RNA [46]
Echinocandins	Caspofungin	Cell wall (β-glucan) by inhibiting β-1,3-glucan synthase [47]
Polyenes	Amphotericin B	Targets ergosterol and forms pores [47]
Others	Griseofulvin	Targets mitosis, inhibiting microtubules [48]

Another molecular mode of action of antifungals involves the inhibition of cell wall synthesis by Echinocandins (e.g., caspofungin**,** micafungin), through the inhibition of β-(1,3)-D-glucan synthase, preventing synthesis of glucan, a major component of the fungal cell wall.

Certain antifungal agents work by the inhibition of nucleic acid synthesis. flucytosine (5-FC) is a nucleoside analog that is converted to 5-fluorouracil in fungal cells, interfering with DNA/RNA synthesis. Griseofulvin is an antifungal that disrupts mitotic spindle formation by binding to tubulin, thereby inhibiting fungal cell division [49, 50].

Fungal resistance to antifungals can arise via target site alterations with mutations in ERG11 (for azoles), FKS1 (for echinocandins). Another mechanism involves the efflux pumps (e.g., overexpression of ABC and MFS transporters which pump drugs out of cells. Furthermore, biofilm formation by fungi reduces drug penetration and support resistant phenotypes. Reduced drug uptake has been documented for flucytosine resistance [51].

Emerging therapies and research directions

Emerging therapies and research directions in the field of antifungal treatment are expanding rapidly to address rising resistance, toxicity concerns, and limitations in existing antifungal agents. One promising development is the introduction of new antifungal agents such as *olorofim*, which operates by inhibiting dihydroorotate dehydrogenase, a key enzyme in pyrimidine biosynthesis. This novel mechanism offers an alternative to traditional antifungals, making it effective against resistant molds. Another agent, *ibrexafungerp*, functions similarly to echinocandins but is notable for its oral bioavailability, offering a more convenient route of administration for patients.

Research is also focusing on targeting fungal virulence mechanisms, such as the inhibition of heat shock protein 90 (Hsp90) and the calcineurin pathway. These molecular chaperones and signaling proteins play essential roles in fungal survival and stress response, and their disruption could enhance susceptibility to antifungal agents or prevent fungal adaptation under host-induced stress [52].

Vaccine development is an exciting frontier, with several early-phase clinical trials investigating vaccines against *Candida*, *Aspergillus*, and *Cryptococcus* species. These efforts aim to provide immunoprophylactic options, particularly for immunocompromised populations at high risk for invasive fungal infections. Advances in nanotechnology and drug delivery systems are also contributing to improved antifungal therapy. Liposomal formulations of amphotericin B, such as *Ambisome*, have significantly reduced the drug's nephrotoxicity while enhancing targeted delivery, leading to better clinical outcomes and tolerability [53].

Finally, resistance surveillance and fungal genomics are becoming essential tools in clinical mycology. Whole-genome sequencing allows for real-time monitoring of resistance mutations and the evolutionary dynamics of fungal pathogens, supporting more effective outbreak control and personalized antifungal strategies. Together,

these emerging therapies and research directions represent a multi-faceted approach to overcoming current challenges in antifungal treatment and improving patient outcomes [54].

Similarities and differences in mechanisms of chemotherapeutic agents

Understanding the mechanisms of action among therapeutic agents is crucial for optimizing treatment strategies and minimizing resistance. Many anticancer and antimicrobial drugs share overlapping cellular targets or modes of interference, such as DNA replication inhibition, protein synthesis disruption, or cell membrane destabilization. For instance, platinum-based chemotherapeutics (e.g., cisplatin) and certain antibiotics (e.g., quinolones) exert their effects through DNA damage and inhibition of repair mechanisms [55].

However, distinct differences exist in specificity and cellular uptake. While chemotherapeutics often target rapidly dividing eukaryotic cells non-selectively, antimicrobials are designed to exploit prokaryotic-specific pathways, such as bacterial ribosomes or cell wall synthesis. These mechanistic distinctions are critical in guiding drug development and therapeutic applications, especially in combination therapies [56].

Cross-resistance and multidrug strategies

Cross-resistance presents a major challenge in both oncology and infectious disease management. Shared efflux pumps, altered drug targets, and enzymatic inactivation can contribute to reduced efficacy across structurally or functionally related compounds. For example, overexpression of ABC transporters like P-glycoprotein can mediate resistance to multiple chemotherapeutic agents, while similar mechanisms in bacteria confer resistance to a broad spectrum of antibiotics [57].

Multidrug strategies aim to circumvent resistance by combining agents with complementary mechanisms or by including inhibitors of resistance pathways. In oncology, regimens such as FOLFIRINOX or CHOP integrate agents with diverse actions to reduce the likelihood of cross-resistance. Similarly, combination antibiotic therapies (e.g., β-lactam with β-lactamase inhibitor) enhance efficacy and reduce resistance emergence. The rational design of multidrug protocols, supported by pharmacogenomic and pharmacokinetic data, is essential for sustained therapeutic success [58].

Toxicity and side effects management

Both chemotherapeutic and antimicrobial treatments are associated with significant toxicity profiles that impact patient compliance and therapeutic outcomes. Shared adverse effects include gastrointestinal disturbances, hematologic suppression, and organ-specific toxicities. Notably, nephrotoxicity is a concern with cisplatin and aminoglycosides, while hepatotoxicity can result from methotrexate and antitubercular agents.

Effective toxicity management requires early monitoring, dose adjustments, and the use of protective agents. Supportive therapies—such as growth factor support (e.g., G-CSF for neutropenia) in oncology or probiotic supplementation to counter antibiotic-associated dysbiosis—can mitigate side effects. Personalized medicine approaches, leveraging biomarkers and genetic profiling, further enable individualized risk assessment and toxicity prevention [59].

Conclusion

In summary, chemotherapy remains a cornerstone in the treatment of both infectious diseases and cancers, offering critical therapeutic benefits across a wide spectrum of conditions. Despite its long-standing efficacy, significant challenges persist—ranging from drug resistance in pathogens and tumor cells, to systemic toxicity and the often-limited specificity of chemotherapeutic agents. These issues underscore the urgent need for more refined, targeted approaches.

The future of chemotherapy lies in the integration of multimodal and precision medicine strategies. Advances in molecular profiling, drug delivery systems, and immunotherapy have opened promising avenues for more personalized and less toxic treatments. Combining traditional chemotherapeutics with targeted therapies,

immunomodulators, and novel agents such as nanoparticles and gene-editing tools holds great potential to overcome current limitations.

Moving forward, a collaborative effort between researchers, clinicians, and pharmaceutical developers will be essential to translate these innovations into clinical success. Continued investment in research and development, along with adaptive regulatory frameworks, will be critical to realizing the full promise of next-generation chemotherapeutic strategies.

Ethical considerations

Data availability

The data that supported the findings in this study are available on request from the corresponding author

Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest.

Compliance with ethical guidelines

Approval for this study and related cases was obtained from the University of Uyo Health Research Ethics Committee

Author's contribution

The authors confirm contributions as follows: study conception and design by SOA; data collection by PJE, GO and RYI; Analysis and interpretation of results by all authors; Draft manuscript preparation by SOA; all authors reviewed the result and approved the final version of the manuscript.

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GUIDE TO AUTHORS

Bioavailability and bioequivalence of drugs: the basic concepts

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ABSTRACT

Bioavailability (BA) and bioequivalence (BE) are foundational concepts in pharmaceutical sciences, critical to ensuring the safety, efficacy, and quality of drug products. Bioavailability refers to the rate and extent to which an active pharmaceutical ingredient (API) becomes available at the site of action, influencing drug performance and therapeutic outcomes. Bioequivalence, meanwhile, signifies the lack of a significant difference in bioavailability between two pharmaceutically equivalent or alternative products when administered at the same molar dose under similar conditions. These parameters are especially pivotal in the development and regulatory approval of generic drugs, where demonstrating bioequivalence to a reference (innovator) product ensures therapeutic consistency and public trust. This review synthesizes current knowledge on the principles, methodologies, and regulatory standards related to BA and BE. A comprehensive literature search was conducted across major scientific databases (PubMed, Scopus, Web of Science, and Google Scholar) for studies and regulatory documents published between 2000 and 2024. Search words were "bioavailability," "bioequivalence," "pharmacokinetics," "generic drugs," "drug absorption," "FDA guidance," and "regulatory standards. Relevant data were extracted using defined inclusion and exclusion criteria and analyzed through qualitative synthesis. Key pharmacokinetic concepts including absolute and relative bioavailability are discussed, with a focus on their measurement using the area under the concentration-time curve (AUC). The review also outlines regulatory requirements set forth by agencies such as the Food and Drug Administration of the United States (FDA) and European medicines Agency (EMA), emphasizing methodological considerations and challenges in BA/BE studies. Ultimately, the evaluation of BA and BE is essential for informed drug development, regulatory decision-making, and the advancement of cost-effective, high-quality generic therapies in modern healthcare.

KEYWORDS: Bioavailability, Bioequivalence, Pharmacokinetics, Generic drugs," Drug absorption, FDA Guidance, Regulatory standards

INTRODUCTION

Bioavailability and bioequivalence are critical concepts in the field of pharmaceutical sciences, playing a central role in the development, evaluation, and regulatory approval of drug products. Bioavailability refers to the rate and extent to which the active pharmaceutical ingredient (API) is absorbed from a drug product and becomes available at the site of action. It is a key determinant of a drug's therapeutic effectiveness. Bioequivalence, on the other hand, denotes the absence of a significant difference in the bioavailability between two pharmaceutical products that are pharmaceutically equivalent or pharmaceutical alternatives when administered at the same molar dose under similar conditions [1].

These concepts are particularly important in the development of generic drug products, where demonstrating bioequivalence to an innovator (brand-name) drug is a prerequisite for approval. Ensuring that a generic product has similar bioavailability to the reference product guarantees comparable safety and efficacy profiles, which is essential for patient care and public health [2].From a regulatory perspective, bioavailability and bioequivalence assessments are fundamental components of the drug approval process. Regulatory agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and others have established stringent guidelines to evaluate these parameters. These evaluations help to safeguard therapeutic equivalence and uphold standards of drug quality, thus enabling more cost-effective healthcare through the availability of generics while maintaining high levels of patient safety and treatment outcomes [3].

In this review, we will explore the principles, methodologies, and regulatory frameworks surrounding bioavailability and bioequivalence, highlighting their indispensable roles in drug development and approval processes.

Methods

A comprehensive literature search was conducted to identify relevant studies, reviews, and regulatory guidelines related to bioavailability (BA) and bioequivalence (BE). Electronic databases including PubMed**,** Scopus**,** Web of Science**,** and Google Scholar were searched for articles published between January 2000 and December 2024. Search terms included combinations of the following keywords: "bioavailability," "bioequivalence," "pharmacokinetics," "generic drugs," "drug absorption," "FDA guidance," and "regulatory standards." Boolean operators (AND, OR) and truncation were used to refine search results.

Inclusion and exclusion criteria

Studies were included if they were written in English and published in peer-reviewed journals or by recognized regulatory authorities (e.g., FDA, EMA, WHO). and discussed the pharmacokinetic principles of BA and BE, reported data or theoretical analyses relevant to clinical or regulatory evaluation of drugs. Exclusion criteria included articles, editorials, or commentaries without data support, and studies not focused on human pharmacokinetics or not directly related to BA/BE, or with insufficient methodological details.

Data extraction and synthesis

Data from eligible studies were independently reviewed by two authors to extract relevant information regarding definitions, study design parameters, statistical analysis methods, regulatory requirements, and key findings related to BA and BE assessments. Discrepancies were resolved by consensus or consultation with a third reviewer. A qualitative synthesis approach was employed to integrate findings across studies, emphasizing trends in regulatory frameworks, methodological challenges, and advances in pharmacokinetic modeling.

Results and Discussion

Fundamental concepts

Bioavailability (BA) refers to the proportion of an administered drug that reaches the systemic circulation in its active form. It is a fundamental pharmacokinetic parameter that determines the extent and rate at which the active moiety of a drug becomes available at the site of action. Bioavailability is crucial in drug development and therapeutic efficacy, influencing dosage form design, route of administration, and overall clinical outcomes. A drug with poor bioavailability may require dose adjustments or reformulation to achieve the desired therapeutic effect [4].

Absolute versus relative bioavailability of drugs

There are two primary classifications of bioavailability. These include absolute bioavailability (Fabs) which measures the

systemic availability of a drug after non-intravenous administration (e.g., oral, subcutaneous) relative to an intravenous (IV) dose, which is considered 100% bioavailable, and relative bioavailability which is the amount of drug from a formulation that reaches the systemic circulation relative to a different formulation (non-IV) such as oral solution, reference formulation, etc. Relative bioavailability is commonly used when an IV formulation of the drug does not exist or cannot be madeAbsolute bioavailability is calculated by comparing plasma levels of a drug given via a particular route of administration (for example, orally) with plasma drug levels achieved by that drug through an IV injection. It is calculated using the area under the plasma concentration-time curve (AUC) with the formula as presented in Equation 1.

$$F(abs) = (AUCoral\ x\ Dose\ iv / AUC\ iv\ x\ Dose\ oral)\ x\ 100$$

....Equation 1

Relative bioavailability is obtained from the computation in Equation 2

$$Frel = (AUC\ test / AUC\ reference) x\ 100$$ **.....Equation 2**

Factors affecting BA

Bioavailability refers to the proportion of a drug or other substance that enters the systemic circulation when introduced into the body and is thus available for therapeutic effect. Several factors influence bioavailability, and these can be broadly categorized into physiological, pharmaceutical, and chemical factors.

One of the primary physiological factors affecting bioavailability is the route of administration. Intravenous administration provides 100% bioavailability since the drug is delivered directly into the bloodstream. In contrast, oral administration often results in reduced bioavailability due to factors such as first-pass metabolism in the liver, enzymatic degradation in the gastrointestinal (GI) tract, and incomplete absorption across the intestinal lining [5].

Gastrointestinal pH and motility also play a significant role. The pH of the stomach and intestines can affect the solubility and stability of the drug. For instance, drugs that are weak acids are better absorbed in the acidic environment of the stomach, while weak bases are more readily absorbed in the alkaline environment of the intestines. Additionally, GI motility influences the time a drug spends in various segments of the digestive system, thereby affecting the window of absorption [6].

The presence of food in the stomach can either enhance or hinder drug absorption. Food may increase the solubility of some drugs or slow gastric emptying, prolonging the absorption window. However, it can also bind to certain drugs or change the pH, reducing absorption efficiency.

Pharmaceutical factors such as drug formulation and delivery system are also crucial. The physical and chemical properties of the drug such as particle size, crystal form, and solubility can influence its dissolution rate, which in turn affects absorption. Controlled-release formulations, coatings, and excipients used in drug formulations can either facilitate or limit the rate and extent of absorption [7].

Chemical stability is another key factor. Some drugs may degrade before they are absorbed due to exposure to stomach acid, enzymes, or light. Ensuring chemical stability through formulation techniques can help preserve the drug until it reaches the site of absorption.

Lastly, interactions with other drugs can significantly impact bioavailability. Some drugs can inhibit or induce enzymes that metabolize other drugs, altering their bioavailability. Similarly, competition for absorption sites in the GI tract can reduce the absorption of one or more of the substances involved [8].

Regulatory guidelines and requirements

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Bioequivalence (BE) refers to the absence of a significant difference in the rate and extent to which the active pharmaceutical ingredient (API) becomes available at the site of action when administered at the same molar dose under similar conditions in an appropriately designed study. Establishing BE is critical for the approval of generic drugs, as it ensures therapeutic equivalence to the innovator (reference) product without the need for extensive clinical trials. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require BE data to confirm that a generic product will perform in the same manner as its branded counterpart [9].

Types of BE studies

Bioequivalence studies are generally categorized into two main types namely the in citro and the in vivo modalities. In vitro studies involve laboratory-based tests, such as dissolution testing,

which evaluate the rate and extent of drug release from the dosage form. In vitro studies are typically used when in vivo testing is not necessary or feasible, particularly for drugs classified under the Biopharmaceutics Classification System (BCS) as highly soluble and highly permeable (BCS Class I), which may qualify for a biowaiver [10]. In vivo studies are clinical studies conducted in human subjects, usually involving crossover designs. In vivo studies directly measure the plasma concentration-time profile of the drug, from which pharmacokinetic (PK) parameters such as Cmax (maximum concentration), Tmax (time to reach Cmax), and AUC (area under the curve) are derived. These parameters are crucial for assessing BE between the test and reference formulations [11].

Criteria for establishing BE

To establish bioequivalence, the 90% confidence interval (CI) for the ratio of the test to reference product's key pharmacokinetic parameters namely, Cmax and AUC must fall within the accepted bioequivalence range of 80% to 125% [12]. This statistical range accounts for intra-subject variability and ensures that any observed differences in drug absorption are not clinically significant. Additionally, study design considerations, such as adequate sample size, appropriate washout periods, and the selection of a suitable reference product, are critical for reliable BE assessment. In special populations or for narrow therapeutic index drugs, stricter criteria or additional endpoints may be required.

International regulatory perspectives

The global regulatory landscape for pharmaceuticals, medical devices, and biologics is shaped by a diverse set of agencies and international bodies, each with its own regulatory frameworks and priorities. Understanding these perspectives is essential for navigating product development, clinical trials, and market approval across multiple jurisdictions.

FDA (United States)

The U.S. Food and Drug Administration (FDA) plays a pivotal role in the regulation of medical products, including drugs, biologics, and medical devices. Known for its rigorous and science-driven evaluation process, the FDA sets high standards for safety, efficacy, and quality. The agency employs a risk-based approach to regulatory oversight and offers various expedited pathways such as Fast Track, Breakthrough Therapy Designation, Accelerated Approval, and Priority Review, especially for products addressing unmet medical needs [13]. The FDA's recent emphasis on real-world evidence, digital health technologies, and decentralized clinical trials underscores its evolving approach to innovation while maintaining public health safeguards.

EMA (European Union)

The European Medicines Agency (EMA) serves as the central regulatory body for the European Union (EU), coordinating the scientific evaluation of medicines developed by pharmaceutical companies for use in the EU. The EMA facilitates centralized marketing authorization, allowing approved products to be marketed across all EU member states. The agency emphasizes a collaborative regulatory environment, working closely with national authorities of member states through its Committee for Medicinal Products for Human Use (CHMP) [14]. The EMA has also prioritized adaptive pathways and conditional marketing authorizations to accelerate access to therapies for serious conditions. Environmental risk assessments and a focus on transparency and stakeholder engagement are notable components of its regulatory ethos.

WHO (World Health Organization)

As a global health authority, the World Health Organization (WHO) plays a critical role in setting international norms and standards, particularly for low- and middle-income countries. The WHO Prequalification Programme is instrumental in assessing the quality, safety, and efficacy of medicines and vaccines intended for global procurement. The organization also issues guidance and technical reports that influence national regulatory policies and practices. WHO collaborates with regulatory authorities through networks like the International Coalition of Medicines Regulatory Authorities (ICMRA) and the WHO-listed authorities framework, aiming to strengthen regulatory capacity globally and harmonize standards [15].

Other national authorities

Several other national regulatory bodies contribute to the global regulatory environment, each with unique mandates and operational nuances:

CDSCO (India)

The Central Drugs Standard Control Organization is India's national regulatory authority. It oversees the approval of new drugs, clinical trials, and the regulation of imported and domestically produced

pharmaceuticals. CDSCO is enhancing its alignment with international standards through policy reforms, digital platforms for regulatory filings, and active participation in global regulatory harmonization initiatives.

TGA (Australia)

The Therapeutic Goods Administration regulates therapeutic goods including medicines, medical devices, and biologicals in Australia. It adopts a life-cycle approach to product regulation and actively engages in international regulatory convergence efforts, particularly through collaborations with agencies such as the FDA and EMA. The TGA is known for its transparent processes and emphasis on risk-based assessments.

PMDA (Japan)

The Pharmaceuticals and Medical Devices Agency supports the Ministry of Health, Labour and Welfare (MHLW) in Japan. It is recognized for its strong post-marketing surveillance programs and for integrating pharmacovigilance data into regulatory decision-making.These authorities often collaborate through multilateral platforms such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S), fostering global regulatory alignment and mutual recognition where possible [16].

Biowaivers and BCS classification

The Biopharmaceutics Classification System (BCS) provides a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. The primary aim of this classification is to predict the in vivo performance of orally administered drugs and to determine the feasibility of waiving in vivo bioequivalence (BE) studies, commonly referred to as "biowaivers," for certain drug products [17].

BCS-based biowaiver criteria

To qualify for a BCS-based biowaiver, a drug product must meet several key criteria outlined by regulatory agencies such as the FDA and EMA. These include the following considerations-

BCS class I or class III

The drug substance must fall into Class I (high solubility, high permeability) or Class III (high solubility, low permeability).

High solubility

The highest single therapeutic dose of the drug must be soluble in ≤ 250 mL of aqueous media over a pH range of 1.0 to 6.8 at 37°C.

Rapid dissolution

The drug product must dissolve ≥ 85% of the labeled amount within 30 minutes in all three dissolution media (pH 1.2, 4.5, and 6.8) using the USP apparatus I or II.

Excipients

The formulation must contain excipients that do not affect drug absorption. For Class III drugs, excipients must be qualitatively the same and quantitatively similar (Q1/Q2 similarity) to the reference product.

Stability

The product must demonstrate chemical and physical stability under intended storage conditions.

These criteria aim to ensure that the in vitro dissolution reliably predicts in vivo performance, thereby justifying the waiver of in vivo BE studies.

Eligibility of class I and class III drugs

Class I drugs, due to their high solubility and high permeability, are considered optimal candidates for biowaivers. Their rapid and complete absorption in the gastrointestinal tract means that the rate-limiting step in absorption is often dissolution. As a result, in vitro dissolution testing is generally predictive of in vivo behavior, provided that the formulation and manufacturing processes are well controlled [18].Class III drugs, despite their low permeability, may also be eligible for biowaivers under more stringent conditions. Since absorption is limited by permeability rather than dissolution, the role of excipients and formulation composition becomes critical. Regulatory authorities typically require that excipients used in the test product do not alter gastrointestinal transit or membrane permeability. Thus, biowaivers for Class III drugs are generally restricted to immediate-release products with Q1/Q2 similarity to the reference listed drug.

Overall, the BCS-based biowaiver approach offers a streamlined path for regulatory approval of generic drug products by reducing the need for in vivo BE studies. However, careful consideration of both drug and formulation characteristics is essential to ensure therapeutic equivalence and patient safety.

Methodologies for assessing BA/BE

The assessment of BA and BE is a cornerstone in the development and approval of generic drug products. Study design plays a critical role in ensuring that the pharmacokinetic parameters measure (i.e., maximum plasma concentration

(Cmax), time to reach maximum concentration (Tmax), and area under the plasma concentration-time curve (AUC), accurately reflect the in vivo performance of the drug formulations being compared. Among the various study designs available, crossover and parallel designs are most commonly employed, each with distinct advantages and limitations depending on the pharmacological properties of the drug and the target population [19].

Crossover versus parallel study designs

The crossover study design is widely regarded as the gold standard in BA/BE studies, especially for drugs with short half-lives and minimal carryover effects. In this design, each subject receives both the test and reference formulations in two or more treatment periods, separated by an appropriate washout phase. The key advantage of this approach lies in its ability to reduce inter-subject variability, as each participant serves as their own control. This results in greater statistical power and typically requires a smaller sample size compared to parallel designs [20].

However, crossover designs are not suitable in all circumstances. For drugs with long half-lives, significant residual effects, or where repeated exposure may be ethically or medically questionable (e.g., cytotoxic agents), a parallel study design is preferred. In parallel studies, subjects are randomized into two or more groups, each receiving only one of the formulations. While this approach avoids carryover effects and is simpler in terms of logistics and subject burden, it requires a larger sample size to account for inter-subject variability and may be more susceptible to confounding factors [20].

Subject selection and ethical considerations

Subject selection is another critical component in the design of BA/BE studies. Typically, healthy adult volunteers are recruited to minimize variability unrelated to the drug formulations, such as underlying disease or concomitant medication use. However, for drugs with significant safety concerns or those intended exclusively for specific patient populations (e.g., pediatric or geriatric), it may be more appropriate to conduct studies within the target population under closely monitored conditions [21].

Ethical considerations are paramount in the conduct of BA/BE studies. All studies must adhere to Good Clinical Practice (GCP) guidelines and obtain approval from an independent ethics committee or institutional review board (IRB). Informed consent must be obtained from all participants, with full disclosure of potential risks, benefits, and the nature of the study. Additional safeguards must be implemented for vulnerable populations, and the risk-benefit ratio should always favor the safety and well-being of the subjects.

In summary, the selection of an appropriate study design and ethical management of study participants are fundamental to the reliability and acceptability of BA/BE studies. The choice between crossover and parallel designs should be driven by the pharmacokinetics of the drug and ethical feasibility, while meticulous attention to subject selection ensures both scientific integrity and participant safety [22].

Pharmacokinetic parameters in BA/BE assessment

Pharmacokinetic (PK) parameters are quantitative measures that describe the time course of a drug's absorption, distribution, metabolism, and excretion. In the context of bioavailability (BA) and bioequivalence (BE) studies, these parameters provide critical insights into the rate and extent of drug absorption following oral administration. The most commonly evaluated PK parameters in BA/BE assessments include the maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), and the area under the plasma concentration-time curve (AUC), among others [23].

Cmax**,** the peak plasma concentration of a drug, serves as an indicator of the rate of absorption. It reflects the highest concentration achieved after administration and is influenced by both the absorption rate and the elimination process. In BE studies, Cmax is a key parameter because differences in formulation can significantly alter how quickly the drug reaches systemic circulation [24].

Tmax, the time required to reach Cmax, is another indicator of the absorption rate. While Tmax is more variable and is generally considered a secondary parameter in BE evaluations, it can still offer important clinical relevance, particularly for drugs where rapid onset of action is critical (e.g., analgesics or antiemetics). Unlike Cmax and AUC, Tmax is typically analyzed using nonparametric statistical methods due to its skewed distribution [25].

AUC (Area under the curve)

The area under the plasma concentration-time curve (AUC) is the most direct measure of the

extent of drug absorption. It quantifies the total systemic exposure to the drug and is calculated from the time of dosing to the last measurable concentration (AUC) and extrapolated to infinity (AUC). The AUC reflects how much of the drug reaches the systemic circulation and is unaffected by the rate of absorption or elimination, making it a robust indicator of bioavailability [26].

In BE studies, regulatory agencies require that the 90% confidence intervals for the ratio of the test to reference product for both Cmax and AUC fall within the predefined acceptance range of 80–125%. This statistical criterion ensures that any differences in systemic exposure between the products are not clinically significant.

Additional parameters

Other pharmacokinetic parameters may be evaluated depending on the study design and the characteristics of the drug. These include elimination half-life (t1/2) which indicates how quickly the drug is removed from the body, clearance (Cl) a measure of the efficiency of drug elimination, and volume of distribution (Vd) which reflects the apparent volume in which the drug is distributed in the body.While these additional parameters are not primary endpoints in standard BE studies, they can provide useful information about the pharmacokinetic behavior of the drug and support interpretation of the primary data.

In conclusion, pharmacokinetic parameters such as Cmax, Tmax and AUC are central to the evaluation of bioavailability and bioequivalence. Accurate measurement and appropriate statistical analysis of these variables are essential to ensure therapeutic equivalence between test and reference drug product [27].

Bioanalytical methods: assay validation and sample analysis

The reliability of bioavailability (BA) and bioequivalence (BE) studies hinges on the precision and accuracy of the bioanalytical methods used to quantify drug concentrations in biological matrices, typically plasma or serum. These methods, usually based on chromatographic techniques such as liquid chromatography coupled with mass spectrometry (LC-MS/MS), must undergo rigorous validation to ensure that the data generated are suitable for regulatory decision-making.

Assay validation and sample analysis

Assay validation is the process of demonstrating that an analytical method is suitable for its intended purpose. Regulatory agencies such as the FDA, EMA, and ICH have issued comprehensive guidelines that outline the parameters to be assessed during method validation. These include **a**ccuracy (the closeness of measured values to the true concentration), precision (the reproducibility of the assay under the same conditions, expressed as intra-day (repeatability) and inter-day (intermediate precision) variability, selectivity/specificity (the ability of the method to accurately measure the analyte in the presence of endogenous components, metabolites, or other potential interferents, **s**ensitivity (typically defined by the lower limit of quantification (LLOQ), which is the lowest concentration that can be measured with acceptable accuracy and precision), linearity and range (the method demonstrates a consistent response over the range of concentrations expected in the study, stability (the analyte remains stable under various conditions, including during sample collection, processing, and storage) [27].

Statistical analysis in BA/BE studies

Statistical analysis is a critical component of bioavailability (BA) and bioequivalence (BE) assessments, serving to determine whether observed differences in pharmacokinetic parameters between test and reference formulations are statistically and clinically insignificant. The analytical approach focuses on key pharmacokinetic endpoints—primarily Cmax, AUC0–t, and AUC0–∞and employs confidence intervals and predefined equivalence margins to establish comparability between products [28].

Confidence intervals

The comparison of test and reference drug products is performed using confidence interval (CI) estimation, typically the 90% confidence interval for the geometric mean ratio of the log-transformed pharmacokinetic parameters. Log transformation is applied to normalize the data and stabilize variance, as pharmacokinetic measures often exhibit right-skewed distributions.

The confidence interval approach offers several advantages over traditional hypothesis testing. Rather than simply detecting a statistically significant difference, it evaluates whether the observed difference lies within a range considered clinically acceptable. If the 90% CI for the ratio of test to reference values for both Cmax and AUC falls entirely within the predefined acceptance limits, bioequivalence is concluded [29].

Acceptance range

Regulatory agencies such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and Health Canada have established a standard acceptance range of 80% to 125% for the 90% confidence interval of the geometric mean ratios. This range represents a ±20% deviation from the reference product and is considered acceptable for most drugs, reflecting a lack of meaningful clinical difference in exposure.

Specifically, **i**f the 90% CI for the test/reference ratio of Cmax and AUC lies entirely within 80.00% to 125.00%**,** the products are deemed bioequivalent. If the CI falls partially or wholly outside this range, the test product fails to meet BE criteria, suggesting potential differences in absorption that could affect safety or efficacy [30].

Certain drug classes, such as narrow therapeutic index drugs (NTIDs)**,** may require tighter BE limits (e.g., 90–111%) due to the small margin between therapeutic and toxic doses. Conversely, some high-variability drugs may be eligible for reference-scaled average bioequivalence approaches, where the acceptance limits can be adjusted based on within-subject variability, subject to regulatory approval.

In conclusion, the use of confidence intervals and a well-defined acceptance range ensures a robust and clinically relevant assessment of bioequivalence. These statistical criteria help safeguard therapeutic interchangeability between generic and innovator products, ensuring consistent quality and efficacy across formulations [31].

Challenges and limitations in BA/BE studies

Despite well-established regulatory frameworks and methodological advances, bioavailability (BA) and bioequivalence (BE) studies face several inherent challenges and limitations that can affect the reliability of outcomes and their translation to clinical practice. These issues may arise from biological variability, physicochemical properties of the drug, therapeutic considerations, and broader concerns about generic substitution.

Inter- and intra-subject variability

One of the most significant sources of uncertainty in BA/BE studies is inter-subject and intra-subject variability in pharmacokinetics. Inter-subject variability refers to differences in drug absorption, metabolism, and elimination across individuals, influenced by factors such as genetics, age, body weight, gastrointestinal physiology, and concurrent medications. Intra-subject variability, on the other hand, occurs within the same individual under different conditions or at different times, often influenced by diet, circadian rhythms, or stress.

High variability can obscure true differences (or lack thereof) between test and reference products, potentially leading to inconclusive or misleading results. For drugs with high within-subject variability, reference-scaled average bioequivalence (RSABE) approaches may be employed, but these require more complex statistical handling and regulatory acceptance.

Poorly soluble drugs

Poorly soluble drugs, particularly those falling into BCS Class II and IV, pose distinct challenges in achieving and demonstrating bioequivalence. Limited solubility can lead to erratic or incomplete absorption, with dissolution rate becoming the rate-limiting step for bioavailability. Small differences in formulation, particle size, or excipients can have disproportionately large effects on systemic exposure, making BE studies for such drugs more sensitive to formulation differences. Innovative formulation strategies such as solid dispersions, nanoformulations, or lipid-based systems may enhance solubility, but also complicate the BE assessment due to altered pharmacokinetic profiles or non-linear absorption.

Narrow therapeutic index drugs

Narrow therapeutic index drugs (NTIDs**),** such as warfarin, phenytoin, and digoxin, present a heightened risk in BE evaluations due to their small margin between therapeutic and toxic concentrations. Even small differences in exposure can lead to under-treatment or toxicity. For these drugs, standard BE limits (80–125%) may not be sufficient to ensure clinical safety and efficacy. Regulatory agencies often require tighter bioequivalence ranges (e.g., 90–110%) and may mandate additional pharmacodynamic or clinical endpoint studies to support generic approval.

Generic substitution concerns

Despite regulatory approval, generic substitution remains a source of concern among healthcare providers and patients, particularly for drugs used in chronic or life-threatening conditions. Concerns may stem from variability in excipients, manufacturing processes, or even patient perception and adherence. These concerns can be magnified in cases where the reference product has a long-established brand identity or when switching between multiple generic versions. Educational efforts and transparent communication of the rigorous standards underpinning BE studies are critical to addressing such concerns.

Additionally, post-marketing surveillance and pharmacovigilance play key roles in ensuring ongoing safety and effectiveness following generic substitution.

In summary, while BA/BE studies are indispensable for ensuring therapeutic equivalence of generic products, several challenges—including biological variability, formulation complexity, and clinical sensitivity—must be carefully managed. Continued refinement of study designs, analytical methods, and regulatory criteria will be essential to address these limitations and uphold the integrity of generic drug development.

Advances and innovations in BA/BE assessment

In recent years, advances in computational methods and pharmaceutical technology have significantly enhanced the assessment of bioavailability (BA) and bioequivalence (BE). Traditional in vivo studies remain the gold standard; however, modeling and simulation**,** in silico bioequivalence (BE) assessments**, and** novel drug delivery systems are transforming how we predict, evaluate, and ensure therapeutic equivalence. These innovations are particularly valuable in cases where standard BE approaches are infeasible or insufficient due to ethical, technical, or scientific limitations.

Modeling and simulation: physiologically-based pharmacokinetic (PBPK) modeling

Physiologically-based pharmacokinetic (PBPK) modeling has emerged as a powerful tool for predicting drug absorption, distribution, metabolism, and excretion using mathematical representations of human physiology. These models integrate data on drug properties (e.g., solubility, permeability, metabolism) with physiological parameters (e.g., organ volumes, blood flow rates) to simulate drug behavior under various scenarios.

PBPK modeling offers several applications in BA/BE including predicting the impact of formulation changes on systemic exposure, supporting BE waivers for specific populations (e.g., pediatrics, geriatrics) where clinical trials may be impractical and assessing food effects or drug-drug interactions without requiring dedicated in vivo studies [32].Regulatory agencies increasingly accept PBPK modeling as part of regulatory submissions, especially when combined with in vitro and in vivo data to provide a comprehensive, mechanistic understanding of drug performance [33].

In silico BE assessments

Building on PBPK principles, in silico BE assessments use computational simulations to predict whether a test formulation is bioequivalent to a reference product. These models, which can incorporate variability, dosing regimens, and virtual populations, allow researchers to explore a wide range of "what-if" scenarios without exposing human subjects to risk. In silico tools are particularly valuable during the early stages of drug development and formulation optimization. While not yet a replacement for in vivo studies, they can serve as supportive evidence to reduce the number or scale of required clinical trials. Moreover, they are instrumental in identifying potential BE failures before they reach the clinical testing phase, thus saving time and resources ( ).

Novel drug delivery systems and their impact on BA/BE

The emergence of novel drug delivery systems including extended-release formulations such as nanoparticles, liposomes, and transdermal patches has introduced new complexities into BA/BE evaluations. These systems are designed to improve therapeutic outcomes by modifying the rate, location, or extent of drug release and absorption. However, such innovations also pose challenges. Standard pharmacokinetic endpoints may not fully capture the release dynamics of these systems. Alternative study designs, such as steady-state or multiple-dose studies, may be required. In some cases, additional pharmacodynamic or clinical endpoint studies are necessary to establish therapeutic equivalence [34].

Regulatory frameworks are evolving to accommodate these technologies, with increased emphasis on in vitro–in vivo correlation (IVIVC), advanced modeling, and quality-by-design (QbD) principles to ensure consistent performance.

Case studies in bioequivalence evaluation

Real-world case studies provide valuable insights into the practical challenges and successes of bioequivalence (BE) testing. These examples illustrate how formulation differences, drug properties, and study design intricacies can significantly influence the outcome of BE evaluations. Examining both successful and unsuccessful cases enhances understanding of critical success factors and common pitfalls in generic drug development.

Successful BE studies: generic atorvastatin

One of the most well-known examples of successful BE evaluation is the case of generic atorvastatin, the widely used lipid-lowering agent originally marketed as Lipitor®. Upon patent expiry, several generic manufacturers developed formulations aimed at replicating the pharmacokinetic profile of the reference product [35].

Key to the success of these generic versions was the use of highly soluble, BCS Class I drug characteristics and well-established formulation science. The generics met all regulatory criteria, with 90% confidence intervals for C_{max} and AUC well within the 80–125% acceptance range. This successful demonstration of BE enabled widespread generic substitution, substantially reducing healthcare costs while maintaining clinical effectiveness.

Successful BE with complex formulations

The generic development of extended-release venlafaxine (Effexor XR®) is another success story involving a modified-release formulation. The challenge lay in matching the extended absorption profile of the innovator product. Manufacturers employed sophisticated formulation techniques and rigorous in vitro–in vivo correlation (IVIVC) to design test products that mimicked the release characteristics of the reference [36].

Using **s**teady-state studies under fasting and fed conditions, BE was successfully demonstrated, leading to FDA approval. This example underscores the importance of tailored study designs and advanced formulation approaches when dealing with complex delivery systems.

Unsuccessful BE example of generic cyclosporine

In contrast, the case of generic cyclosporine, an immunosuppressant with a narrow therapeutic index (NTI)**,** highlights the difficulties in achieving BE for certain drugs. Early generic formulations failed to demonstrate bioequivalence due to significant variability in absorption and a narrow margin between therapeutic and toxic concentrations.

Despite meeting pharmacopoeial standards for content and dissolution, some generics exhibited inconsistent bioavailability, leading to clinical concerns about graft rejection in transplant patients. These failures emphasized the need for tighter BE acceptance ranges (e.g., 90–111%) and, in some cases**,** additional clinical endpoint studies for NTI drugs.

Failure due to high variability: bupropion XL

Another prominent example is bupropion extended-release (Budeprion XL® 300 mg), a generic version of Wellbutrin XL®. Although the 150 mg version was found bioequivalent, the 300 mg strength exhibited variable absorption **and** delayed peak concentrations. Post-marketing reports of reduced efficacy and increased adverse events prompted an FDA investigation.

Subsequent bioequivalence testing revealed that the 300 mg formulation failed to meet BE criteria**,** and the product was withdrawn from the market. This case highlighted the limitations of relying on biowaivers or extrapolation between dosage strengths and stressed the importance of full BE testing for all strengths, especially for drugs with complex pharmacokinetics or dose-dependent absorption [37]**.**

Future perspectives in bioavailability and bioequivalence assessment

As pharmaceutical science advances and the demand for high-quality, cost-effective generic and complex drug products increases, the field of bioavailability (BA) and bioequivalence (BE) assessment is entering a transformative era. Future progress will depend on international regulatory alignment, integration of digital technologies, and a shift beyond traditional pharmacokinetic (PK) paradigms toward more holistic, patient-centered measures of therapeutic equivalence.

Harmonization of global regulatory standards

The globalization of pharmaceutical development has amplified the need for harmonized regulatory standards in BE evaluation. Currently, variations exist between agencies such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada, and agencies in Asia and Latin America regarding study design, acceptance ranges, and biowaiver policies. Efforts led by organizations like the International Council for Harmonisation (ICH) and the World Health Organization (WHO) aim to bridge these gaps through unified guidelines. Such harmonization would reduce duplication of studies across regions, facilitate simultaneous global submissions, and encourage consistency in drug quality and access,

Achieving this requires ongoing dialogue, alignment on scientific principles, and recognition of emerging tools like modeling and simulation in

regulatory decision-making.

Role of digital health and artificial intelligence

Digital health technologies and artificial intelligence (AI) are poised to play a growing role in the design, execution, and analysis of BE studies. Wearable biosensors, mobile health apps, and remote monitoring tools offer real-time, high-resolution data on physiological responses, adherence, and exposure, potentially complementing or even replacing traditional PK endpoints in certain contexts. Meanwhile, AI and machine learning are being applied to predict individual pharmacokinetic responses, optimize study design by simulating virtual populations, analyze complex datasets for patterns of variability or outliers, and support real-time quality assurance during bioanalytical sample processing [38]. These tools can enhance efficiency, reduce costs, and generate deeper insights, especially in adaptive and personalized BE frameworks.

Evolution beyond traditional pharmacokinetics

The future of BE assessment may also involve a fundamental shift beyond the sole reliance on pharmacokinetic parameters such as AUC and Cmax. As drug products become more complex—such as biosimilars, nanomedicines, and targeted delivery systems where there is increasing recognition that PK measures may not always capture the full therapeutic impact.

Alternative complementary approaches include pharmacodynamic (PD) endpoints for drugs with measurable biological effects, clinical endpoint studies where surrogate biomarkers or patient outcomes are more informative in vitro – in vivo correlations (IVIVC) and model-integrated evidence (MIE) that combine multiple data sources to predict real-world performance, and finally patient-reported outcomes and digital biomarkers for a more holistic evaluation of therapeutic equivalence.

Such innovations align with the broader shift in healthcare toward precision medicine and value-based care, where drug performance is measured not just by plasma concentration curves, but by its meaningful impact on patient health and well-being.

Conclusion

Bioavailability and bioequivalence studies are foundational elements of modern pharmaceutical development, regulatory evaluation, and public health policy. They ensure that therapeutic alternatives, particularly generic and reformulated drugs, deliver comparable safety and efficacy to their

Over the course of this review, we have outlined the essential methodologies, regulatory frameworks, pharmacokinetic parameters, and analytical tools that underpin BA/BE assessment. Key points discussed include the principles of study design, such as crossover versus parallel approaches, and the importance of proper subject selection and ethical conduct. Pharmacokinetic metrics like Cmax, Tmax, and AUC remain central to establishing bioequivalence, while robust bioanalytical methods and validated assays ensure the accuracy and reproducibility of data. The statistical framework, particularly the use of 90% confidence intervals within the 80–125% acceptance range, provides a rigorous yet practical threshold for determining equivalence.

We also explored the challenges that complicate BE studies, including inter- and intra-subject variability, poorly soluble compounds, and the stringent demands of narrow therapeutic index drugs. Case studies highlighted both successful and failed BE determinations, offering lessons in formulation science, study design, and regulatory compliance. Innovations such as PBPK modeling, in silico BE assessments, and novel delivery systems demonstrate how the field continues to evolve, while future perspectives emphasize the promise of global regulatory harmonization and digital technologies. Despite ongoing advances, the core mission of BA/BE studies remains unchanged: to safeguard therapeutic equivalence and ensure that all patients—regardless

Ethical Considerations

Data availability

The data that supported the findings in this study are available on request from the corresponding author

Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest.

Compliance with ethical guidelines

Approval for this study and related cases was obtained from the University of Uyo Health Research Ethics Committee

Author's contribution

The authors confirm contributions as follows: study conception and design by SOA; data collection by NME, GO and RYI; Analysis and interpretation of results by all authors; Draft manuscript preparation by SOA; all authors

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GUIDE TO AUTHORS

Nanotechnology in drug delivery systems and insights to advances in nanocarriers, liposomes, and micelles for targeted drug delivery and controlled release

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ABSTRACT

Nanotechnology has revolutionized the field of drug delivery, offering innovative solutions to longstanding challenges such as poor bioavailability, systemic toxicity, and non-specific distribution of therapeutic agents. This review highlights recent advances in nanocarrier systems particularly liposomes, micelles, and other engineered nanoparticles for targeted drug delivery and controlled release. A comprehensive literature review was conducted across leading scientific databases, including PubMed, ScienceDirect, Scopus, Web of Science, and Google Scholar, to explore recent advancements in nanotechnology-based drug delivery systems. The search utilized a combination of relevant keywords such as "nanotechnology," "drug delivery systems," "nanocarriers," "liposomes," "micelles," "controlled release," "targeted delivery," "nanoformulations," and "nanomedicine." The review synthesized current developments in the design and application of nanocarriers—particularly liposomes, polymeric micelles, and other nanoformulations—that enhance drug solubility, stability, bioavailability, and site-specific delivery. Key strategies in controlled and sustained drug release were examined, along with the role of surface functionalization and stimuli-responsive mechanisms in achieving precise therapeutic targeting. Emphasis was placed on the integration of active targeting approaches, including ligand-mediated delivery systems, which have shown significant promise in oncology, infectious diseases, and neurological disorders. While nanotechnology has markedly advanced the field of drug delivery, several challenges persist, including issues related to biocompatibility, large-scale manufacturing, regulatory approval, and long-term safety. This review highlights the potential of nanomedicine to address the limitations of conventional drug delivery and improve clinical outcomes. Continued interdisciplinary research and strategic development are essential to overcome current barriers and facilitate the successful translation of nanocarrier technologies from the laboratory to clinical practice.

KEYWORDS: *Drug delivery systems, Nanocarriers, Liposomes, Micelles, Controlled release, Targeted drug delivery*

INTRODUCTION

Effective drug delivery remains one of the most critical challenges in modern medicine. Despite significant advances in pharmaceutical development, many therapeutic agents suffer from limitations such as poor bioavailability, rapid degradation or clearance, dose-limiting toxicity, and unintended interactions with healthy tissues [1]. These issues can reduce therapeutic efficacy, increase side effects, and hinder the treatment of complex diseases such as cancer, neurodegenerative disorders, and infectious diseases. Traditional drug delivery methods often fail to adequately address these challenges, necessitating innovative approaches to improve drug targeting, control release, and minimize systemic toxicity.

Nanotechnology has emerged as a transformative solution to these drug delivery challenges. By engineering materials at the nanoscale, researchers can develop drug carriers with enhanced properties such as improved solubility, prolonged circulation time, controlled release profiles, and the ability to target specific tissues or cells. Nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, and inorganic nanomaterials can be functionalized with ligands for active targeting, allowing for precise delivery of therapeutic agents while sparing healthy tissues. This precision not only increases treatment efficacy but also reduces adverse effects, representing a paradigm shift in therapeutic strategies [2-4].

This review aims to provide a comprehensive overview of the current state of nanotechnology-enabled drug delivery systems, focusing on how these platforms address key limitations of conventional therapies. We will examine the various types of nanocarriers, their mechanisms of action, and recent advancements in their design and application. Additionally, the review will discuss the challenges and future prospects of translating nanotechnology-based drug delivery systems from bench to bedside. Through this discussion, we seek to highlight the potential of nanomedicine to revolutionize therapeutic delivery and improve patient outcomes across a broad spectrum of diseases [5].

Methods

This review was conducted using a systematic and integrative approach to collect, analyze, and synthesize relevant scientific literature on the applications of nanotechnology in drug delivery systems, with a specific focus on nanocarriers, liposomes, and micelles. The methodology followed ensures comprehensive coverage and critical evaluation of current advances in the field. A comprehensive literature search was performed across several major scientific databases, including **PubMed, ScienceDirect, Scopus, Web of Science, Google Scholar.** Keywords and search terms used included combinations of: *"nanotechnology", "drug delivery systems", "nanocarriers", "liposomes", "micelles", "controlled release", "targeted drug delivery", "nanoformulations", and "nanomedicine"*. Boolean operators (*AND*, *OR*) were used to refine the search and retrieve the most relevant articles. Filters were applied to focus on peer-reviewed articles published in English from **2010 to 2025**, prioritizing recent developments and breakthrough studies in the last five years.

Inclusion criteria

Peer-reviewed journal articles, reviews, and research papers were included in the study. Studies focusing on nanocarriers used in drug delivery, including liposomes, micelles, and polymeric nanoparticles alongside articles discussing controlled release, targeted delivery, or enhanced bioavailability were also considered. Publications highlighting clinical trials, in vitro/in vivo studies, or translational applications were similarly included.

Exclusion criteria

Non-English articles and studies unrelated to drug delivery or nanotechnology were excluded from this study. Articles without accessible full text, conference abstracts, editorials, or non-peer-reviewed materials were similarly excluded from this study.

Data extraction and analysis

After initial screening based on titles and abstracts, full texts of the eligible articles were reviewed. Key information was extracted and categorized under the following themes: Types of nanocarriers (e.g., liposomes, micelles, dendrimers, solid lipid nanoparticles) Mechanisms of drug delivery (passive vs. active targeting, stimuli-responsive release) Physicochemical properties (size, charge, surface modification) Therapeutic applications (oncology, infectious diseases, CNS disorders, etc.) Advantages and limitations Emerging trends and future perspectives A qualitative synthesis

was conducted, identifying patterns, common challenges, and novel innovations. Critical comparisons were made across nanocarrier platforms to highlight the most promising strategies for clinical translation.

Quality Assessment

To ensure reliability, only articles from high-impact journals or those frequently cited in the field were considered as core references. Where possible, the quality of included studies was assessed based on: Study design and reproducibility Clarity of methodology and experimental validation.

Results and Discussion

Fundamentals of nanotechnology in drug delivery

Nanotechnology involves the design, production, and application of materials and devices with dimensions typically ranging from 1 to 100 nanometers. At this scale, materials often exhibit unique physical, chemical, and biological properties that differ significantly from their bulk counterparts. In the context of drug delivery, nanotechnology refers to the use of nanoscale systems such as nanoparticles, nanocapsules, nanoshells, and nanogels to encapsulate therapeutic agents and enhance their delivery to specific sites in the body. These nanocarriers can be engineered to improve the pharmacokinetics and pharmacodynamics of drugs, enabling more precise, efficient, and safer treatments [6].

Advantages of nanotechnology in pharmaceutical sciences

Nanotechnology offers several significant advantages in the field of drug delivery. One of the most prominent is the ability to enhance the solubility and stability of poorly water-soluble drugs, which are otherwise difficult to deliver effectively. Nanocarriers can also protect drugs from premature degradation in the biological environment, thus extending their circulation time and therapeutic window [7]. Moreover, due to their small size and surface modifiability, nanoparticles can cross biological barriers, such as the blood-brain barrier, that are typically impermeable to conventional drugs. Additionally, nanocarriers can be functionalized with targeting ligands (e.g., antibodies, peptides, or small molecules) that enable selective delivery to diseased tissues, thereby minimizing off-target effects and systemic toxicity [8].

Mechanisms of targeted and controlled drug release at the nanoscale

Nanotechnology enables both passive and active targeting strategies for drug delivery. Passive targeting exploits the enhanced permeability and retention (EPR) effect, a phenomenon observed in tumor and inflamed tissues where leaky vasculature allows nanoparticles to accumulate preferentially. Active targeting, on the other hand, involves the functionalization of nanocarriers with ligands that bind to specific receptors overexpressed on target cells, facilitating cellular uptake [9].

Controlled drug release is another critical feature of nanoscale drug delivery systems. Release profiles can be tailored by modifying the carrier composition, surface characteristics, and environmental responsiveness. Stimuli-responsive nanocarriers are particularly promising; they can release their payload in response to specific internal (e.g., pH, redox potential, enzymes) or external (e.g., temperature, light etc) [10].

Nanocarriers classification and mechanisms

Nanocarriers are nanoscale delivery systems designed to transport therapeutic agents to specific sites in the body, improving drug efficacy while minimizing side effects. These advanced drug delivery vehicles have become essential in modern medicine, particularly in cancer therapy, gene delivery, and diagnostics. They function by protecting the drug from degradation, enhancing absorption, and enabling targeted or controlled release [11].

Nanocarriers are broadly classified into several types based on their composition and structure. One of the most commonly used types is polymeric nanoparticles, which are composed of biodegradable polymers such as PLGA (poly(lactic-co-glycolic acid)), PEG (polyethylene glycol), or chitosan. These nanoparticles are valued for their controlled release properties, biocompatibility, and the ease with which they can be modified to suit different therapeutic needs.

Another important category is solid lipid nanoparticles (SLNs). These consist of a solid lipid core stabilized by surfactants. They combine the advantages of liposomes and polymeric nanoparticles, offering high drug stability and controlled release, and are well-suited for various routes of administration, including oral and topical [12].

Dendrimers represent a unique class of nanocarriers characterized by a highly branched, tree-like structure. Their architecture allows for a high degree of functionalization, enabling the attachment of multiple drugs, targeting ligands, or imaging agents. Their precise molecular size and shape make them especially useful for applications in gene therapy and diagnostic imaging.

Nanoemulsions, which are emulsified systems with nanometer-sized droplets, are also widely used. These can be oil-in-water or water-in-oil formulations and are particularly effective at delivering poorly water-soluble drugs. Their high surface area enhances absorption and bioavailability, making them ideal for oral, topical, and ocular drug delivery [13].

Lastly, inorganic nanoparticles, such as gold and silica nanoparticles, offer unique physical and chemical properties. These include optical and magnetic characteristics that make them suitable for theranostic applications simultaneously diagnosing and treating diseases. Gold nanoparticles, for example, can be used for photothermal therapy, while silica nanoparticles are often employed in imaging and biosensing [14].

The mechanisms by which nanocarriers deliver drugs can vary. Passive targeting takes advantage of the enhanced permeability and retention (EPR) effect, particularly in tumor tissues where leaky vasculature allows nanoparticles to accumulate. Active targeting involves modifying the nanocarrier surface with specific ligands, such as antibodies or peptides, which bind to receptors on target cells, enhancing specificity and uptake.

Additionally, nanocarriers can be engineered for controlled or stimuli-responsive release, where the drug is released in response to specific triggers such as changes in pH, temperature, or the presence of certain enzymes. This allows for spatial and temporal control over drug delivery. Once at the target site, nanocarriers often enter cells via endocytosis and can release their payloads intracellularly, sometimes reaching the cytoplasm or even the nucleus, depending on the application [15].

Mechanisms of drug loading and release

Drug delivery systems have evolved significantly over the past decades, with liposomes emerging as one of the most versatile and widely studied carriers. These spherical vesicles, composed of one or more phospholipid bilayers surrounding an aqueous core, offer a unique structure that allows for the encapsulation of both hydrophilic and lipophilic drugs. Hydrophilic drugs are typically housed in the aqueous core, while lipophilic compounds integrate into the lipid bilayer, making liposomes suitable for a wide range of therapeutic agents [17].

The release of drugs from liposomal systems can occur through several primary mechanisms. Diffusion is the most straightforward, where drug molecules gradually migrate out of the liposome due to a concentration gradient. This process is influenced by factors such as the drug's solubility, membrane permeability, and environmental conditions. Another mechanism is erosion, where the liposomal membrane or carrier matrix degrades over time, leading to the gradual release of the encapsulated drug. This is particularly useful for achieving sustained or controlled release profiles [17-19].

In recent years, stimuli-responsive release mechanisms have gained attention due to their potential for precise, site-specific drug delivery. These systems are designed to respond to specific physiological triggers such as changes in pH, temperature, or the presence of certain enzymes. For instance, pH-sensitive liposomes remain stable in the bloodstream but release their payload in acidic environments like tumor tissues or intracellular endosomes. Similarly, thermo-sensitive liposomes are engineered to release their contents when exposed to mild hyperthermia, a condition often induced during cancer treatment. Enzyme-responsive systems exploit overexpressed or disease-specific enzymes to initiate drug release, adding another layer of selectivity [20].

Liposome technology has progressed beyond conventional formulations to include a range of advanced delivery systems. Conventional liposomes, while effective at encapsulating drugs, are often rapidly recognized and cleared by the body's immune system, particularly by the mononuclear phagocyte system (MPS). This limits their circulation time and, by extension, their therapeutic efficacy.

To overcome these limitations, stealth liposomes were developed. These are typically modified with polyethylene glycol (PEG), a process known as PEGylation, which masks the liposome surface from immune detection. As a result, stealth liposomes exhibit significantly prolonged circulation times and enhanced bioavailability,

making them suitable for chronic conditions and cancer therapy. An example of this technology in clinical use is Doxil®, a PEGylated liposomal formulation of doxorubicin [21]. Further enhancements include ligand-targeted liposomes, which are functionalized with specific ligands such as antibodies, peptides, or aptamers. These ligands bind selectively to receptors overexpressed on target cells, such as cancerous cells, enabling targeted drug delivery and minimizing off-target effects. This active targeting approach holds great promise for personalized medicine and treatments requiring high specificity [22].

In addition, stimuli-sensitive liposomes represent a cutting-edge advancement in liposomal design. These smart systems respond to specific internal or external triggers such as acidic pH, elevated temperatures, or disease-specific enzymes thus ensuring that the drug is released precisely where and when it is needed. Such precision not only improves therapeutic outcomes but also reduces systemic toxicity and side effects.

Diffusion, erosion, stimuli-responsive triggers

Micelles have emerged as powerful vehicles for drug delivery, particularly due to their unique ability to encapsulate hydrophobic drugs within their core and deliver them in a controlled, targeted fashion. These nanoscale structures form through the self-assembly of amphiphilic molecules—compounds that possess both hydrophilic (water-attracting) and hydrophobic (water-repelling) regions—when placed in an aqueous environment. Above a certain concentration, known as the critical micelle concentration (CMC), these molecules spontaneously organize into micelles. The hydrophobic segments cluster inward to avoid water, creating a core, while the hydrophilic portions form an outer shell that interfaces with the surrounding aqueous medium [23].

There are two primary types of micelles commonly used in drug delivery: surfactant micelles and polymeric micelles. Surfactant micelles are formed from low-molecular-weight surfactants and tend to be small and relatively unstable in the bloodstream due to their higher CMC. This makes them prone to disassembly upon dilution, which can lead to premature drug release. In contrast, polymeric micelles are made from amphiphilic block copolymers and exhibit significantly greater stability due to their lower CMC values and stronger core–shell architecture. These structures are generally larger and more stable, making them more suitable for systemic drug delivery where prolonged circulation and controlled release are essential.

Micelles can also be functionally enhanced to improve their performance in vivo. One important advancement is the development of stimuli-responsive micelles, which are engineered to release their drug payload in response to specific physiological triggers. For example, pH-sensitive micelles can exploit the acidic environment of tumor tissues or intracellular compartments to initiate drug release. Other micelles may respond to temperature changes, redox conditions, or the presence of specific enzymes, each trigger enabling precise spatial and temporal control over drug delivery [24].

In addition to responsiveness, micelles can be modified to actively target specific cells or tissues. This is achieved by attaching targeting ligands to their surface, such as antibodies, peptides, aptamers, or small molecules. These ligands are chosen to recognize and bind to receptors that are overexpressed on the surface of diseased cells, such as tumor cells. Targeted micelles can significantly enhance the uptake of therapeutic agents by diseased cells through receptor-mediated endocytosis while minimizing off-target effects on healthy tissues [25].

The most significant application of micelles in drug delivery lies in their ability to carry hydrophobic drugs. Many potent chemotherapeutic agents suffer from poor water solubility, limiting their clinical effectiveness. Micelles can encapsulate these drugs within their hydrophobic cores, improving solubility, stability, and bioavailability. Furthermore, polymeric micelles, in particular, benefit from prolonged circulation times in the bloodstream. Their hydrophilic outer shells, often composed of poly(ethylene glycol) (PEG), help evade the immune system by reducing protein adsorption and clearance by phagocytic cells. This “stealth” behavior allows micelles to accumulate in tumors through the enhanced permeability and retention (EPR) effect, a phenomenon where the leaky vasculature of tumor tissues permits the passive accumulation of nanoparticles, while poor lymphatic drainage limits their removal [26].

By combining long circulation times, responsive release mechanisms, and targeted delivery

capabilities, micelles enhance therapeutic efficacy while minimizing systemic toxicity. Their versatility makes them an attractive platform for cancer therapy and other diseases that benefit from localized drug action. As research advances, micelle-based drug delivery systems are expected to play an increasingly important role in the development of next-generation therapeutics, offering safer and more efficient treatments for complex medical conditions [27].

Controlled drug release mechanisms

Controlled drug release mechanisms are a cornerstone of modern pharmaceutical science, offering precise regulation over when and where a therapeutic agent is released in the body. These systems are designed to optimize drug efficacy, reduce side effects, and improve patient compliance by tailoring the delivery profile to the needs of specific diseases or patient conditions. One major area of innovation in controlled drug delivery involves temporal and spatial control. Temporal control refers to how the drug is released over time. In sustained release systems, drugs are delivered gradually over an extended period, maintaining consistent therapeutic levels and minimizing dosing frequency [28]. Delayed release systems are engineered to hold off on drug release until a specific time or until the dosage form reaches a particular part of the body—for example, enteric-coated tablets that resist stomach acid and dissolve in the intestine. Another approach is pulsatile release, where the drug is discharged in bursts at predetermined intervals. This can be particularly beneficial for treating diseases with circadian patterns, such as asthma or rheumatoid arthritis [29].

Spatial control, on the other hand, focuses on delivering drugs to specific sites within the body. This precision targeting can be achieved through a variety of strategies, such as attaching ligands that bind to receptors on target cells, using magnetic fields to guide drug-laden particles, or employing external triggers like ultrasound or light to localize the release.

Beyond time and location-based control, researchers have developed stimuli-responsive drug delivery systems, also known as "smart" systems. These mechanisms rely on either internal or external stimuli to trigger drug release. Internal stimuli-responsive systems take advantage of physiological differences in the body. For example, pH-responsive systems are designed to release drugs in environments with abnormal pH levels, such as the acidic microenvironment of tumors. Redox-responsive systems exploit the higher concentration of reducing agents like glutathione inside cells to initiate drug release. Other systems respond to enzymes that are overexpressed in diseased tissues [30].

External stimuli-responsive systems are activated by external forces. Temperature-sensitive carriers can release drugs when exposed to heat, often through localized hyperthermia. Magnetic field-responsive systems use magnetic nanoparticles that can be guided and heated by external magnets to trigger release. Similarly, light-activated systems, including those triggered by UV or near-infrared (NIR) light, enable precise control of drug release at targeted sites. Ultrasound can also be used, employing mechanical vibrations or localized heating to initiate release [31].

At the heart of many of these advanced strategies are smart nanocarriers with engineered nanoscale delivery systems that combine multiple functionalities. These include liposomes, dendrimers, polymeric micelles, mesoporous silica nanoparticles, and metal-organic frameworks. Smart nanocarriers can be designed to recognize and bind to specific cells, respond to environmental stimuli, and release their payloads in a controlled fashion. Their surfaces can be functionalized with ligands, antibodies, or peptides for active targeting, and they are typically engineered to be biocompatible and minimize immune system activation.

These sophisticated delivery systems are particularly promising for treating complex conditions such as cancer, inflammatory diseases, neurological disorders, and infections. By integrating temporal control, spatial targeting, and stimuli-responsiveness, controlled drug release systems—especially smart nanocarriers which represent a powerful and versatile approach in the field of precision medicine [32].

Clinical applications and translational progress

Nanomedicine has rapidly evolved from a conceptual field into a practical approach with significant clinical impact. Early research focused on preclinical studies where various nanocarriers such as liposomes, dendrimers, polymeric nanoparticles, and inorganic systems having demonstrated considerable promise. These nanoscale delivery systems offered notable improvements in drug solubility, protection from degradation, targeted delivery to specific tissues or cells, and controlled release over time. In

animal models, such platforms often resulted in enhanced therapeutic efficacy, reduced toxicity, and more favorable pharmacokinetics compared to conventional formulations.

Building upon these successes, numerous nanomedicine products have progressed into clinical trials. Human studies have explored their safety profiles, biodistribution, metabolism, and therapeutic benefits across a range of diseases. These trials typically evaluate endpoints such as tumor accumulation, treatment efficacy, and systemic side effects. The ongoing success of these trials continues to bridge the gap between laboratory innovation and real-world clinical application [33].

Several nanoformulations have already received FDA approval, signaling a key milestone in the translation of nanotechnology to mainstream medicine. One of the earliest and most well-known examples is Doxil®, a pegylated liposomal formulation of doxorubicin, approved for the treatment of ovarian cancer and Kaposi's sarcoma. Another widely used formulation is Abraxane®, an albumin-bound form of paclitaxel that eliminates the need for toxic solvents and is approved for breast, lung, and pancreatic cancers. In hematological malignancies, Vyxeos®, a liposomal formulation combining daunorubicin and cytarabine at a fixed molar ratio, has shown improved outcomes in certain types of leukemia. The approval of Onpattro®, a lipid nanoparticle formulation delivering small interfering RNA (siRNA), marked the first FDA-approved RNA interference therapy, representing a new class of gene-silencing treatments. More recently, lipid nanoparticle platforms have also played a critical role in the rapid development and deployment of mRNA-based COVID-19 vaccines, such as those by Pfizer-BioNTech and Moderna.

Nanomedicine has found significant applications in several major disease areas. In oncology, nanocarriers are particularly valuable due to their ability to exploit the enhanced permeability and retention (EPR) effect, leading to preferential accumulation in tumor tissues. Liposomal and polymeric systems allow for more targeted chemotherapy with reduced systemic toxicity. Additionally, nanoparticles are increasingly being engineered for combination therapies, imaging-guided treatment, and immunotherapy enhancement [34, 35].

In the field of infectious diseases, nanoformulations like liposomal amphotericin B have improved safety profiles, notably reducing the nephrotoxicity associated with antifungal treatment. Nanocarriers are also being investigated for targeted antibiotic delivery and as vaccine adjuvants to improve immune responses. The success of lipid nanoparticle-based mRNA vaccines has further highlighted the value of nanotechnology in infectious disease prevention and management.

Central nervous system (CNS) disorders represent another frontier where nanomedicine shows great potential. One of the major challenges in treating CNS conditions is the presence of the blood-brain barrier (BBB), which restricts the entry of most drugs into the brain. Nanoparticles are being designed to cross this barrier via receptor-mediated transport mechanisms, enabling the delivery of therapeutic agents for diseases such as Alzheimer's, Parkinson's, and glioblastoma. Preclinical studies in this area are promising, with various platforms showing the ability to deliver neuroprotective agents, anti-inflammatory drugs, and even gene therapies directly to brain tissue [36].

In summary, nanomedicine has made impressive strides in clinical translation. With multiple FDA-approved products and many more in development, it is reshaping how we approach the diagnosis, treatment, and prevention of complex diseases. As new materials, targeting strategies, and regulatory frameworks continue to evolve, nanotechnology is poised to play an even greater role in the future of personalized and precision medicine.

Challenges and future perspectives

Nanomedicine, while offering transformative potential for diagnostics and therapeutics, faces several key challenges that must be addressed to fully realize its promise. One of the primary concerns is stability and scalability. Many nanomaterials exhibit instability under physiological conditions, which can compromise their therapeutic efficacy and safety. Furthermore, scaling up the production of these materials while maintaining consistency (i.e., size, shape, and functionality), remains a complex and costly endeavor [37]. These issues hinder the transition from laboratory research to large-scale clinical application.

Another significant challenge lies in toxicity and immunogenicity. Although nanomaterials can be engineered for biocompatibility, unintended toxic effects and adverse immune responses are still

common. The interaction of nanoparticles with biological systems is highly complex and not yet fully understood, making it difficult to predict long-term effects. Comprehensive and standardized toxicity studies are needed to ensure that nanomedicines do not pose risks to patients.

Regulatory and manufacturing challenges further complicate the development of nanomedicines. Regulatory frameworks have yet to catch up with the unique properties and mechanisms of action associated with nanoscale therapeutics. There is a lack of standardized protocols for characterization, testing, and quality control, which delays approval processes and increases the burden on developers. Additionally, manufacturing nanomedicines with reproducibility and in compliance with good manufacturing practices (GMP) is technically demanding and often expensive [38].

Looking ahead, the field of nanomedicine is expected to evolve in exciting new directions. Personalized nanomedicine is a particularly promising trend, aiming to tailor nanoparticle-based therapies to individual patients based on their genetic, biochemical, and environmental profiles. This approach could significantly improve treatment efficacy and reduce side effects. Another emerging area is the development of hybrid systems, which combine different types of nanomaterials or integrate nanotechnology with other therapeutic modalities, such as gene editing or immunotherapy. These systems can offer multifunctionality, enhanced targeting capabilities, and synergistic therapeutic effects.

Looking ahead, nanotechnology is poised to play a transformative role in the next generation of therapeutic strategies. Advances in precision engineering, biomimicry, and smart nanomaterials will continue to enhance the safety and efficacy of nanodrugs. However, challenges such as large-scale manufacturing, long-term toxicity studies, and regulatory approval must be addressed to fully realize the clinical potential of these systems. As interdisciplinary collaborations grow and regulatory pathways mature, nanotechnology is expected to become an integral part of mainstream medical treatments.

In summary, while nanomedicine holds enormous potential, overcoming current challenges related to stability, safety, regulation, and production is essential. Continued interdisciplinary research, innovation in nanomaterial design, and the development of adaptive regulatory frameworks will be critical in shaping the future of this rapidly evolving field.

Conclusion

Recent developments in nanotechnology have revolutionized the field of drug delivery, offering targeted, efficient, and controlled therapeutic options. Key advances include the creation of stimuli-responsive nanocarriers, surface-functionalized nanoparticles for specific cell targeting, and multifunctional platforms that combine diagnostics with therapeutics (theranostics). Innovations in lipid-based, polymeric, and inorganic nanocarriers have also improved the solubility, bioavailability, and stability of drugs, while reducing systemic toxicity. The integration of nanotechnology in modern medicine holds the potential to overcome many of the limitations of traditional drug delivery systems. Personalized nanomedicine approaches can optimize treatment outcomes for various diseases, especially cancer, neurological disorders, and infectious diseases. Furthermore, nanocarriers can traverse biological barriers, such as the blood-brain barrier, and enable site-specific drug delivery, reducing side effects and improving patient compliance.

Ethical Considerations

Data availability

The data that supported the findings in this study are available on request from the corresponding author

Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest.

Compliance with ethical guidelines

Approval for this study and related cases was obtained from the University of Uyo Health Research Ethics Committee

Author's contribution

The authors confirm contributions as follows: study conception and design by SOA; data collection by PJE, GO and AEA; Analysis and interpretation of results by all authors; Draft manuscript preparation by SOA; all authors reviewed the result and approved the final version of the manuscript.

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GUIDE TO AUTHORS

Molecular mechanisms of action (MOA) of some selected drug classes

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ABSTRACT

Understanding the molecular mechanism of action (MOA) of drug classes is fundamental to pharmacology, therapeutics, and drug development. This review provides a comprehensive overview of the molecular and cellular mechanisms by which major classes of drugs exert their effects. It explores how drugs interact with biological targets such as receptors, enzymes, ion channels, and transporters to modulate physiological processes and produce therapeutic outcomes. The keywords and Boolean operators used in the search included "mechanism of action" AND "drug classes", "pharmacodynamics" OR "MOA" AND "therapeutic agents", "antibiotics", "antivirals", "antifungals", "analgesics", "antidepressants", "antihypertensives", and "drug mechanism" AND "clinical pharmacology". Publications were within the years 2020 -2025. Key drug classes discussed include analgesics, antibiotics, antihypertensives, antidepressants, antineoplastics, and more, with emphasis on both classical mechanisms and emerging insights from recent research. The review also highlights the clinical relevance of MOA knowledge in guiding drug selection, predicting therapeutic responses, and anticipating adverse effects. By

KEYWORDS: Therapeutic agents, Antibiotics, Clinical pharmacology, Drug classes, Cellular mechanisms

INTRODUCTION

Understanding the mechanism of action (MOA) of drug classes is a cornerstone of pharmacology and therapeutics. The MOA refers to the specific biochemical interaction through which a drug produces its pharmacological effect. This typically involves binding to a molecular target such as a receptor, enzyme, ion channel, or nucleic acid and modulating its activity to alter a physiological process [1]. By elucidating these interactions, researchers and clinicians can better predict therapeutic outcomes, optimize drug selection, and anticipate adverse effects.

Drug classes are typically grouped based on shared structural features, target sites, or pharmacodynamic properties. Each class operates via a characteristic MOA that defines its clinical utility. For instance, beta-blockers exert their effects by antagonizing beta-adrenergic receptors, leading to reduced cardiac output and blood pressure, while antibiotics like penicillins inhibit bacterial cell wall synthesis by targeting penicillin-binding proteins. These fundamental differences underscore the importance of class-specific mechanisms in guiding clinical application and drug development [2].

Recent advances in molecular biology, structural bioinformatics, and high-throughput screening have greatly expanded our understanding of how drugs interact with their targets at the atomic level. This has not only facilitated the discovery of novel agents but also enabled the repurposing of existing drugs and the development of precision medicine approaches tailored to individual patients' genetic profiles [3].

This review provides a comprehensive overview of the mechanisms of action of major drug classes, highlighting the molecular targets, signal transduction pathways, and therapeutic implications associated with each. By integrating classical pharmacological principles with contemporary scientific insights, this work aims to serve as a reference for students, researchers, and healthcare professionals seeking a deeper understanding of drug function at the mechanistic level.

Method

This review was conducted using a structured, narrative approach to compile and synthesize current knowledge on the mechanisms of action of major drug classes. The methodology involved a comprehensive literature search, selection of relevant publications, and critical evaluation of findings.

Literature search strategy

A systematic search was performed using electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, covering literature published up to May, 2025. Keywords and Boolean operators used in the search included:"mechanism of action" AND "drug classes", "pharmacodynamics" OR "MOA" AND "therapeutic agents", "antibiotics", "antivirals", "antifungals","analgesics","antidepressants","anti hypertensives",and"drug mechanism" AND "clinical pharmacology".

Inclusion and exclusion criteria

Publications were included if they provided detailed descriptions of the mechanisms of action of one or more drug classes. Similarly considered were peer-reviewed articles, reviews, and authoritative pharmacology textbooks published in English. Excluded were articles focusing solely on pharmacokinetics without MOA discussion. Case reports or anecdotal studies without mechanistic insights alongside non-English publications and preprints not peer-reviewed.

Data extraction and synthesis

Key data were extracted from selected sources, including the molecular targets of drug classes, downstream biochemical pathways, cellular or systemic effects, and clinical implications. Information was grouped and categorized by therapeutic class, such as antimicrobials, cardiovascular drugs, central nervous system agents, and anticancer drugs. Mechanisms were described at the molecular, cellular, and systemic levels, where appropriate, with emphasis on clinically relevant targets such as receptors, enzymes, ion channels, and

transporters. Where applicable, known resistance or tolerance mechanisms or pathway redundancies were also noted that provide context for drug efficacy and limitations.

Quality assessment

To ensure reliability, priority was given to high-impact review articles, recent pharmacology textbooks, and clinical guidelines. Conflicting information was resolved through cross-referencing with authoritative sources, and consensus viewpoints were emphasized.

Results and Discussion

Antibiotics

Beta-lactams

These include penicillins, cephalosporins, carbapenems, and monobactams. They inhibit bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs), disrupting peptidoglycan cross-linking. β-lactam antibiotics, a class that encompasses penicillins, cephalosporins, carbapenems, and monobactams, exert their potent antibacterial effects through a precise and highly targeted mechanism that disrupts the integrity of the bacterial cell wall which is a critical structural component essential for bacterial survival, particularly in Gram-positive and Gram-negative organisms. These agents are unified by the presence of a highly reactive β-lactam ring, which is central to their mechanism of action.

At the core of their bactericidal activity lies the ability to inhibit bacterial cell wall synthesis, specifically by interfering with the final stages of peptidoglycan biosynthesis [4]. The peptidoglycan layer is a rigid, mesh-like polymer composed of linear chains of alternating N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) residues, which are cross-linked by short peptide bridges [5]. This complex structure provides mechanical strength and osmotic protection to the bacterial cell. β-lactams act by covalently binding to and inactivating penicillin-binding proteins (PBPs) a group of essential bacterial enzymes that catalyze the cross-linking of the peptidoglycan chains via transpeptidation and transglycosylation reactions [6]. These PBPs are located in the bacterial cytoplasmic membrane and are so named because they were initially identified by their ability to bind radiolabeled penicillin.

When a β-lactam antibiotic binds irreversibly to the active site of a PBP, it forms a stable acyl-enzyme complex that blocks the enzyme's catalytic activity. This inhibition prevents the formation of cross-links between the peptidoglycan strands, thereby compromising the structural integrity of the cell wall. As a result, the bacterial cell becomes increasingly susceptible to osmotic lysis due to the internal turgor pressure that the weakened cell wall can no longer withstand [7]. Moreover, the accumulation of cell wall precursors and incomplete peptidoglycan fragments may trigger the activation of autolytic enzymes, such as a utolysins and murein

In summary, β-lactam antibiotics eliminate susceptible bacteria by sabotaging the fundamental architecture of their protective cell walls through the inactivation of the PBPs, culminating in cell lysis and death. This elegant mechanism underscores both their clinical effectiveness and the ongoing need to understand and overcome bacterial resistance

Macrolides

Macrolides inhibit bacterial protein synthesis by binding to ribosomal subunit, blocking translocation [9]. Macrolides exert their antibacterial effect by specifically targeting bacterial protein synthesis. Their action is centered on the bacterial ribosome, a complex molecular machine responsible for translating messenger RNA (mRNA) into functional proteins. The bacterial ribosome is composed of two subunits: the 30S (small) subunit, which decodes the mRNA, and the 50S (large) subunit, which catalyzes peptide bond formation and provides an exit tunnel for the nascent polypeptide chain.

This class of drugs are characterized structurally by a large macrocyclic lactone ring which are typically 14 to 16 atoms in size decorated with deoxy sugar residues such as desosamine and cladinose [10]. These structural features are critical for the antibiotic's interaction with the ribosome. The primary binding site for macrolides is located within the 50S ribosomal subunit, specifically in a region of the 23S ribosomal RNA (rRNA) known as domain V [11]. Within this domain lies the nascent peptide exit tunnel (NPET), a conduit through which the newly synthesized polypeptide chain must pass as it emerges from the ribosome [12].

Upon binding to the NPET, macrolides occupy a position adjacent to the peptidyl transferase center (PTC), the enzymatic core of the ribosome responsible for forming peptide bonds [13]. The interaction is stabilized through multiple non-covalent forces, including hydrogen bonding and hydrophobic contacts with key nucleotides of the 23S rRNA. Of particular importance is the adenine residue at position 2058 (A2058, in *E. coli* numbering), which plays a central role in anchoring the macrolide molecule within the exit tunnel [14].

Unlike antibiotics such as chloramphenicol, which directly inhibit peptide bond formation, macrolides do not interfere with the catalytic activity of the peptidyl transferase center itself. Rather, they block the elongation of the polypeptide chain by physically obstructing its passage through the exit tunnel. This steric hindrance prevents proper translocation, a key step in which the ribosome shifts along the mRNA to allow the entry of a new aminoacyl-tRNA into the A site [14]. As a result, the ribosome stalls on the mRNA template, leading to premature termination of translation and an overall inhibition of protein synthesis.

Interestingly, the inhibitory effect of macrolides can be context-dependent. That is, the degree of ribosomal stalling and translational arrest may vary depending on the sequence of the nascent peptide and the structure of the macrolide itself. In some cases, specific amino acid sequences enhance the likelihood of ribosome stalling when a macrolide is bound, illustrating a nuanced interplay between the antibiotic, the ribosome, and the emerging peptide [16].

Macrolides are typically bacteriostatic, meaning they suppress bacterial growth without directly killing the cells. However, under certain conditions such as high drug concentrations or in specific bacterial species they can exhibit bactericidal activity. Importantly, macrolides demonstrate a high degree of selectivity for bacterial ribosomes over eukaryotic ones. This selectivity arises from structural differences between prokaryotic and eukaryotic ribosomes, particularly at the macrolide [17].

As a result, macrolides prevent the progression of translation by inhibiting the translocation step the movement of the ribosome along the messenger RNA (mRNA) after a peptide bond has formed. This prevents the addition of further amino acids to the growing polypeptide chain. Interestingly, recent research has shown that this inhibition can be context-specific: macrolides can cause ribosomes to stall at specific amino acid sequences, depending on the nature of the nascent peptide and the conformation of the ribosome. This selective inhibition means that not all proteins are equally affected, leading to nuanced and often organism-specific effects on bacterial protein synthesis.

Macrolides are particularly effective against Gram-positive bacteria and several atypical pathogens, including *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, and *Legionella pneumophila*. Their effectiveness against Gram-negative bacteria is generally limited due to the outer membrane barrier and the presence of efflux pumps that reduce intracellular drug concentration. Additionally, mutations in the 23S rRNA or in ribosomal proteins L4 and L22 can

alter ribosomal conformation in ways that reduce macrolide binding. In rare cases, macrolides can be inactivated by bacterial enzymes through hydrolysis or phosphorylation [18].

Their excellent tissue penetration, including into phagocytes and other immune cells, enhances their efficacy against intracellular pathogens. Macrolides also have notable anti-inflammatory and immunomodulatory properties, which contribute to their use in certain non-infectious inflammatory conditions.

To address resistance, newer macrolide derivatives such as ketolides have been developed. Ketolides, like telithromycin, have modifications that improve their binding affinity and efficacy even in the presence of methylated rRNA. They also tend to have dual binding interactions within the ribosome, making them more resilient to resistance mechanisms.

Fluoroquinolones

Fluoroquinolones are a potent class of broad-spectrum antibiotics whose molecular mode of action centers on the inhibition of bacterial DNA replication and transcription. They exert their bactericidal effects by targeting two essential bacterial enzymes: DNA gyrase and topoisomerase IV [19]. These enzymes are members of the type II topoisomerase family and play critical roles in maintaining the topology of bacterial DNA during replication and cell division.

DNA in bacterial cells is tightly coiled and supercoiled. For replication and transcription to proceed, this supercoiling must be dynamically modulated. DNA gyrase, which is particularly important in Gram-negative bacteria, introduces negative supercoils into DNA using the energy from ATP hydrolysis. This process relieves the torsional strain that builds up ahead of replication forks. Topoisomerase IV, which is especially important in Gram-positive organisms, is primarily involved in decatenation the separation of interlinked daughter DNA molecules following replication.

Fluoroquinolones, such as ciprofloxacin, levofloxacin, and moxifloxacin, work by stabilizing the transient DNA-enzyme complex that is formed during the normal catalytic cycle of these topoisomerases. Under normal circumstances, these enzymes cut both strands of DNA, pass another segment of the double helix through the break, and then re-ligate the DNA to restore its integrity. Fluoroquinolones bind at the interface of the DNA and the enzyme, effectively "freezing" this complex in its cleaved state [20].

This stabilization of the DNA cleavage complex leads to the accumulation of double-stranded breaks in the bacterial chromosome. These breaks are highly toxic because they cannot be easily repaired, especially given the concurrent inhibition of replication forks and the interference with cell division. The persistence of these unrepaired breaks eventually triggers cell death, making fluoroquinolones bactericidal rather than merely bacteriostatic.

At the molecular level, fluoroquinolones interact with conserved amino acid residues and magnesium ions within the catalytic core of the topoisomerase enzymes. The presence of a fluorine atom at position 6 of the quinolone core increases the compound's lipophilicity and enhances its ability to penetrate bacterial cells and bind its target with high affinity. The carboxyl and ketone groups on the quinolone ring are involved in chelating the divalent metal ions necessary for enzyme function and binding to the DNA-enzyme complex. The relative importance of DNA gyrase versus topoisomerase IV as the primary target varies between bacterial species. In *Escherichia coli* and other Gram-negative organisms, DNA gyrase is the main target. In contrast, in *Streptococcus pneumoniae* and other Gram-positive organisms, topoisomerase IV tends to be the more critical enzyme for fluoroquinolone activity. This dual targeting contributes to the broad spectrum and potency of fluoroquinolone **[21].** Despite their effectiveness, resistance to fluoroquinolones has become increasingly common. Resistance mechanisms primarily include point mutations in the quinolone resistance-determining regions

(QRDRs) of the genes encoding DNA gyrase (gyrA and gyrB) and topoisomerase IV (parC and parE). These mutations reduce the binding affinity of fluoroquinolones to their targets. Additionally, efflux pumps can actively expel the drug from bacterial cells, and plasmid-mediated resistance mechanisms (e.g., qnr proteins) can protect DNA gyrase from fluoroquinolone binding [22].

In summary, fluoroquinolones kill bacteria by inhibiting DNA gyrase and topoisomerase IV, enzymes essential for DNA replication and chromosome segregation. They act by stabilizing a normally transient enzyme-DNA complex, resulting in lethal double-stranded DNA breaks. Their precise targeting and bactericidal activity have made them essential in the treatment of a wide range of infections, though growing resistance poses a significant clinical challenge [23].These drugs inhibit DNA gyrase and topoisomerase IV, enzymes critical for bacterial DNA replication and transcription [24].

Antihypertensives

Angiotensin converting enzyme (ACE) inhibitors

Angiotensin Converting Enzyme (ACE) inhibitors are a widely used class of medications that function by interfering with the body's renin–angiotensin–aldosterone system (RAAS), a critical regulator of blood pressure, fluid balance, and vascular tone. At the molecular level, ACE inhibitors exert their effects by blocking the activity of the angiotensin-converting enzyme, a

key zinc-dependent metalloprotease found predominantly on the surface of endothelial cells, especially in the lungs [25].

ACE plays two primary roles in the RAAS pathway. First, it converts angiotensin I, an inactive decapeptide, into angiotensin II, an octapeptide that is a potent vasoconstrictor and stimulator of aldosterone secretion. Angiotensin II raises blood pressure by constricting blood vessels, increasing sodium and water retention through aldosterone, and enhancing sympathetic nervous activity. Second, ACE also degrades bradykinin, a peptide that normally acts as a vasodilator by promoting the release of nitric oxide and prostaglandins from the endothelium [26].

ACE inhibitors, such as captopril, enalapril, lisinopril, and ramipril, are designed to bind directly to the active site of the ACE enzyme. They mimic the natural substrate, angiotensin I, and occupy the catalytic site in a competitive manner. A defining feature of their molecular action is their interaction with a zinc ion located at the core of the ACE active site. This zinc ion is essential for the enzyme's catalytic function. ACE inhibitors typically possess functional groups—such as thiol, carboxyl, or phosphinyl moieties—that can chelate the zinc ion, thereby preventing the enzyme from converting angiotensin I to angiotensin II [27].

By blocking this enzymatic activity, ACE inhibitors reduce the production of angiotensin II, leading to a cascade of physiological effects. Vasoconstriction is diminished, resulting in lowered systemic vascular resistance and blood pressure. Aldosterone secretion is reduced, decreasing sodium and water reabsorption in the kidneys, which contributes to a decrease in blood volume. The reduction in angiotensin II also leads to less stimulation of the sympathetic nervous system and reduced oxidative stress and inflammation in the cardiovascular system. These effects are particularly beneficial in patients with hypertension, heart failure, or diabetic nephropathy [28].

An additional consequence of ACE inhibition is the accumulation of bradykinin, since its degradation is also suppressed. Elevated bradykinin levels further contribute to vasodilation and enhanced endothelial function by stimulating the production of nitric oxide and prostacyclin. While this effect adds to the antihypertensive and cardioprotective properties of ACE inhibitors, it also explains some of their common side effects. For example, increased bradykinin is thought to be responsible for the persistent dry cough experienced by some

patients, as well as the rare but potentially serious occurrence of angioedema [29].

Structurally, different ACE inhibitors vary in how they interact with the ACE enzyme, which influences their pharmacokinetics and potency. Captopril, for instance, contains a thiol group that binds strongly to the zinc ion and has a relatively short half-life, requiring multiple daily doses. In contrast, enalapril and lisinopril use carboxyl groups for zinc binding and have longer durations of action.

In summary, ACE inhibitors lower blood pressure and provide cardiovascular and renal protection by directly blocking the angiotensin-converting enzyme. This action reduces angiotensin II production, enhances bradykinin levels, and leads to vasodilation, decreased fluid retention, and reduced sympathetic activity. The molecular specificity of these drugs for the ACE active site particularly their interaction with the enzyme's catalytic zinc ion—is central to their therapeutic effectiveness [30].

Calcium channel blockers

Calcium channel blockers (CCBs) are a class of pharmacological agents that inhibit the influx of calcium ions (Ca^{2+}) through voltage-gated calcium channels, with a primary focus on the L-type calcium channels found in cardiac muscle, vascular smooth muscle, and nodal tissues. Calcium ions play a critical role in excitation-contraction coupling and signal transduction in excitable cells. By modulating the function of these ion channels, CCBs exert significant effects on vascular tone, myocardial contractility, and cardiac electrophysiology [31].

The L-type calcium channel, also known as Cav1.2, is a high-voltage-activated channel composed of several subunits, of which the α1C subunit forms the ion-conducting pore and contains the voltage-sensing domains. This subunit is organized into four homologous domains (I–IV), each containing six transmembrane segments (S1–S6). The fourth segment in each domain (S4) functions as a voltage sensor, responding to changes in membrane potential by undergoing conformational shifts that lead to channel opening.

When open, the channel permits the selective entry of extracellular calcium ions into the cytoplasm, a process crucial for initiating muscle contraction and propagating electrical signals [32].

Calcium channel blockers interfere with this process by binding to specific sites on the α1C subunit, thereby altering the channel's gating behavior. Importantly, CCBs do not physically occlude the pore like some other ion channel inhibitors. Instead, they function as allosteric modulators, stabilizing the channel in a non-conductive conformation, typically the inactivated state, or hindering the voltage-induced transitions that lead to opening. This results in a decreased probability that the channel will open during depolarization, thereby reducing the magnitude of calcium influx [33].

There are three major classes of calcium channel blockers, each with distinct binding characteristics and tissue selectivity. Dihydropyridines (e.g., amlodipine, nifedipine) preferentially target vascular smooth muscle and are potent vasodilators. Phenylalkylamines (e.g., verapamil) act primarily on cardiac myocytes and nodal tissue, while benzothiazepines (e.g., diltiazem) exert intermediate effects on both vascular and cardiac tissues [34]. The binding affinity of these drugs can be influenced by the state of the channel; for instance, verapamil and diltiazem exhibit use-dependent binding, meaning they bind more effectively to channels that open frequently or are held in depolarized states—a characteristic particularly relevant in fast-firing cardiac cells.

At the molecular level, inhibition of calcium influx leads to tissue-specific effects. In vascular smooth muscle, the reduction in intracellular calcium limits the activation of calmodulin and myosin light chain kinase (MLCK), enzymes essential for initiating contraction. The result is relaxation of the smooth muscle, vasodilation, and a

subsequent decrease in blood pressure. In cardiac myocytes, calcium influx through L-type channels during the plateau phase (phase 2) of the action potential triggers further calcium release from the sarcoplasmic reticulum—a process known as calcium-induced calcium release. By limiting this initial calcium entry, CCBs reduce the strength of myocardial contraction, resulting in a negative inotropic effect [34].

In nodal tissue, particularly the sinoatrial (SA) and atrioventricular (AV) nodes, calcium currents are responsible for the upstroke of the action potential

(phase 0). Inhibition of L-type calcium channels in these cells leads to a slowed rate of depolarization, reducing heart rate (a negative chronotropic effect) and delaying conduction through the AV node (a negative dromotropic effect). These effects make CCBs particularly useful in managing conditions such as supraventricular tachycardia and angina [35].

In summary, calcium channel blockers act at the molecular level by binding allosterically to L-type voltage-gated calcium channels, specifically targeting the α1C subunit. This binding alters the channel's voltage-dependent gating properties, reducing calcium influx into excitable cells. The downstream effects vasodilation, reduced cardiac contractility, and slowed nodal conduction form the basis of their clinical utility in treating hypertension, angina pectoris, and certain cardiac arrhythmias.

Beta-blockers

Beta blockers, also known as beta-adrenergic receptor antagonists, are a class of drugs that exert their effects by blocking the action of endogenous catecholamines primarily adrenaline (epinephrine) and noradrenaline (norepinephrine) on beta-adrenergic receptors. These receptors are part of the sympathetic nervous system and play a critical role in regulating cardiovascular function, including heart rate, contractility, and vascular tone [36].

There are three main types of beta-adrenergic receptors: β_1, β_2, and β_3**.** The β_1 receptors are primarily located in the heart and kidneys, while β_2 receptors are found predominantly in the lungs, vascular smooth muscle, liver, and skeletal muscle. β_3 receptors, though less well understood, are found in adipose tissue and are involved in lipolysis and thermogenesis. Most beta blockers used clinically target β_1 and β_2 receptors, though some are selective for β_1 (cardioselective), while others block both β_1 and β_2 receptors (non-selective).

At the molecular level, beta blockers act as competitive antagonists. They bind to the β-adrenergic receptors without activating them, thereby blocking the binding of catecholamines like adrenaline. This inhibition prevents the normal downstream signaling cascade mediated by the activation of the G-protein-coupled

receptor (GPCR) pathway. Under normal circumstances, stimulation of β_1 receptors in the heart activates the Gs protein, which in turn activates adenylate cyclase. This enzyme converts ATP to cyclic AMP (cAMP), which activates protein kinase A (PKA). PKA then phosphorylates various target proteins, including calcium channels, leading to increased intracellular calcium and, consequently, enhanced heart rate (positive chronotropy), increased contractility (positive inotropy), and faster conduction through the atrioventricular node (positive dromotropy) [37].

By blocking this pathway, beta blockers reduce the effects of sympathetic stimulation on the heart**.** This results in a decrease in heart rate, myocardial contractility, and cardiac output, thereby lowering blood pressure and reducing myocardial oxygen demand. These effects are particularly beneficial in conditions like hypertension, angina pectoris, myocardial infarction, arrhythmias, and chronic heart failure. In heart failure, long-term use of certain beta blockers (such as carvedilol, bisoprolol, and

metoprolol succinate) has been shown to improve survival by attenuating the harmful effects of chronic sympathetic overactivity on the heart [38].

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors are a widely prescribed class of antidepressant medications that work by modulating the levels of serotonin, a key neurotransmitter involved in mood regulation, anxiety, sleep, and appetite. These drugs are used primarily in the treatment of major depressive disorder, anxiety disorders, obsessive-compulsive disorder, and other psychiatric conditions associated with dysregulation of serotonin signalling [39].

At the molecular level, SSRIs act on the serotonergic synapse, where neurons communicate using serotonin (5-hydroxytryptamine, or 5-HT). Under normal conditions, serotonin is released from the presynaptic neuron into the synaptic cleft in response to neuronal firing. It then binds to specific receptors on the postsynaptic membrane to exert its effects. Once the signal is transmitted, serotonin is typically reabsorbed by the serotonin transporter protein (SERT) located on the presynaptic neuron. This process, known as reuptake, terminates the action of serotonin and recycles it for future use [40].

SSRIs exert their therapeutic effect by selectively inhibiting the serotonin transporter (SERT). By blocking this transporter, SSRIs prevent the reuptake of serotonin back into the presynaptic neuron, thereby increasing the concentration of serotonin in the synaptic cleft. The elevated serotonin levels result in prolonged stimulation of postsynaptic serotonin receptors, which helps to enhance and stabilize mood over time. It is important to note that while SSRIs increase serotonin levels relatively quickly, their clinical effects typically take several weeks to manifest. This delay is thought to be due to downstream neuroadaptive changes in the brain, such as receptor desensitization, changes in gene expression, and enhanced neuroplasticity. For example, chronic SSRI use has been associated with increased expression of brain-derived neurotrophic factor (BDNF), which supports neuronal survival and synaptic remodeling, particularly in regions like the hippocampus that are affected in depression [41].

SSRIs are considered "selective" because they primarily target serotonin reuptake, with minimal effects on other neurotransmitters, such as norepinephrine or dopamine. This selectivity contributes to their relatively favorable side effect profile compared to older antidepressants like tricyclics or monoamine oxidase inhibitors (MAOIs), which affect multiple neurotransmitter systems.

However, because serotonin is involved in many physiological processes, SSRIs can still cause side effects. Common adverse effects include nausea, insomnia, sexual dysfunction, and gastrointestinal disturbances. In some individuals, especially at the beginning of treatment or during dose changes, SSRIs can increase anxiety or agitation. Rarely, they may contribute to serotonin syndrome, a potentially life-threatening condition resulting from excessive serotonergic activity, particularly when combined with other serotonergic agents.

Examples of commonly prescribed SSRIs include fluoxetine, sertraline, citalopram, escitalopram, paroxetine, and fluvoxamine. Although their mechanism of action is similar, these agents differ in terms of pharmacokinetics, side effect profiles, and specific indications, allowing clinicians to tailor treatment based on individual patient needs [42].

Tricyclic antidepressants (TCAs)

Tricyclic antidepressants (TCAs) are a class of psychotropic agents named for their characteristic chemical structure, which consists of three fused rings. Developed in the 1950s, TCAs were among the first pharmacological treatments for major depressive disorder. Although largely supplanted in clinical practice by newer antidepressants with improved safety profiles, TCAs remain therapeutically relevant,

particularly for treatment-resistant depression, chronic pain syndromes, and certain anxiety disorders [44].

At the molecular level, TCAs exert their primary antidepressant effect by inhibiting the reuptake of monoamine neurotransmitters, particularly norepinephrine (NE) and serotonin (5-hydroxytryptamine, 5-HT), from the synaptic cleft. This action is mediated by high-affinity binding to the presynaptic transporters responsible for the reuptake of these neurotransmitters—namely, the norepinephrine transporter (NET) and the serotonin transporter (SERT) [45].

By blocking NET and/or SERT, TCAs prevent the reabsorption of NE and 5-HT into the presynaptic neuron following their release into the synaptic cleft. The resulting elevation in extracellular concentrations of these monoamines enhances their postsynaptic signaling, which is believed to contribute to the antidepressant effect over time. Chronic elevation of monoamines leads to downstream adaptive changes, including receptor desensitization, gene expression modulation, and neurotrophic factor regulation, particularly the upregulation of brain-derived neurotrophic factor (BDNF). These neuroadaptive processes are thought to underlie the delayed onset of therapeutic effects observed with TCAs and other antidepressants [45]. In addition to their effects on monoamine transporters, TCAs interact with a variety of other molecular targets, contributing to their side effect profile [46]:

Muscarinic acetylcholine receptors (M1 blockade) causes anticholinergic effects such as dry mouth, blurred vision, constipation, urinary retention, and cognitive disturbances. Histamine H1 receptors antagonism results in sedation and weight gain. Similarly, alpha-1 adrenergic receptors blockade causes orthostatic hypotension and dizziness. The pharmacodynamics of individual TCAs vary depending on their relative affinity for SERT vs. NET. For instance, imipramine and amitriptyline show relatively balanced inhibition of both SERT and NET, whereas nortriptyline and desipramine preferentially inhibit NET. These differences can influence both efficacy and side effect profiles in clinical use [47].

From a pharmacokinetic standpoint, TCAs are lipophilic and well-absorbed, with high protein binding and extensive hepatic metabolism, primarily via cytochrome P450 enzymes (e.g., CYP2D6). Their metabolites may retain pharmacologic activity, and polymorphisms in metabolic enzymes can significantly impact drug levels and tolerability [48].

In summary, the primary molecular mechanism of tricyclic antidepressants involves inhibition of norepinephrine and serotonin reuptake through blockade of their respective transporters (NET and SERT), thereby enhancing monoaminergic neurotransmission in the central nervous system. While effective, their non-selective receptor binding contributes to a broad range of anticholinergic, antihistaminic, and cardiovascular side effects, which limits their tolerability and necessitates caution in their clinical use—particularly in overdose settings.

TCAs inhibit the reuptake of both norepinephrine and serotonin but also interact with other receptors, contributing to side effects.

Monoamine oxidase inhibitors (MAOIs)

Monoamine oxidase inhibitors (MAOIs) are a class of antidepressant agents that exert their therapeutic effect by increasing the levels of monoamine neurotransmitters—primarily serotonin (5-hydroxytryptamine, 5-HT), norepinephrine (NE), and dopamine (DA)—within the central nervous system. These neurotransmitters play key roles in regulating mood, arousal, and emotional stability, and their dysregulation has been closely associated with depressive disorders and certain anxiety conditions [49].

The molecular target of MAOIs is the enzyme monoamine oxidase (MAO), which is responsible for the oxidative deamination and inactivation of monoamines both in the brain and peripheral tissues. This enzyme exists in two isoforms:

MAO-A, which preferentially metabolizes serotonin, norepinephrine, and epinephrine, and MAO-B, which primarily breaks down phenylethylamine and dopamine. Both isoforms are flavin adenine dinucleotide (FAD)-dependent enzymes, located on the outer mitochondrial membrane of neurons and other cells. MAOIs function by binding to these enzymes and inhibiting their catalytic activity, thereby reducing the breakdown of monoamine neurotransmitters. This inhibition leads to an accumulation of neurotransmitters in the synaptic cleft, enhancing monoaminergic signaling and, over time, exerting antidepressant effects. The precise therapeutic action is not solely due to the immediate increase in neurotransmitter levels, but also involves downstream neuroadaptive changes such as altered receptor sensitivity, modulation of intracellular signaling cascades, and increased expression of neurotrophic factors like brain-derived neurotrophic factor (BDNF), which supports neuronal plasticity and survival [50].

MAOIs can be classified based on their reversibility and selectivity. Some MAOIs, such as phenelzine and tranylcypromine, are irreversible and non-selective, meaning they covalently bind to both MAO-A and MAO-B, resulting in long-lasting inhibition that persists until new enzymes are synthesized—a process that may take up to two weeks. Others, like moclobemide, are reversible and selective, primarily inhibiting MAO-A in a competitive and transient manner. Selective MAO-B inhibitors such as selegiline are used in the treatment of Parkinson's disease, where they enhance dopaminergic transmission [51].

Despite their efficacy, MAOIs are associated with significant clinical limitations, particularly due to their interaction with dietary amines, most notably tyramine. Under normal conditions, MAO in the gut and liver breaks down tyramine, a naturally occurring compound found in aged cheeses, cured meats, and fermented products. Inhibition of this metabolic pathway allows tyramine to accumulate and enter the systemic circulation, where it displaces norepinephrine from presynaptic vesicles, causing a potentially dangerous hypertensive crisis—a reaction sometimes referred to as the "cheese effect" [52]. Moreover, MAOIs pose a risk for serotonin syndrome when used concurrently with other serotonergic drugs, such as SSRIs, SNRIs, or certain opioids. This condition is characterized by autonomic instability, neuromuscular hyperactivity, and altered mental status and it can be life-threatening without prompt intervention.

Antidiabetics

Biguanides

Biguanides are a class of oral antihyperglycemic agents, with metformin being the only widely used drug in this group today. Metformin is considered the first-line pharmacologic treatment for type 2 diabetes mellitus due to its efficacy, safety profile, and positive effects on weight and cardiovascular outcomes [53]. Metformin's primary mechanism of action is reduction of hepatic glucose production, particularly by inhibiting gluconeogenesis in the liver. This effect is largely mediated by activation of AMP-activated protein kinase (AMPK), a central energy-sensing enzyme that regulates cellular metabolism. At the molecular level, metformin enters hepatocytes via organic cation transporters (OCTs). Inside the cell, it accumulates in mitochondria and inhibits complex I of the electron transport chain, leading to a reduction in ATP production and an increase in the cellular AMP:ATP ratio. This shift activates AMPK, which subsequently suppresses expression of genes involved in gluconeogenesis, promotes fatty acid oxidation, enhances insulin sensitivity and inhibits hepatic lipogenesis [54].

By reducing hepatic glucose output and improving peripheral glucose uptake, metformin lowers fasting and postprandial blood glucose levels without stimulating insulin secretion. This insulin-independent mechanism greatly reduces the risk of hypoglycemia, a major advantage over

some other antidiabetic agents. Metformin also has beneficial cardiometabolic effects, including modest weight loss, improved lipid profiles, and anti-inflammatory actions. Recent research has explored its potential use in conditions such as polycystic ovary syndrome (PCOS), certain cancers, and aging-related diseases, due to its effects on metabolic and cellular stress pathways.
The most common side effects of metformin are gastrointestinal, including nausea, diarrhea, and abdominal discomfort. Rarely, it can cause lactic acidosis, a serious complication, particularly in patients with renal or hepatic impairment [55].

Sulfonylureas

Sulfonylureas are a class of antidiabetic drugs that lower blood glucose levels by stimulating insulin secretion from the pancreatic beta cells. They are particularly effective in individuals with type 2 diabetes who retain some degree of endogenous insulin production. Unlike metformin, sulfonylureas act directly on the pancreatic islets,

and their action is glucose-independent, meaning they can trigger insulin release even when blood glucose levels are not elevated—a feature that increases the risk of hypoglycemia. The molecular mechanism of sulfonylureas involves their binding to the sulfonylurea receptor **1** (SUR1), a regulatory subunit of the ATP-sensitive potassium (K-ATP) channel on the surface of pancreatic beta cells. Normally, these potassium channels remain open during low glucose states, keeping the cell membrane hyperpolarized and preventing insulin release. When glucose levels rise, intracellular ATP increase, closing these channels, leading to membrane depolarization, calcium influx, and insulin secretion [55].
Sulfonylureas mimic this natural process by binding to SUR1 and forcibly closing the K_ATP channels, regardless of the actual glucose level. This triggers membrane depolarization, opens voltage-dependent calcium channels, and allows calcium to enter the cell, which in turn promotes the exocytosis of insulin granules. As a result, sulfonylureas significantly increase circulating insulin levels, promoting glucose uptake by peripheral tissues and suppressing hepatic glucose production. However, their reliance on beta cell function means they may become less effective over time as pancreatic function declines—a phenomenon known as secondary failure.
Sulfonylureas are generally well-tolerated but are associated with weight gain and a higher risk of hypoglycemia, particularly in the elderly or those with renal or hepatic impairment. Common agents in this class include glipizide, glyburide, and glimepiride, each with slight variations in potency, half-life, and risk profiles [56].

Sodium-glucose cotransporter 2(SGLT2) inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a relatively new class of oral antidiabetic drugs used primarily for the treatment of type 2 diabetes mellitus, and more recently, for chronic kidney disease and heart failure, due to their broad metabolic and cardiovascular benefits [57].
The molecular target of this drug class is the SGLT2 protein, a transporter located in the proximal convoluted tubule of the nephron in the kidney. Under normal physiological conditions, approximately 90% of the filtered glucose in the glomerular filtrate is reabsorbed back into the bloodstream via SGLT2, which couples glucose

reabsorption with sodium reabsorption. The remaining 10% is reabsorbed by SGLT1, primarily in the distal tubule.
SGLT2 inhibitors, such as empagliflozin, canagliflozin, and dapagliflozin, act by selectively and reversibly inhibiting the SGLT2 protein. By blocking this transporter, these drugs prevent the reabsorption of glucose and sodium from the renal tubular lumen back into the blood. As a result, excess glucose is excreted in the urine, a process known as glucosuria. This directly lowers

blood glucose levels in an insulin-independent manner [58-60].

The insulin-independent mechanism is a key advantage of SGLT2 inhibitors, as it means their efficacy does not rely on beta-cell function or insulin sensitivity. This allows them to be used effectively in combination with other antidiabetic agents, including metformin, insulin, and sulfonylureas.

Conclusion

In conclusion, this review underscores the critical importance of understanding the molecular mechanisms of action across major drug classes in advancing pharmacological knowledge and improving clinical practice. By integrating classical pharmacodynamic principles with recent research findings, it provides a comprehensive framework for interpreting how therapeutic agents achieve their effects at the cellular and molecular levels.

Ethical Considerations

Data availability

The data that supported the findings in this study are available on request from the corresponding author

Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest.

Compliance with ethical guidelines

Approval for this study and related cases was obtained from the University of Uyo Health Research Ethics Committee

Author's contribution

The authors confirm contributions as follows: study conception and design by SOA; data collection by PJE and AEA; Analysis and interpretation of results by all authors; Draft manuscript preparation by SOA; all authors reviewed the result and approved the final version of the manuscript.

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GUIDE TO AUTHORS

Artificial intelligence: redefining the contours of drug discovery by transforming pharmaceutical research

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ABSTRACT

The integration of artificial intelligence (AI) into drug discovery and development is rapidly transforming pharmaceutical research, offering unprecedented opportunities to streamline processes, reduce costs, and accelerate timelines. The objectives of this review was to explore how artificial intelligence transforms drug discovery by enhancing target identification, lead optimization, and clinical development while addressing current challenges and future opportunities. Major scientific databases including PubMed, Scopus, ScienceDirect, Web of Science, and Google Scholar were searched for articles published between 2010 and 2025. The search strategy involved combinations of keywords such as “artificial intelligence,” “machine learning,” “deep learning,” “drug discovery,” “drug development,” “pharmaceutical research,” “clinical trials,” and “computational drug design.” AI-driven technologies ranging from machine learning algorithms to deep learning models are increasingly employed across various stages of the drug development pipeline, including target identification, lead compound discovery, preclinical validation, and clinical trial optimization. By leveraging large-scale biological, chemical, and clinical datasets, AI enables the identification of novel drug candidates, prediction of drug-target interactions, and assessment of pharmacokinetic and pharmacodynamic profiles with improved accuracy and efficiency. Additionally, AI facilitates the repurposing of existing drugs and supports personalized medicine approaches by analyzing patient-specific genomic and clinical data. Despite its promise, the adoption of AI in pharmaceutical research faces challenges, such as data quality and standardization, algorithm transparency.

KEYWORDS: Artificial intelligence, Machine learning, Lead optimization, Clinical trials, Pharmaceutical research

INTRODUCTION

The pharmaceutical industry is undergoing a paradigm shift driven by the integration of artificial intelligence (AI) into drug discovery and development. Traditional drug development is often time-consuming, costly, and prone to high failure rates, with an average of over a decade and billions of dollars required to bring a new drug to market. In contrast, AI offers innovative solutions to streamline the process by enabling faster, data-driven decision-making, reducing development costs, and accelerating timelines from target identification to clinical approval [1].

AI encompasses a broad range of computational techniques, including machine learning, deep learning, and natural language processing, that can analyze and interpret complex biomedical data. These technologies are now being applied across multiple stages of the drug development pipeline, ranging from the identification of novel drug targets and the design of lead compounds to preclinical evaluation and optimization of clinical trials [2]. By leveraging vast datasets from genomics, proteomics, chemical libraries, and electronic health records, AI enhances the ability to predict drug-target interactions, optimize pharmacokinetic and pharmacodynamic properties, and support drug repurposing and personalized medicine initiatives. While the potential of AI in pharmaceutical research is immense, its successful implementation is challenged by issues such as data quality, standardization, model interpretability, and regulatory acceptance. Addressing these barriers is essential to fully realize the benefits of AI-driven innovation in drug development [3].

This review aims to explore the transformative impact of AI in pharmaceutical research, examining key applications, recent advancements, ongoing challenges, and future directions for this rapidly evolving field.

Method

A comprehensive literature search was conducted to identify relevant studies, reviews, and reports on the application of artificial intelligence (AI) in drug discovery and development. Major scientific databases including PubMed, Scopus, ScienceDirect, Web of Science, and Google Scholar were searched for articles published between 2010 and 2025. The search strategy involved combinations of keywords such as “artificial intelligence,” “machine learning,” “deep learning,” “drug discovery,” “drug development,” “pharmaceutical research,” “clinical trials,” and “computational drug design.”

Articles were selected based on relevance to AI applications in any stage of the pharmaceutical pipeline, including target identification, lead optimization, preclinical evaluation, and clinical trial design. Priority was given to peer-reviewed journal articles, high-impact reviews, and authoritative white papers. Additional references were obtained by reviewing the bibliographies of selected articles.

Inclusion criteria

The inclusion focused on studies written in English language involving AI algorithms or tools in drug research and case studies or applications demonstrating AI integration in pharmaceutical settings.

Exclusion criteria

Exclusion criteria included articles adjudged lacking scientific rigor or relevance alongside editorials, non-systematic commentaries, or opinion pieces without empirical basis.

Results and Discussion

AI Technologies in Drug Discovery

Artificial intelligence (AI) has rapidly emerged as a transformative force in the pharmaceutical sciences, particularly within the domain of drug discovery [4]. Traditional drug development is often a laborious, costly, and time-intensive process [5]. However, the integration of AI technologies has the potential to significantly streamline this pipeline, from target identification and compound screening to lead optimization and clinical trial design. At the heart of AI-driven drug discovery lies three key methodological paradigms namely machine learning (ML), deep

learning **(DL),** and **hybrid approaches,** that combine elements of either of the domain-specific heuristics or physics-based models [6].

Machine learning, particularly supervised learning, has been extensively applied to model structure-activity relationships (SAR), predict pharmacokinetic and toxicity profiles (ADMET), and classify molecular bioactivity. Algorithms such as support vector machines (SVM), random forests (RF), and gradient boosting methods have proven effective in analyzing high-dimensional chemical and biological datasets [7].

Deep learning, a subfield of machine learning, offers enhanced capabilities through artificial neural networks especially convolutional neural networks (CNNs) and recurrent neural networks (RNNs). These architectures excel at capturing complex patterns in unstructured data such as molecular graphs, images, and sequences. Recent innovations such **as** graph neural networks (GNNs) and transformer models (TMs) have further empowered deep learning to predict molecular properties, generate novel compounds, and simulate protein-ligand interactions with unprecedented accuracy [8].

Hybrid AI approaches are gaining traction by combining ML/DL models with established methods in cheminformatics and computational chemistry. For instance, reinforcement learning (RL) has been used in de novo drug design to iteratively refine molecules toward optimal pharmacological profiles. Integration with molecular docking and molecular dynamics simulations allows these models to incorporate thermodynamic and structural constraints, enhancing biological relevance [9].

The rise of AI in drug discovery is further supported by a growing ecosystem of computational platforms and tools. DeepChem**,** RDKit**,** Schrödinger's Suite**,** and MOE (Molecular Operating Environment) are widely used for molecular manipulation, descriptor generation, and predictive modeling. Open-source ML libraries such as TensorFlow**,** PyTorch, and scikit-learn serve as the backbone for developing custom models, while platforms like AtomNet**,** AlphaFold**,** and ChemProp illustrate the success of AI in solving specific tasks like structure prediction and virtual screening [10]. Cloud-based platforms and collaborative frameworks are also becoming essential, enabling high-throughput screening and federated learning across organizations. Examples include IBM Watson for Drug Discovery**,** BenevolentAI**,** Insilico Medicine**,** and Exscientia**,** which leverage AI to accelerate the identification of viable drug candidates [11].

Applications of AI across the drug development pipeline

Artificial Intelligence (AI) is reshaping the landscape of drug development, offering a transformative force across every stage of the pipeline. From early discovery to post-market surveillance, AI-driven tools are accelerating timelines, reducing costs, and improving the probability of success in a notoriously complex and expensive process [12].

Drug discovery and target identification

The journey begins with understanding the biology of disease. Traditionally, this has required years of painstaking research, but AI, particularly machine learning (ML) and deep learning models, can analyze vast datasets such as are found in genomic sequences, protein structures, and disease phenotypes to identify novel drug targets with unprecedented speed and accuracy [12]. Natural language processing (NLP) tools comb through millions of scientific papers and patents to surface promising connections that might otherwise remain buried. AI-driven platforms such as DeepMind's and AlphaFold have revolutionized protein structure prediction, enabling researchers to model molecular interactions in silico, often before laboratory experiments begin [13].

Lead compound identification and AI

Once a target is identified, AI accelerates the search for potential drug candidates. Generative models—such as variational autoencoders and generative adversarial networks—are used to design novel molecules with desired properties. These systems not only suggest viable compounds but also predict their

pharmacokinetics, toxicity, and synthetic feasibility. Virtual screening powered by AI can narrow down millions of possibilities to a shortlist of compounds with the best chances of successes. This drastically reduces the time spent in wet-lab testing [14].

Preclinical studies

In preclinical development, AI models help simulate biological systems and predict how a drug might behave in the body. By integrating data from in vitro assays, animal studies, and historical databases, AI can forecast efficacy and toxicity, potentially flagging risks early in development. Moreover, AI-enhanced imaging and pattern recognition tools assist in interpreting histopathological data, increasing the precision of safety assessments [15].

Clinical trial design and execution

Clinical trials are one of the most resource-intensive phases of drug development. AI is making these processes more efficient and patient-centric. Algorithms analyze electronic health records (EHRs), genomic data, and social determinants of health to identify optimal patient populations and tailor inclusion criteria. AI also supports adaptive trial designs by dynamically adjusting parameters based on interim results, thereby improving trial efficiency and ethical outcomes. Real-time monitoring through wearable devices and AI-powered apps enhances patient adherence and enables proactive safety monitoring [16].

Regulatory submission and approval

AI tools aid in compiling and organizing vast amounts of data required for regulatory approval. NLP systems streamline the writing of clinical study reports and dossiers by extracting relevant findings and structuring them for submission. Predictive models also assess the likelihood of approval based on prior regulatory decisions and provide insights that can guide submission strategy [17].

Post-market surveillance

Even after a drug reaches the market, AI continues to play a crucial role. Pharmacovigilance systems leverage AI to detect adverse events in real-time by analyzing data from EHRs, social media, and insurance claims. These tools enhance the ability to identify safety signals quickly, enabling timely interventions to protect public health [18].

Target identification and validation

The first step in the journey of drug development, target identification and validation, is both foundational and formidable. At its core, this phase involves discovering molecular entities, such as genes or proteins, that are causally linked to a disease and can be modulated by therapeutic intervention. Traditionally, this has relied on labor-intensive experimental biology, requiring years of research and often leading to uncertain results. Today, however, AI is redefining what's possible at this critical stage, bringing new clarity and speed to a process long marked by complexity [19].

AI's influence begins at the genomic and proteomic levels. Advances in high-throughput sequencing and omics technologies have produced an overwhelming volume of biological data—far more than any human or traditional statistical model could feasibly interpret. AI algorithms, particularly machine learning and deep learning techniques, can sift through these vast datasets to reveal hidden patterns and correlations. In genomics, AI identifies gene variants associated with disease by analyzing large-scale genome-wide association studies (GWAS) and transcriptomic data. In proteomics, it detects altered protein expressions, post-translational modifications, and complex signaling cascades that may indicate disease-driving mechanisms [20].

But AI goes beyond pattern recognition. Through systems biology approaches, it constructs and simulates intricate biological networks mapping how genes, proteins, metabolites, and pathways interact in the context of health and disease. These network models, built from diverse data sources including omics, literature, and experimental data, enable researchers to predict how modulating one part of the system may

affect the whole. By identifying key nodes or hubs in these networks, AI helps prioritize targets that are not only mechanistically relevant but also have the potential to exert broad therapeutic impact [21].

Predictive modeling further enhances this process by assigning likelihood scores to potential targets based on known and inferred biological relationships. These models can incorporate diverse features such as structural druggability, evolutionary conservation, and prior clinical relevance to rank and validate targets systematically. AI also assists in validating these candidates by simulating drug-target interactions and predicting downstream biological effects, often revealing off-target risks or compensatory mechanisms that might undermine efficacy [22].

Ultimately, the integration of AI into target identification and validation is transforming the process from one of hypothesis-driven guesswork to data-driven precision. It allows researchers to not only discover novel targets more rapidly but also to do so with a higher degree of confidence, setting the stage for more effective and efficient drug development downstream. In this new paradigm, AI is not just a tool for analysis, it is a co-investigator, guiding us through the complexity of human biology toward the next generation of therapies [23].

Lead compound discovery and optimization

Once a biological target has been identified and validated, the next critical step in the drug development pipeline is the discovery and optimization of lead compounds (i.e., those molecules that can bind to the target and exert a therapeutic effect). Traditionally, this phase has been a laborious process involving the screening of vast chemical libraries, iterative synthesis, and extensive laboratory testing [24]. But the integration of artificial intelligence (AI) has brought about a paradigm shift, enabling researchers to explore chemical space with far greater speed, precision, and creativity [25].

AI plays a central role in both virtual screening and *de novo* drug design. In virtual screening, machine learning models evaluate millions of existing compounds in silico, predicting which are most likely to interact with the target based on structural and biochemical features. These models are trained on large datasets of known drug-target interactions and can rapidly prioritize candidates for further testing. Rather than physically screening every possibility, researchers can now focus only on the most promising leads, saving enormous time and resources.

Beyond screening known compounds, AI enables *de novo* drug design by creating entirely new molecular structures tailored to specific targets. Generative models, such as variational autoencoders and generative adversarial networks (VANs and GANs), learn the underlying rules of molecular structure and then use that knowledge to design novel compounds with desired properties [26]. These models can even be guided by specific constraints, such as binding affinity, selectivity, or synthetic accessibility, producing drug candidates that are not only effective but also feasible to manufacture. However, identifying a molecule that binds to a target is only the beginning.

Preclinical testing: advancing toxicity and efficacy assessment

Preclinical testing serves as the critical bridge between discovery and clinical development, where the safety and efficacy of a lead compound are rigorously evaluated in laboratory and animal models. This stage determines whether a drug is suitable to enter human trials (a decision that carries significant scientific, ethical, and financial implications) [27]. Historically, preclinical testing has relied heavily on time-consuming in vitro experiments and in vivo studies, often with limited predictability for human outcomes. Today, artificial intelligence (AI) is reshaping this phase by introducing powerful in silico models and automated data interpretation tools,

significantly enhancing both efficiency and predictive accuracy [28].

One of the most transformative applications of AI in preclinical testing is the development of in silico models for predicting toxicity and efficacy. These computational models use historical datasets from chemical structures and biological responses to toxicological profiles to simulate how a compound might behave in a biological system.

AI algorithms, particularly those based on machine learning, can identify subtle patterns and correlations that escape traditional analysis, enabling the early detection of potential safety concerns such as hepatotoxicity, cardiotoxicity, or neurotoxicity [29]. This proactive risk assessment allows researchers to refine or eliminate compounds before investing in costly and ethically complex animal testing.

Similarly, AI-driven models can predict a compound's likely therapeutic efficacy by simulating interactions with biological targets and mapping downstream effects across molecular pathways. These virtual experiments are not only faster and more scalable than traditional methods, but they also cost-effective [30].

Clinical trial design and optimization: empowering precision and agility

Clinical trials represent the most resource-intensive and high-stakes phase of drug development. They are essential for demonstrating the safety and efficacy of a new therapy in humans, yet they are often plagued by inefficiencies ranging from slow patient recruitment and rigid protocols to high dropout rates and inconclusive results. Artificial Intelligence (AI) is rapidly emerging as a powerful ally in transforming how clinical trials are designed, conducted, and optimized, introducing new levels of precision, adaptability, and speed [31].

One of the most immediate and impactful contributions of AI is in patient stratification and recruitment. Finding the right participants for a clinical trial has traditionally been a slow and manual process, often constrained by geographic and demographic limitations. AI dramatically enhances this by analyzing vast and diverse data sources—including electronic health records (EHRs), genomic profiles, medical imaging, social determinants of health, and even wearable device data to identify patients who meet complex inclusion and exclusion criteria. More importantly, AI can uncover subtle patterns that indicate which patients are most likely to respond to a treatment, enabling more refined stratification based on molecular subtypes, disease progression, or lifestyle factors. This precision approach not only improves recruitment speed but also enhances the likelihood of detecting meaningful therapeutic effects [32].

Drug repurposing and personalized medicine for precision therapeutics

In the evolving landscape of medicine, two approaches are gaining extraordinary momentum: drug repurposing and personalized treatment. At the heart of both is a common goal—to accelerate therapeutic innovation and deliver more effective care to patients. Artificial Intelligence (AI) is playing a transformative role in advancing these strategies, bringing together vast, complex datasets to uncover hidden opportunities and tailor treatments to the unique biology of each individual [33].

Drug repurposing, or repositioning, involves finding new therapeutic uses for existing drugs. It is a promising shortcut in drug development, leveraging compounds that already have known safety profiles. However, uncovering new indications for approved drugs is far from straightforward; it requires sifting through massive volumes of biomedical literature, clinical trial data, molecular profiles, and real-world evidence. AI excels in this domain. Machine learning models, particularly those using natural language processing (NLP), can scan scientific

publications, drug databases, and patient records to detect previously overlooked connections between drugs and diseases. For instance, an AI system might identify that a cancer drug modulates a pathway also involved in an autoimmune condition—an insight that could spark new clinical investigations [34].

In parallel, AI is propelling the promise of personalized medicine. Rather than treating all patients with a "one-size-fits-all" approach, personalized medicine seeks to tailor therapies based on an individual's genetic makeup, health history, and even lifestyle. This requires the integration and interpretation of enormous and heterogeneous datasets found in genomic sequences, proteomic signatures, clinical biomarkers, imaging data, and longitudinal health records [35].

Challenges in AI-driven drug development

While the promise of artificial intelligence (AI) in drug development is immense, the journey toward fully realizing its potential is far from straightforward. Despite remarkable advances in machine learning, data integration, and predictive modeling, AI-driven drug discovery faces a complex set of challenges that stem from the very nature of the technology, and the deeply nuanced world of biomedical science in which it operates [36]. Key among these is issues of data quality and integration, model interpretability and bias, and the evolving landscape of regulatory and ethical oversight [37].

Fundamental obstacles to AI-driven drug development

One of the most fundamental obstacles is the quality, availability, and compatibility of data. AI systems are only as powerful as the data they are trained on, yet biomedical datasets are often fragmented, incomplete, or inconsistent. Clinical trial records, electronic health records (EHRs), genomic sequences, and lab results come from diverse sources and exist in various formats, making integration a formidable task. Missing values, mislabeled data, or batch effects can significantly distort the learning process, leading to unreliable or misleading results. Moreover, many valuable datasets remain proprietary or siloed due to privacy concerns, intellectual property constraints, or institutional barriers limiting the ability of AI models to learn from the full breadth of available knowledge [38].

Even when high-quality data is available, another pressing challenge lies in model interpretability. Many of the most advanced AI systems, especially deep learning networks, operate as "black boxes," generating predictions without transparent explanations. In the context of drug development where safety, efficacy, and regulatory scrutiny are paramount, this lack of interpretability becomes a serious liability [39]. Researchers, clinicians, and regulators alike need to understand *why* a model recommends a certain compound, target, or patient subgroup. Without clear rationale, even accurate predictions can be met with skepticism or remain untrusted for decision-making in critical contexts. Compounding this issue is the risk of algorithmic bias. AI models trained on biased or unrepresentative data can unintentionally reinforce existing disparities in healthcare. For example, if training datasets lack sufficient diversity across age, gender, ethnicity, or socioeconomic status, the resulting models may produce skewed outcomes such as underestimating risks in certain populations or misclassifying diseases. In a domain as sensitive as medicine, such biases can have serious real-world consequences, undermining both scientific validity and public trust [40].

Regulatory and ethical concerns

Overlaying these technical and scientific challenges are broader regulatory and ethical concerns. The use of AI in drug development raises difficult questions about accountability, data privacy, informed consent, and the standards for evidence. Current regulatory frameworks were not designed with machine learning in mind, and agencies like the FDA and EMA are still developing guidelines to assess the reliability, reproducibility, and safety of AI-

generated insights.

Ethical considerations also loom large: how should patient data be used and protected? Who is responsible if an AI-guided decision leads to harm? And how do we ensure equitable access to AI-driven medical advances [41]? In sum, the integration of AI into drug development holds extraordinary promise but that promise comes with complex, multilayered challenges. Addressing them will require not only advances in technology, but also a concerted effort across disciplines: data scientists collaborating with clinicians, ethicists working alongside engineers, and regulators engaging with innovators. Only through such collaboration can we build AI systems that are not only intelligent, but also trustworthy, transparent, and aligned with the values at the heart of medicine.

Future directions and opportunities: *the next frontier in AI-driven drug development*

As artificial intelligence continues to evolve, the future of drug development is poised for a fundamental transformation, one marked not just by faster discovery, but by deeper biological insight, smarter decision-making, and unprecedented levels of automation. The convergence of technological innovation, multi-omics integration, and human-machine collaboration is opening new pathways that promise to reshape how we understand disease and develop therapies. What lies ahead is not merely incremental progress, but the emergence of a more intelligent, adaptive, and personalized drug development ecosystem [42].

A key driver of this future is the rapid evolution of AI technologies and their application to increasingly complex biological data. Emerging trends in AI innovation include the use of self-supervised learning, reinforcement learning, and foundation models that can generalize across diverse datasets and tasks. These models are better equipped to uncover previously unseen relationships within massive biological systems, enabling more holistic and predictive representations of disease mechanisms. Moreover, generative AI tools are beginning to move beyond single-molecule design to suggest entire drug development strategies, integrating knowledge from chemistry, biology, and clinical science in a unified framework [42].

Crucially, this innovation is being powered by the integration of multi-omics data from genomics, transcriptomics, proteomics, metabolomics, and beyond. Rather than examining disease through a single lens, AI now enables the simultaneous analysis of multiple layers of biological information, providing a multidimensional view of human health and pathology. This systems-level understanding allows researchers to identify subtle molecular drivers of disease, tailor drug interventions to specific patient profiles, and anticipate downstream effects long before clinical symptoms emerge. Multi-omics integration, supported by AI, is at the heart of the transition toward truly personalized medicine [43].

The future of AI in drug development

The future of AI in drug development is not about replacing human expertise, it is about augmenting it [44]. AI-human collaboration is becoming a cornerstone of the new paradigm, where machines generate insights and recommendations, and human scientists provide critical context, interpretation, and ethical oversight. This partnership enables more informed and confident decision-making at every stage, from target selection to clinical trial design. Interactive AI platforms can help teams explore hypotheses, visualize complex data, and test scenarios in silico, fostering a more iterative and exploratory research environment.

Looking further ahead, the vision of fully automated and intelligent drug development platforms is coming into focus. These platforms would integrate AI across all phases of the pipeline by automating literature review, target discovery, compound generation, preclinical testing, and even trial simulation [45]. Robotic labs powered by AI could design and execute experiments in real time, optimizing protocols on the fly based on incoming data. In such a system, the cycle from disease hypothesis to clinical candidate could be compressed from years to

months, or even weeks dramatically accelerating the path from scientific insight to therapeutic reality [46].

Of course, realizing this vision will require overcoming significant scientific, technical, and regulatory hurdles. But the direction is clear: the

future of drug development will be shaped not by AI alone, but by the seamless integration of AI with biology, human expertise, and ethical governance. As these forces converge, they hold the potential to not only make drug development faster and more efficient, but also more intelligent, equitable, and responsive to the needs of patients around the world.

Conclusion

The integration of artificial intelligence into the drug development pipeline marks a pivotal moment in pharmaceutical innovation. Across every stage from target identification and lead optimization to preclinical testing and clinical trials, AI is reshaping traditional approaches by enabling faster, more precise, and more insightful decision-making. Its capacity to analyze vast and complex biological data, predict drug behavior, and optimize trial design promises not only to accelerate the development of new therapies but also to enhance their safety and efficacy.

The transformative potential of AI lies in its ability to turn data into actionable knowledge, uncover hidden connections within biology, and support personalized medicine tailored to the unique genetic and clinical profiles of patients. By augmenting human expertise with powerful computational tools, AI is helping to usher in an era of smarter, more efficient drug discovery and development that could profoundly improve health outcomes worldwide. However, realizing this promise requires concerted, collaborative efforts that span disciplines and sectors. Challenges such as data quality, algorithmic transparency, bias mitigation, and evolving regulatory frameworks must be addressed through partnerships among scientists, clinicians, data experts, ethicists, and policymakers. Only by working together can the pharmaceutical industry overcome these barriers and ensure that AI-driven innovations are both scientifically robust and ethically sound.

Ethical considerations

Data availability

The data that supported the findings in this study are available on request from the corresponding author

Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest.

Compliance with ethical guidelines

Approval for this study and related cases was

obtained from the University of Uyo Health Research Ethics Committee

Author's contribution

The authors confirm contributions as follows: study conception and design by SOA; data collection by FN, PJE, AEA and GO; Analysis and interpretation of results by all authors; Draft manuscript preparation by SOA and MAN; all authors reviewed the result and approved the final version of the manuscript.

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