A Comprehensive Review of Repurposing Existing Drugs for Antimicrobial Therapy: Challenges, Opportunities, and Future Directions

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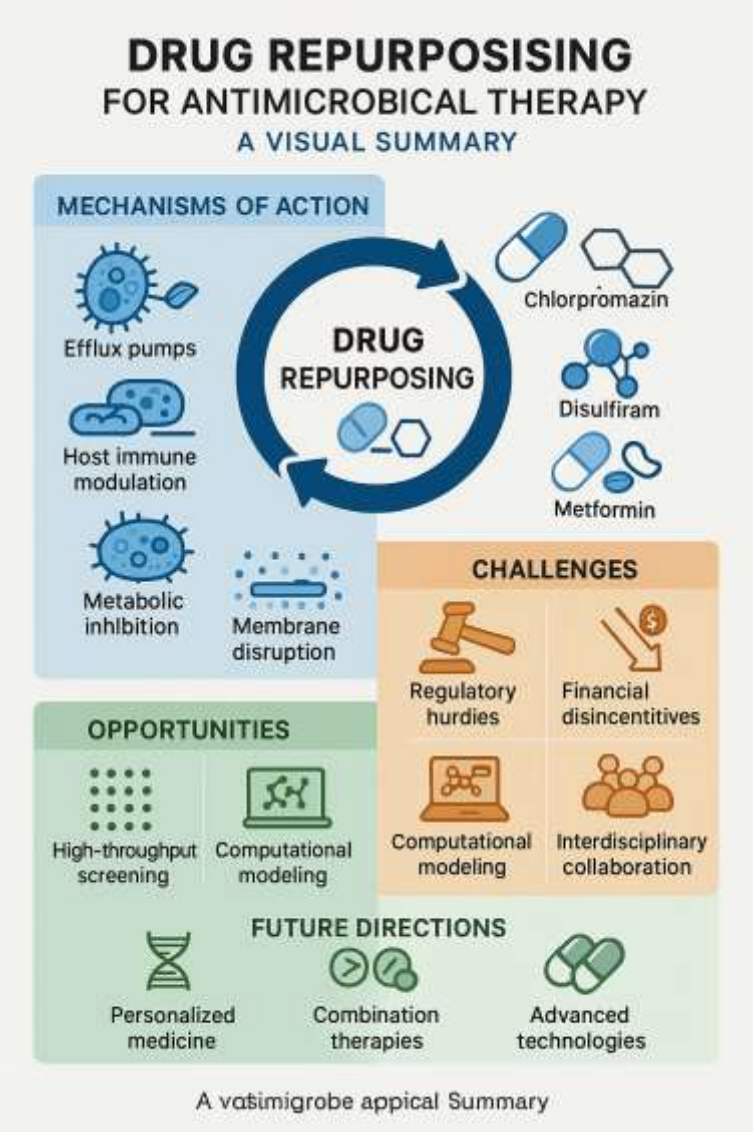
Abstract:

The repurposing of existing pharmacological agents for antimicrobial therapy presents a promising strategy to combat the escalating issue of antibiotic resistance. This approach leverages the established safety profiles and pharmacokinetics of previously approved drugs, allowing for expedited clinical application compared to novel drug discovery processes. By utilizing advanced screening methodologies and computational techniques, researchers can identify potential candidates that exhibit antimicrobial properties, thereby addressing the urgent need for effective treatments against resistant bacterial strains. Repurposed drugs, such as chlorpromazine and disulfiram, have shown efficacy in inhibiting bacterial resistance mechanisms, including efflux pumps and biofilm formation, which are critical for bacterial survival. Furthermore, the integration of precision medicine strategies, which tailor antimicrobial protocols based on individual patient biomarkers, holds the potential to significantly enhance therapeutic outcomes. Despite the promising outlook, the repurposing of drugs faces several challenges, including regulatory hurdles, financial disincentives, and the need for comprehensive clinical validation. Collaborative efforts among academic institutions, regulatory bodies, and the pharmaceutical industry are essential to optimize approval processes and overcome these obstacles.

Keywords: Drug Repurposing, Antimicrobial Therapy, Antibiotic Resistance, Precision Medicine, Synergistic effects.

Graphical Abstract



1. Introduction:

The escalation of antimicrobial resistance (AMR) has rendered numerous traditional antibiotics ineffective, consequently resulting in heightened mortality rates and increased healthcare expenditures (1, 2). Taking into account the extended timeframe involved in developing new antibiotics, the strategy involving drug repurposing has emerged as a legitimate alternative for pinpointing innovative antimicrobial solutions sourced from existing drugs (3). This methodology effectively bypasses the protracted and financially burdensome process associated with de novo drug discovery by capitalizing on the established pharmacokinetics, safety profiles, and mechanisms of action of previously approved therapeutic agents (4).

The repurposing of pre-existing pharmacological agents for the purpose of antimicrobial therapy is particularly compelling due to its capacity for expedited clinical application (5, 6).

Considering that these agents have already undergone comprehensive assessment for safety and efficacy within human cohorts, their approval for new therapeutic applications can be expedited in comparison to novel compounds (7) . Also, the tactic of drug repurposing grants the chance to research different mechanisms of action that may be effective against bacterial strains that exhibit resistance (6, 8). This approach is gaining traction with the incorporation of computational methodologies, high-throughput screening techniques, and extensive data analytics, which facilitate the identification of promising candidates possessing antimicrobial characteristics (9). Notwithstanding its potential, the repurposing of drugs continues to confront numerous challenges, including regulatory barriers, insufficient economic incentives, and the intricacies involved in translating in vitro outcomes into clinical efficacy (10, 11).

1.1 Mechanisms of Drug Repurposing in Antimicrobial Therapy

The premise of drug repurposing is built upon several mechanisms that assist in producing antimicrobial effects (12). The following mechanisms illustrate how existing drugs can be effectively repurposed for antimicrobial applications:

1.1.1 Investigating Bacterial Resistance Mechanisms: Many bacterial species have adapted to resist antibiotics by employing efflux pumps that discharge these drugs, forming biofilms that serve as protective barriers for their populations, and using enzymes to dismantle antibiotic compounds (13, 14). Repurposed pharmaceuticals, such as chlorpromazine, have demonstrated the capacity to inhibit efflux pump activity, thereby reinstating the efficacy of antibiotics (15, 16). In a like manner, various non-antibiotic remedies affect biofilm generation, thereby reducing bacterial defense tactics and heightening their exposure to antibiotic remedies (17).

1.1.2 Modulating Host Immune Response: A subset of repurposed medications operates by augmenting the host's immune response to combat infectious agents (18, 19). To illustrate, metformin, initially intended for diabetes care, has been demonstrated to strengthen immune responses to Mycobacterium tuberculosis (19, 20). By supporting autophagy and improving the activity of immune cells, these pharmacological options present an innovative tactic for managing bacterial infections without a direct focus on the pathogens (21, 22).

1.1.3 Inhibiting Essential Pathways: Numerous repurposed drugs, originally formulated for the treatment of non-infectious diseases, exhibit antibacterial activity by disrupting critical bacterial metabolic pathways (23, 24). Take disulfiram, that is known for its role in managing alcohol dependency, which has proven to be effective against Gram-negative bacteria by hindering their necessary metabolic enzymes (25). Furthermore, specific kinase inhibitors designed for oncological applications have been identified to target bacterial protein synthesis, thereby compromising bacterial viability (26)

1.1.4 Synergistic Effects with Existing Antibiotics: There are non-antibiotic medications that can significantly enhance the performance of standard antibiotics when employed in a

combined treatment approach (27). This strategy may prove beneficial in overcoming antibiotic resistance and improving clinical outcomes (28). The antipsychotic trifluoperazine has been found to elevate the efficacy of aminoglycoside antibiotics when addressing resistant bacterial populations (29). In the same manner, statins, predominantly prescribed for cholesterol control, have been evidenced to heighten the effectiveness of beta-lactam antibiotics by jeopardizing the integrity of bacterial membranes (30, 31).

1.1.5 Disrupting Bacterial Cell Membrane and Structural Integrity: Several repurposed pharmaceuticals function by undermining the integrity of bacterial cell membranes, leading to cellular lysis and subsequent death (32). The antiparasitic drug Ivermectin has revealed some antibacterial properties through changes in membrane permeability within Gram-positive bacteria (33, 34). Additionally, antiviral compounds such as ribavirin interfere with bacterial RNA synthesis, disrupting fundamental bacterial processes and culminating in cell death (35, 36).

1.1.6 Addressing Bacterial Virulence Elements: Selected repurposed treatments function by suppressing virulence components that are vital in bacterial disease-causing ability (37). As an illustration, proton pump inhibitors, which are frequently recommended for managing acid reflux, have demonstrated a capacity to lower bacterial toxin levels and obstruct bacterial adhesion to host cells (38). By attenuating bacterial virulence, these drugs can facilitate more manageable infections and enhance the effectiveness of conventional antibiotics (39).

2. Recent Advances in Antimicrobial Drug Repurposing

2.1 Non-Antibiotic Drugs with Antibacterial Properties:

2.1.1 Metformin: Initially developed for the management of diabetes mellitus, metformin demonstrates notable antimicrobial properties against Mycobacterium tuberculosis and significantly enhances the host's immune response (40, 41).

2.1.2 Chlorpromazine: This antipsychotic agent disrupts bacterial efflux mechanisms, thereby augmenting the susceptibility of bacteria to antibiotic treatment (42).

2.1.3 Disulfiram: Primarily employed in the treatment of alcohol dependence, it has exhibited promising efficacy against Gram-negative bacterial infections through the inhibition of bacterial metabolic pathways (25, 43).

2.2 Cancer Drugs as Antimicrobial Agents:

2.2.1 Imatinib: A notable tyrosine kinase inhibitor, imatinib possesses activity against intracellular bacterial pathogens, including Mycobacterium tuberculosis (21)

2.2.2 Dactinomycin: showcases its antibacterial prowess against strains of Gram-positive bacteria that have developed resistance to drugs (44).

2.2.3 Gefitinib: A pharmacological agent utilized in oncology that targets bacterial DNA synthesis and cellular division, demonstrating potential effectiveness against multidrug-resistant bacterial populations (45, 46).

2.2.4 Bortezomib: A known proteasome inhibitor in cancer therapy, bortezomib has been found to obstruct bacterial stress response pathways, consequently boosting bacterial exposure to antibiotic therapy (47).

2.3 Antiviral and Antiparasitic Agents with Antibacterial Activity:

2.3.1 Ivermectin: An antiparasitic medication that exhibits antimicrobial activity against Staphylococcus aureus and Mycobacterium tuberculosis (48).

2.3.2 Ribavirin: An antiviral drug that may possess effects against bacterial infections, including tuberculosis (49).

2.3.3 Nitazoxanide: serves as a versatile agent in fighting parasites and viruses, with significant antibacterial power against Clostridium difficile and Helicobacter pylori (50, 51).

3. Challenges in Antimicrobial Drug Repurposing

In light of the positive outlook, the reformation of available medicinal therapies for application against infections encounters several noteworthy difficulties (52). A predominant challenge pertains to the absence of financial incentives, as pharmaceutical enterprises frequently prioritize the development of novel therapeutics over repurposing initiatives due to constraints imposed by patents and diminished profitability (53). Furthermore, regulatory frameworks are predominantly tailored for the approval of new pharmaceuticals, thereby rendering the process of securing approval for repurposed agents intricate and protracted (54). An additional challenge lies in the insufficient clinical validation of repurposed agents, as in vitro and preclinical results do not invariably correlate with clinical efficacy (55). Also, when pharmaceuticals are redirected for antimicrobial applications, the potential for off-target impacts and unforeseen toxicities may arise, which calls for comprehensive safety evaluations (11).

Another significant obstacle is the inconsistency in antimicrobial effectiveness across various bacterial strains and patient demographics (56). A pharmaceutical that exhibits efficacy in vitro may not yield anticipated results in human clinical trials due to variables such as pharmacokinetics, host immune responses, and bacterial adaptation (8, 57). This inconsistency complicates the process of identifying the most promising candidates for subsequent development (58).

Besides, the redirection of pharmaceutical compounds for the aim of antimicrobial action necessitates significant collaboration across a range of research fields, covering microbiology, pharmacology, and clinical medical practices (59, 60). The establishment of standardized

methodologies for the assessment of repurposed agents is crucial for guaranteeing reproducibility and dependability in clinical outcomes (61). The absence of harmonized protocols across institutions and regulatory authorities further impedes the transition from laboratory discovery to clinical application (62).

4. Opportunities in Antimicrobial Drug Repurposing

The domain of antimicrobial drug repurposing offers a multitude of opportunities (63). A primary benefit is the expedited timeline for clinical application, as repurposed pharmaceuticals have already undergone comprehensive evaluations concerning safety and pharmacokinetics (64). The advancements in high-throughput screening and computational modeling persist in enhancing drug discovery initiatives, thus facilitating the identification of innovative antimicrobial candidates derived from pre-existing medications (5, 65). Moreover, partnerships among academic institutions, governmental bodies, and private enterprises can aid in securing research funding and optimizing regulatory procedures (66). The employment of combination therapies—integrating repurposed drugs with established antibiotics—also demonstrates potential in improving treatment efficacy and diminishing the probability of resistance emergence (11, 67).

Clinical pharmacists assume a crucial function in the realm of antimicrobial drug repurposing by refining medication regimens, ensuring precise dosing, and mitigating adverse effects (64, 68). Their specialization in pharmacokinetics and drug interactions is of paramount importance in the identification of viable candidates for repurposing and the monitoring of their clinical outcomes (10, 69). In addition, they may significantly contribute to antimicrobial stewardship initiatives by advising healthcare practitioners on the safe and effective administration of repurposed pharmaceuticals (70, 71). A valuable opportunity presents itself in the deployment of omics technologies, including genomics, proteomics, and metabolomics, as they can highlight essential data regarding how drugs interact with bacteria and the underlying resistance mechanisms (72, 73). By harnessing these sophisticated analytical methodologies, researchers can unveil novel antimicrobial properties within existing drugs and enhance treatment strategies (74, 75). Future endeavors should also prioritize the expansion of clinical trial networks and the promotion of interdisciplinary collaborations to guarantee the effective translation of repurposed medications into standard clinical practice (76, 77).

5. Future Directions

Future research endeavors must aim at increasing the scale of thorough clinical trials to validate the safety and effectiveness of repurposed pharmacological compounds in antimicrobial therapy (11, 32). The fortification of collaborative efforts among academic institutions, regulatory bodies, and the pharmaceutical sector will facilitate the optimization of approval mechanisms and surmount financial obstacles (78, 79). Moreover, leveraging precision medicine strategies, including bespoke antimicrobial protocols driven by unique patient biomarkers, has the capability to substantially boost therapeutic success (80, 81).

Additional innovations in combination therapies and novel drug delivery systems will likewise be instrumental in maximizing the clinical utility of repurposed antimicrobial compounds (82, 83).

6. Conclusion

The adaptation of current medications for the treatment of microbial infections offers a sound and swift strategy to deal with the growing concern of antibiotic resistance internationally. Notwithstanding the obstacles posed by regulatory impediments and economic disincentives, the continuous endeavors in research and the fostering of interdisciplinary partnerships persist in propelling advancements within this domain. Through the amalgamation of cutting-edge screening methodologies and augmented collaboration from clinical pharmacists, repurposed pharmacotherapeutics may present a viable and enduring remedy to the worldwide challenge posed by antimicrobial resistance.

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8. Conflict of interest

The authors declare no conflicts of interest related to this review article.

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