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Review on Repurposing of Drug Molecules for Anti-Microbial Activity

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ABSTRACT

Antimicrobial diseases have a tremendous impact on health, socially and economically. Diseases caused by Microbes like bacteria, Fungus, protozoa and Viruses such as candida albicans (bacterial infection), malaria (Protozoal infection) and recent emerged viruses like Ebola, SARS, MERS, COVID-19, caused by many Micro-organisms resulted in morbidity and mortality approximately 1.1 million combined deaths. Diseases has increased a lot may be due to lack of licensed Vaccines or may be because of non-safe or ineffective Drugs resulted in occurrence of diseases and its ineffective treatment, even if related drugs are available their Pharmacological actions are threatened by drug resistance. The research for new drug discovery such as anti-bacterial, anti-fungal, anti-viral, and anti-parasitic globally requires new innovative strategies in search of lead compounds which are time consuming processes. In present review, it is focused and discussed on one of the approaches that is drug repurposing or repositioning, with a major focus on major human parasitic protozoan diseases such as malaria, Tuberculosis, COVID-19 etc.

INTRODUCTION

DRUG REPURPOSING:

Drug repurposing also known as drug repositioning or drug reprofiling, which is a new method of investigating an already established i.e., marketed drug for different therapeutic uses. Such kind of research is like a shortcut in translational research i.e., from bed-side to bench-side. The introduction of modern cheminformatic and bioinformatics tools has lessened the time consumption of identifying hits and leads in drug discovery. By using these techniques, we can also find alternative therapeutic benefits of established/marketed drugs.

Drug repurposing, especially in new combination therapies, or in diseases helps to find unmet clinical needs, such as orphan and neglected diseases. The advantage is the decreased need for investment in drug discovery and optimization, as well as in safety and pharmacokinetic studies since the profiles of the repurposed drugs are already established. The repurposing of old drugs can be identified by serendipity, observations of side effects, target searching, or novel insights, and they can act either by the same mechanism of action as their traditional use or by new mechanisms. One of the most used strategies for drug repositioning is the in-silico screening of compound libraries in new targets.

One famous example of drug repurposing is the drug thalidomide. First used as an over-the-counter antiemetic for the treatment of pregnancy associated morning sickness, it was quickly withdrawn after reports of teratogenicity and dysmelic. However, in 1998, the Food and Drug Administration (FDA) approved thalidomide for the treatment of cutaneous manifestations of erythema nodosum lepro sum. In 2006, thalidomide was approved for the treatment of myeloma, due to its anti-angiogenic properties. This example proves how important drug repurposing can be in drug discovery. However, many other examples of old drugs with new uses have been described[1].

ANTI-MICROBIALS-AN INTRODUCTION:

An Antimicrobial is any substance of natural, Semi synthetic or synthetic origin that kills or inhibits the growth of microorganisms but causes little or no damage to the host.

The word **antimicrobial** was derived from the Greek words anti (against), mikros (little) and bios (life) and refers to all agents that act against microbial organisms.

The Word "antimicrobials" includes all the agents that acts against all types of microorganisms like:

1) Antibacterial which acts against Bacteria

2) Antiviral which acts against viruses

3) Antifungal which acts against fungi and

4) Antiprotozoal which acts against protozoa

Antimicrobial drugs are classified in a variety of ways. They are:

1. **Based on Cidal or Static Action (effect on bacteria):**

- **Bactericidal drugs:** Does action by killing eg: penicillins
- **Bacteriostatic drugs**: Inhibit bacterial growth and replication.eg: sulfonamides
- **Both bacteriostatic and bactericidal** eg: aminoglycosides

2. **Based on Mechanism of Action of the Drugs:**

Inhibitors of:

- Cell wall synthesis.
- Cell membrane function.
- Protein synthesis.
- Nucleic acid synthesis.
- Other metabolic processes.

3. **Based on Spectrum of Activity:**

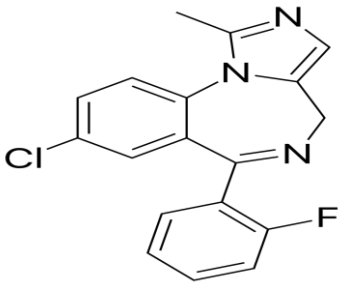
- Broad spectrum
- Narrow spectrum

REPURPOSING OF DRUGS FOR ANTIFUNGAL ACTIVITY:

1. MIDAZOLAM AND DIAZEPAM:

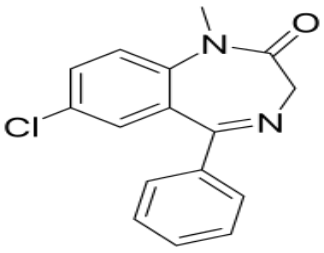
In 2016 Freija Van den Driessche reported that exploring the potential of existing drugs for their unknown properties may offer advantages over conventional drug development by saving time and money. Candida albicans, an important human opportunist, shares many properties with humans. This study encouraged to know drugs that are not originally antifungals against C. albicans. In his study, they have tested six antiepileptic drugs for their activity against C. albicans. Their effects on growth, time-dependent killing, yeast-to-hyphal form switching, and biofilms formation by C. Albicans were studied out of the drugs studied, four drugs, which are y-aminobutyric acid (GABA) receptor agonists in human, inhibitor growth, yeast-to-hyphal from switching and biofilm formation in C. Albicans. Lorazepam inhibited growth of C. albicans at 25µg/ml, followed by Midazolam and Diazepam (minimum inhibitory concentration 100 and 400µg/ml, respectively). Members from other group voltage-gated sodium channel blockers failed to inhibit C. albicans. His study has identified GABA receptor agonists used in epileptic therapy as potential candidates for antifungal candidates for antifungal drug development against the human pathogen C. albicans[7].

Midazolam



8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazolo [1, 5-a] [1, 4] benzodiazepine

Diazepam



7-chloro-1-methyl-5-phenyl-3*H*-1, 4-benzodiazepin-2-one

REPURPOSING OF DRUGS FOR ANTIVIRAL ACTIVITY [9]:

Several emerging viruses, for example Ebola virus, MERS, Nipah virus, and recently COVID-19, caused many deaths so there is immediate need of Drug therapy for treatment at this condition development of new drug is time taking process so drug repositioning is life saving therapy.

Some examples of drugs falls in this category are:-

1. Tocilizumab: Recent report from Scientists and china

2. Thalidomide: A case report from Wenzhou medical university has proved that thalidomide has adjuvant effects in COVID-19 treatment.

3. Remdesivir

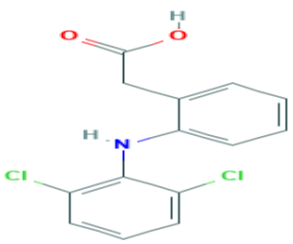
4. Chloroquines: FDA and CDC allowed hydroxyquinoline as potential therapy for COVID-19 Treatment.

REPURPOSING OF DRUGS FOR ANTI TUBERCULAR ACTIVITY:

1. DICLOFENAC

In 2016, Arundathi Maitra et al., reported that Diclofenac sodium was found to be bacterial against Escherichia coli, Listeria monocytogenes as well as Tuberculosis. Encouraged by in vitro and in vivo studies using the drugs, investigations were extended and synergism was identified with streptomycin in murine TB.

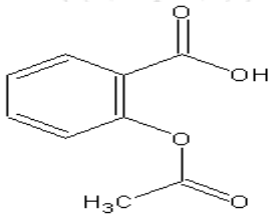
Diclofenac acid hydrazones and amides have also been shown to reduce lung and spleen bacillary loads by `3.66 log10 in mouse infection models at a dose of 25mg/kg. Inhibition of incorporation thymidine, vital to DNA synthesis, has been reported as one of the likely mechanisms for the bactericidal action of diclofenac in E. coli and Listeria SPP[10].



2-[2-(2,6-dichloroanilino)phenyl]acetic acid

2. ASPIRIN:

In 2016, Arundathi Maitra et al. reported that Aspirin is a salicylate anti-inflammatory drug which in addition to primary use has shown to potentiate or act synergistically when used in conjunction with the front-line anti-TB drug, Pyrazinamide in a mouse-infection model study. Gene expression profiling of Tuberculosis in response to salicylate has shown to down-regulate genes involved in energy production. This could explain the synergy between the salicylate and pyrazinamide which is also known to deplete membrane energy and potential and thereby disrupt transport. However, aspirin has also demonstrated modest antagonistic activity towards isoniazid raising the importance of evaluating at what time-point in the treatment regimen should NSAIDs be included in the therapy. A randomized study on the role of aspirin in TB meningitis suggested that aspirin in combination with corticosteroids reduced the incidence of strokes and mortality. A similar study on the role of aspirin as an adjunct with steroids for the treatment of HIV negative adults with TB meningitis in Vietnam is still ongoing[10].



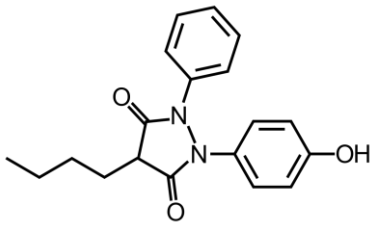
Aspirin

2-(acetyloxy)benzoic acid

3. OXYPHENBUTAZONE:

In 2015, Arundhati Maitra et al., reported that a high-throughput phenotypic screen revealed that oxyphenbutazone selectively inhibits the non-replicating subset of the M. tuberculosis pathogen Whilst having no effect on the replicating bacteria. One of the primary reasons for the lengthy duration of TB treatment is the need to eliminate non-replicating bacteria or ‘per sisters’, that are difficult to treat due to their physiological status and unique endogenous metabolism. In the Gold et al. model, the environment to which the drug was exposed (mildly acidic and high in reactive nitrogen intermediates) resulted in its hydroxylation; and the compound produced was shown to be active against both replicating and non-replicating bacilli in isolation. In addition, it was also found to be synergistic with oxidants and several

conventional anti-tubercular drugs such as P-amino salicylate. The modified oxyphenbutazone served to deplete thiols and flavins, thereby potentially affecting a number of enzymatic reactions within the cell. The inability to generate spontaneous mutants further reinforces the argument that the endogenous mechanism of action of this drug may be multifactorial. However, in spite of being used regularly in veterinary medicine, its use in humans is restricted in the light of sporadic reports of fatal bone marrow depression caused as a side effect of the medication[11].

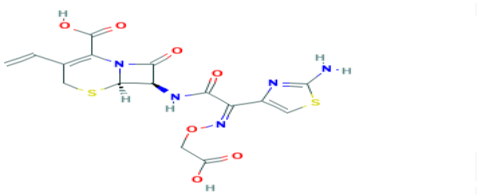


4-butyl-1-(4-hydroxyphenyl)-2-phenylpyrazolidine-3,5-dione

4. CELECOXIB:

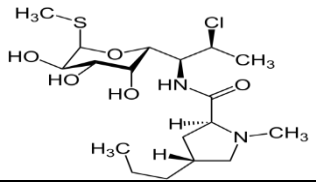
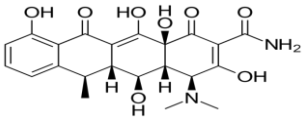
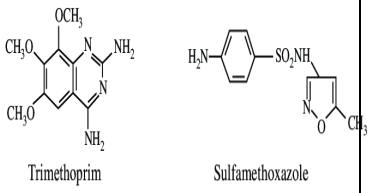
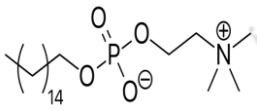
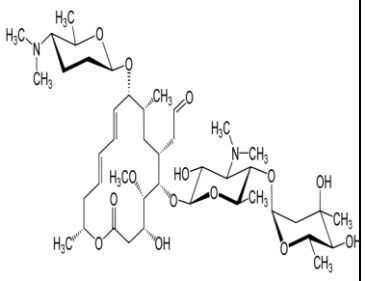
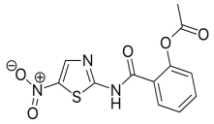
In 2015, S Thangamani et al. reported that amongst the NSAIDs promising fewer adverse effects, the COX-2 selective celecoxib was reported to reverse MDR of methicillin-resistant Staphylococcus aureus by inhibiting the bacterial efflux mechanism. A similar effect was noted in Mycobacterium smegmatis and its action is expected to be through an unknown protein that regulates the MDR-1 efflux pump in bacteria. This hypothesis is further substantiated by the fact that the drug exerts effects on COX-2 which in turns regulates the homologous MDR-1 pump in humans. Debilitating the extrusion mechanism of bacteria is a powerful strategy to reverse resistance and tolerance is seen in planktonic and bacterial biofilms. In the context of combination therapy, this introduces the possibility of reducing the dose or shortening the duration of treatment.

Based on the active pharmacophore of celecoxib, analogues that show potent inhibitory activity against M. tuberculosis have been synthesized and efforts to further optimize these compounds are ongoing[12].



4-[5-(4-methyl phenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide

REPURPOSING OF DRUGS FOR ANTI PROTOZOAL ACTIVITY[8]:

Drug	Structure	Initial Use(s)	Repurposed Use(s)	References
Clindamycine		Anti-bacterial (e.g. acne)	Malaria	Miller et al.
Doxycycline		Broad-spectrum bacteriostatic agent	Malaria	Tan et al. (2011)
Co-trimoxazole (trimethoprim/ sulfamethoxazole)	 Trimethoprim Sulfamethoxazole	Urinary-tract infection, otitis media, shigellosis, and P. carinii pneumonia	P. falciparum malaria in nonpregnant adults and children	Gleckman et al. (1979), Montoya and Liesenfeld (2004), Manyando et al. (2013)
Miltefosine		Skin metastases (breast cancer)	Vischeral leishmaniasis	Smorenburg et al. (2000), Paladin Labs Inc (2010), Dorlo et al. (2012)
Spiramycin		Bacterial infection	Congenital toxoplasmosis	Desmonts and Couvreur (1974a), Couvreur et al.(1988), Descotes et al.(1988), Robert-Gangneux and Darde (2012)
Nitazoxanide		Anti protozoal agent	Leishmania parasites	White (2004), Muller et al (2008a, b)

REPURPOSING OF DRUGS FOR ANTI-BACTERIAL ACTIVITY:

What are antibiotics?

- Antimicrobial is not same with antibiotics, its derived from the Greek word anti (against) and biotikos (concerning life). The word "**antibiotic**" refers to substances produced by microorganisms that act against another microorganism.

- An antibiotic is a type of antimicrobial fights against bacteria and important type of antibacterial agent. Antibiotics are not effective against viruses such as the common cold or influenza[2].

NEED FOR NEW ANTIBACTERIAL DRUGS:

What is anti-microbial resistance?

Anti-microbial resistance (AMR or AR) is the ability of the microbe to resist the effects of medication that once successfully treat the microbes. The term anti-biotic resistant applies only to bacteria. Resistant microbes are more difficult to retrofiring alternative medications or higher doses of antimicrobial. These approaches may be more expensive, more toxic or both[3].

RISING DRUG RESISTANCE AND THREAT TO HEALTH:

Rising drug resistance is caused mainly by use of antimicrobials in humans and other animals and spread of resistant strains between the two. Growing resistance has also been lined to dumping of inadequately treated effluents from the pharmaceutical industry, especially in countries where bulk drugs are manufactured. Antibiotics increase selective pressure in bacterial populations causing vulnerable bacteria to die. Even at very low levels of antibiotics, resistant bacteria can have a growth advantage and grow faster than vulnerable bacteria with resistance to antibiotics becoming more common there is greater need for alternative treatments[4].

EASY ACCESS TO ANTIBIOTICS AND ITS EFFECTS:

Resistance to antimicrobials is increasing all over the world due to immense access. Estimated about 700,000 to several million deaths per year. Each year at least 2.8 million people become infected with bacteria that are resistant to antibiotics and at least 35,000

people die as a result. Worldwide antibiotic resistance is not completely identified, but poorer countries with weaker health care systems are more effected[5].

DRUGS THAT HAVE BEEN REPOSITIONED[6]:

S.No	DRUG	INITIAL INDICATION OR USE	ADDITIONAL INDICATION
1	Acetyl salicylic acid	Analgesic	Antiplatelet
2	Allopurinol	Cancer	Gout
3	Amantadine	Antiviral	Parkinson's disease
4	Arsenic	Syphilis	Leukemia
5	Beta-blocker	Arrhythmia/ angina	Hypertension
6	Doxepin	Anti-depressants	Topical anti pruritic
7	Lidocaine	Local anesthetic	Anti-arrhythmic
8	Minoxidil	Hypertension	Hair loss
9	Nitric oxide	Angina	Pulmonary hypertension
10	Penicillamine	Copper chelating agent	Antirheumatic
11	Raloxifene	Contraceptive	Osteoporosis
12	Thalidomide	Insomnia/ antiemetic	Cancer
13	Tretinoin	Severe acne	Leukemia
14	Astemizole	Anti-histamine	Malaria
15	Ivermectin	Elephantiasis	Tuberculosis
16	Miltefosin	Antineoplastic	Leishmaniasis
17	Tamoxifen	Anticancer	Leishmaniasis
18	Amphotericin b	Antifungal	Leishmaniasis
19	Amantadine	Influenza	Parkinson's disease
20	Bromocriptine	Parkinson's disease	Diabetes mellitus
21	Bupropion	Depression	Smoking cessation
22	Colchicine	Gout	Recurrent pericarditis
23	Gabapentin	Epilepsy	Neuropathic pain
24	Miltefosine	Cancer	Visceral leishmaniasis
25	Retinoic acid	Acne	Acute promyelocytic leukemia
26	Ropinirole	Parkinson's disease	Restless leg syndrome
27	Zidovudine	Cancer	HIV/AIDS
28	Finasteride	Prostate cancer	Hair Loss

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