

# Reuse of Old, Existing, Marketed Non-antibiotic Drugs as Antimicrobial Agents: a New Emerging Therapeutic Approach

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The most fruitful basis for the discovery of a new drug is to start with an old drug". Historically, 'repurposing' old drugs has proved successful in bringing new therapies to the developing world. Today, even with the billions of research dollars available to create new drugs through public-private partnerships, and the promise of genomic data, there remains an enormous unmet need for therapies for several microbial diseases such as bacterial, viral, protozoan parasitic and fungal infection. Investigating new uses for existing drugs in different doses is a proven short cut bridge between the lab and the clinic, reducing drug discovery hazards related to cost, time and scientific challenges. To establish on past successes in drug rediscovery, a classical example is the new findings like anti-bacterial, anti-fungal and anti-parasitic efficacy of hypotensive drugs like amlodipine, lacidipine (1,4 dihydro pyridine analogs) and anti-depressant sertraline, a selective serotonin reuptake inhibitor, anti-microbial activity of phenothiazine based anti-psychotics and tricyclic antidepressants, anti viral therapy (HIV) with hydroxyurea (anti neoplastic agents), cyclosporine and thalidomide (sedative), anti-leishmanial (anti-parasitic) efficacy of anti-ulcer agent: omeprazole, anti bacterial activity of dobutamine (non antibiotic). Considering the above novel concepts, this chapter, we describe the antimicrobial effect, mechanism of preventive or killing mode against several types of microbial diseases, dosage regimen, for new purpose. This idea may also enhance the anti microbial drug development process, reducing the chances of pharmacokinetic, toxicity and ADR related failure associated with new molecule.

**Keywords** Repurposing; old drug; non antimicrobial compound; reuse as antimicrobial agents; anti-virus; ant-parasitic; anti-bacterial; anti-fungal effect

## 1. Introduction

"New uses for old drugs" is an innovative and looming concept for drug discovery progression, as argued by Curtis R. Chong and David J. Sullivan Jr. It is not also taken huge time and too much cost to market new molecule as drug, but faces lot of challenging struggle and hazards ahead including determination of the optimal doses, schedules, and response monitoring (end points) [1, 2]. Moreover survey report suggests that it takes 15 years and US\$800 million including preclinical and clinical costs to bring single drug into market. This statistics estimates that more than 300 yrs will be required to double the amount of drug number as per the current rate [3]. Furthermore, high manufacturing together with research and development costs may found to be loss, if the new molecule is withdrawing from market at phase 4, due to unsatisfactory adverse drug reaction (ADR) or toxicity.

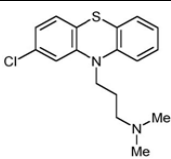
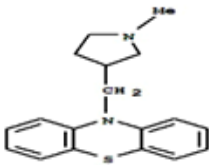
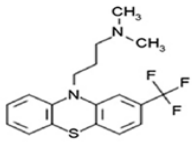
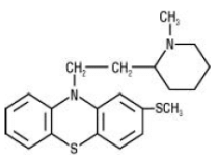
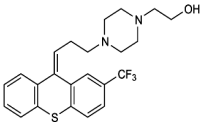
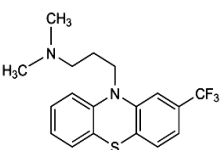
In order to repair such difficulties in drug discovering process, only solution is to reinvestigating new uses for existing marketed old drugs. As the pharmacologist and Nobel laureate James Black said, "The most fruitful basis for the discovery of a new drug is to start with an old drug." Pharmaceutical companies are also screening existing marketed old drugs to identify new uses at different dosage regimen to accelerate the drug approval process and increase the productivity and affectivity by passing ADR and toxicity. Known safety profiles and pharmacokinetic datas of existing drugs are often help to evaluate their new uses in phase II clinical trials rapidly. Time course for analysis and ethical evaluation in human trial, normally last two years and cost \$17 million. In this manner, drug researchers and pharmaceutical company can circumvent almost 40% of the overall cost of bringing a drug from lab to market by get rid of much of the toxicological and pharmacokinetic assessments[1].

Historically, 'repurposing' old drugs has appeared to be successful in bringing new therapies to the developing world. Investigating new uses for existing drugs is a proven short cut bridge between the lab and the clinic. [3,4]. To establish on past successes in drug rediscovery, a classical example of anti-inflammatory drug, Aspirin has been redeveloped as antihypertensive agents, omeprazole (antiulcer agents) [5], sertraline (selective serotonin reuptake inhibitor antidepressant)[6], amlodipine (anti-hypertensive agents) [7] were found to be reported for the management of neglected diseases such as visceral leishmaniasis, bacterial and fungal infection: will mean screening all known pharmacological space in a systematic way. Researcher has also got benefited through *in silico* repurposing via drug modeling towards new target along with systemic *in vitro* and *in vivo* drug screening effort for the successful aiming of new uses of old, approved drugs [8, 9].

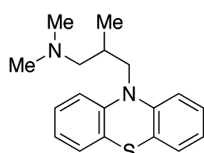
From a scientific and academic viewpoint, the most achieving research objective is to discover novel therapies for unmet clinical requirement, a process that appears more reasonable via drug repurposing and repositioning apart from its existing activity [10,11], as opposed to *de novo* drug discovery. Thus drug petitioner are reducing their financial burden associated with clinical trial as well as drug safety evaluation with *de novo* new drug molecule discovery with the reclaiming for newer indication of old drugs. Such economic approach takes to balance both profit and the service drive, where financial gain will be channelized to improve other important aspects like research grants, patent and publication, faculty promotion and tenure decisions etc, implemented by academic and pharmaceutical institutions [9]. Clinical survey reports suggest that already 24 existing drugs are already being remarketed by the pharmaceutical industry for new uses [10]. A recent example is the introduction of miltefosine as promising repurposed oral antileishmanial drug, which was preapproved for the treatment of breast cancer. Visceral leishmaniasis, the neglected disease is caused by a sand fly-transmitted parasite and kills an estimated 500,000 people each year.

Considering the above cited emerging therapeutic approach, we have summarized the antimicrobial activity and killing mechanism of reported non antibiotic, old existing marketed drugs in this book chapter. Herein, we are reviewing the reports of anti-bacterial, anti-viral, anti-parasitic and anti-fungal activity of existing marketed non-antibiotic drug (Table 1), which already been reported in scientific journals as preclinical model.

**Table 1** Additional use of drugs discovered during or after clinical usage

Drug (Classification)	Structure	Initial Use	Additional or New Primary Use
<b>Chlorpromazine</b> (antipsychotics)		Dopamine antagonist to treat schizophrenia	Anti-amoebic, anti-bacterial agents
<b>Phenothiazine prototype</b> <b>Methdilazine</b> (antihistaminic as anti-cholinergic)		Skin allergy	Anti-bacterial agents
<b>Trifluoperazine</b> <b>Phenothiazine</b> (antipsychotics)	 <b>Triflupromazine</b>	Dopamine antagonist to treat schizophrenia	Anti-bacterial agents
<b>Thioridazine</b> Phenothiazine (group of piperidine subclass)		Treatment of schizophrenia and psychosis dopamine antagonist	Anti-bacterial and anti-tubercular agents
<b>Flupenthixol</b> (antipsychotic drug of the thioxanthene class)		To treat schizophrenia and related depression	Anti-bacterial agents
<b>Triflupromazine</b> (antipsychotics)		Nausea, vomiting and psychosis	Anti-bacterial agents

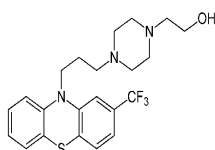
**Trimeprazine** (anti-allergic, anti-histamine receptor antagonist)



Pruritic, used as sedative

Anti-bacterial agents

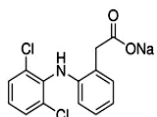
**Fluphenazine Phenthiazine** (antipsychotics)



Used in schizophrenia, manic phases of bipolar disorder, agitation, and dementia

Anti-bacterial agents

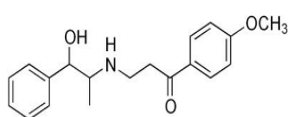
**Diclofenac sodium** (NSAID drugs)



Used in all type of pain management and treat inflammation

Anti-bacterial agents

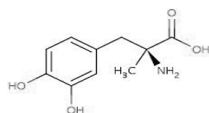
**Oxyfedrine hydrochloride** (antianginal drug)



Used in the treatment of cardiovascular disorders like angina pectoris as vasodilators'

Anti-bacterial agents (therapeutic use against both gm positive and gm negative bacterial infection)

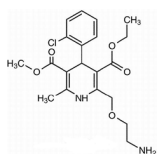
**Methyl-L-DOPA**



Used in the treatment of Hypertension and Parkinson

Anti-bacterial and anti-tubercular agents

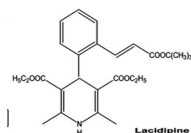
**Amlodipine**



Antihypertensive agent's

Anti-bacterial agents including listeriosis and salmonellosis, Anti leishmanial, anti trypanosomal

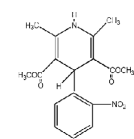
**Lacidipine**



Antihypertensive agents

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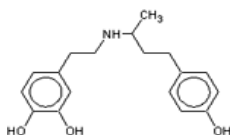
**Nifedipine**



Antihypertensive agents

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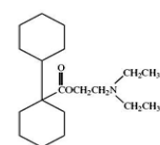
**Dobutamine**



Antihypertensive agents

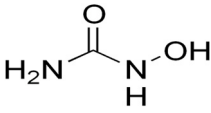
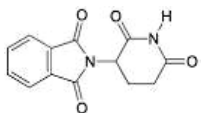
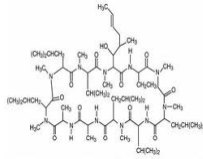
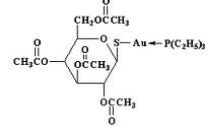
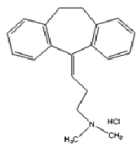
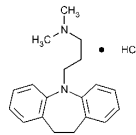
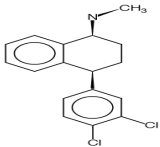
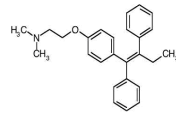
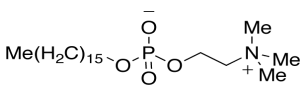
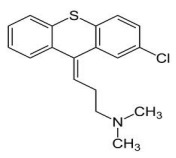
Anti-bacterial agents

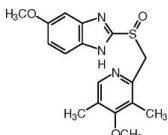
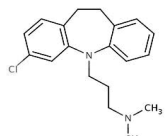
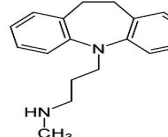
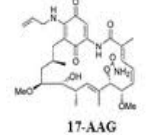
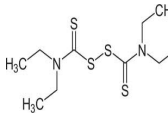
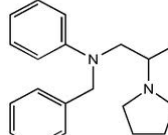
**Dicyclomine**



Anti-spasmodic agent

Anti-bacterial agents

<b>Hydroxyurea</b>		Antineoplastic agent	Anti-HIV agents, used for AIDS management
<b>Thalidomide</b>	 thalidomide	Sedative agent	Anti-retroviral agent
<b>Cyclosporine</b>		Immunosuppressant	Prevents HIV diseases progression
<b>Auranofin</b>		Gold-based antiarthritic drug	Antimalarial agent
<b>Amitriptyline</b>		Tricyclic antidepressants	Antimalarial and anti leishmanial agent
<b>Imipramine</b>		Tricyclic antidepressants	Antimalarial, anti-leishmanial, anti-amoebic agent
<b>Sertraline</b>		Antidepressant	Anti leishmanial, anti-bacterial, anti-fungal agent
<b>Tamoxifen</b>		Anticancer compound	Anti leishmanial, anti-fungal agent
<b>Miltefosine</b>		Anti-cancer alkylphosphocholines derivative	Significant antifungal and leishmanicidal agent
<b>Chlorprothixene</b>		Tricyclic antidepressants	Used against trypanosomiasis and leishmaniasis

<b>Omeprazole</b>		Antiulcer compound	Anti-leishmanial agent
<b>Clomipramine</b>		Tricyclic neuroleptics	Anti-protozoal agents ( <i>Crithidia luciliae</i> , <i>trichomonas vaginalis</i> , amoeba parasite)
<b>Desipramine</b>		Tricyclic neuroleptics	”
<b>17-AAG, a geldenamycin derivative</b>		Potential anti-cancer drugs	Anti- candidiasis (anti fungal)
<b>Disulfiram</b>		An anti-alcoholic agent	Anti-fungal for reversal of drug resistance
<b>Bepiridil</b>		Hypotensive, Ca <sup>+</sup> channel blocker	Anti leishmanial agent

## 2. Brief reports on repurposing and reuse of old drugs

### 2.1. Antibacterial activity of antipsychotic drugs

An antibiotic is basically a substance produced by a microorganism that kills or inhibits the growth of another microorganism. In contradiction of an antibiotic, there are lot medicinal compounds, which are used for the therapeutic management of functional disorders derived diseases, and several time, that have being reused as anti-bacterial agents[12].Such type of compounds are called as “Non –antibiotic”[13], and that have potentiality to manage some problematic bacterial infections.[14,15]. The intention of this review of ‘non-antibiotics as helper compounds’ is to discuss the mechanisms, dosing and other benefits by which some non-antibiotics have explored antibacterial activity.

Previous reports demonstrated that patients receiving chlorpromazine (CPZ) therapy could be cured of bacterial infections [16]. This compound is active against several multidrug resistant bacterial strain [17]. The following table 1 displays the wide range of antibacterial activities of phenothiazines derivatives such as methdilazine; fluphenazine; chlorpromazine; thioridazine; flupenthixol; trifluoperazine; trimeprazine; triflupromazine. Nevertheless, phenothiazines derivatives, such as trimethoprim and trimeprazine, at concentrations that are tolerated by the mouse, defend the animal from growing *Salmonella* infections [18]. Non-antibiotic phenothiazines and their derivatives have been found to be fruitful against *Escherichia coli* infection in mice model [19].

Apart from their promising anti bacterial activity, a large number of phenothiazines appear to have great potentiality against MDR tuberculosis (TB) [20-24]. Probably, thioridazine [25] promote the killing of intracellular mycobacteria, mice infected with *M. Tuberculosis*. Because a given phenothiazine has the same activity against *M. tuberculosis* regardless of its resistance to one, two or more antibiotics [26].

### 2.1.1. Mechanism of anti-bacterial action.

Due to increased permeability of phenothiazine molecules, eventually reach the DNA, intercalate between the bases [27], inhibit all DNA-based processes [28] and hence inhibit bacterial replication. *In vitro* concentrations of the phenothiazine that inhibit replication of the bacterium are generally many hundred-fold lesser than that which can be achieved in the patient. Moreover phenothiazines may also enhance killing of bacteria by the inhibition of K<sup>+</sup> and Ca<sup>2+</sup> transport mechanism, these ions are essential for acidification of the phagolysosome and subsequent activation of its hydrolases inside the bacteria [29]. Such novel class of non antibiotic also induce the T cell subtype cytokines inside macrophages to kill and reduce the infective bacteria via *in vivo* immuno modulation [30]. Phenothiazine derivatives showed antitubercular activity may due to inhibition of *Mycobacterium tuberculosis* type-II type-II NADH-menaquinone oxidoreductase (NDH-2), as supported by earlier report [31]

### 2.2. Antibacterial activity of analgesic drugs.

Similarly, diclofenac sodium, a NSAID, novel non antibiotic showed significant protection of the mouse against infection by wide variety of highly virulent *Salmonella* strains, *Staphylococcus aureus*, *Shigella* spp., *Vibrio cholera*, *Vibrio parahaemolyticus* and *E. Coli* at lower doses in comparison to its *in vivo* analgesic dose [32-36]. Diclofenac sodium showed bactericidal effect against both gram positive and gram negative bacteria through inhibition of DNA synthesis [34]. Moreover NSAID drugs such as sulindac sulfide, ibuprofen, indomethacin were found to be bacteriostatic and bactericidal against *Helicobacter pylori* *in vitro*, as reported previously [37].

### 2.3. Antibacterial activity of cardiovascular drug.

An antianginal and coronary vasodilator, cardiovascular drug, oxyfedrine hydrochloride was observed to acquire potential antibacterial activity both *in vitro* and *in vivo* against *Staphylococcus*, *Bacillus*, *Vibrio* spp. and some enterobacteria. Oxyfedrine was found to be bacteriostatic *in vitro* against both gram positive and gram negative bacteria. Since this drug is in routine therapeutic usage, devoid of human toxicity [38].

Methyl-L-DOPA, both an antihypertensive and anti-parkinsonian drug, was established to have noticeable antibacterial activity on testing against 405 strains of bacteria including a large number of gram-positive and gram-negative genera, MIC ranging from 10-200 µg/mL. It further displayed a remarkable antitubercular activity against diverse mycobacteria, MIC of 10-25 µg/mL [39].

Previous reports suggest that numerous cardio vascular drugs such as amlodipine (AML), dobutamine, lacidipine, and nifedipine were found to be effective as promising antibacterial agents. Out of these, AML confirmed to have the most noteworthy antibacterial activity against Gram-positive and Gram-negative bacteria, exhibiting protection against listeriosis and salmonellosis at non toxic doses. It elicits bactericidal effect by concentrating within the macrophage rather than the bacterium, leads to intracellular killing, avoiding mutation responses that lead to resistance to the drug [40, 41].

### 2.4. Antibacterial activity of antispasmodic drug.

Dicyclomine hydrochloride, an antispasmodic drug demonstrated an outstanding inhibitory action against several pathogenic bacteria, like *Staphylococcus aureus*, *Salmonella typhimurium*, *Shigella boydii* [42]

### 2.5. Reuse of old and existing non antibiotic drugs as Antiviral agents

In order to explore the repurposing concept, herein the antiviral, especially anti-HIV activity of few non antiviral drugs have been presented. Hydroxyurea, a classical antineoplastic drug agent, demonstrated protective activity against AIDS virus, inhibiting retroviral reverse transcription by targeting a cellular enzyme responsible for the synthesis of deoxynucleoside triphosphates. It may also reduce viral load via a modulation of T-cell activation. A number of clinical trials have been reported on beneficial effects of hydroxyurea in combination with didanosine and/or stavudine on viral load.

Nevertheless, cyclosporine, a known immunosuppressant, prevents proper HIV virion maturation, thus reduces the probable growth of HIV for diseases progression.

Reports suggested that thalidomide, sedative agent, demonstrated antiretroviral effects through blocking of the production of tumor necrosis factor alpha (TNF-α), as it induces expression of HIV through stimulating a cellular transcription factor. Thalidomide has found to be potential in treating some AIDS-related conditions like cachexia (weight loss and muscle wasting), and aphthous oral, esophageal or genital ulcers [43].

Moreover, hydroxyurea, old low-cost drug showed notable antiviral effects in the treatment of chronic hepatitis B in patient model through blocking of hepatitis B virus (HBV) replication [44].

## 2.6. Antiparasitic effect of non-antibiotic marketed drugs.

Gold-based anti-arthritis drug auranofin (AF) demonstrated potential antimalarial effect against *Plasmodium falciparum* through inhibition of mammalian thioredoxin reductases releasing severe intracellular oxidative stress leading to killing parasites. The secure toxicity profile of these gold compounds guarantees their rapid assessment for malaria treatment in animal models [45]. Earlier reports suggested that the tricyclic antidepressants, imipramine and amitriptyline, hold considerable antimalarial properties via reducing (3H)hypoxanthine uptake by intra-erythrocytic parasites leading to haemolytic growth inhibition of malaria in presence of ferriprotoporphyrin IX (FP).[46]. Amitriptyline presumably blocks both sphingomyelinases, which is a marker of progression of infection and, thus, its reuse might be a novel strategy to treat malaria of *Plasmodium berghei*-infected mice [47]. Methotrexate and trimetrexate, anti-cancer agents are potentially active against artemisinin resistant malaria parasites and pyrimethamine-resistant *Plasmodium vivax* in nano molar ranges *in vitro* as reported earlier [48,49]. This findings warrant and deserves the bright future Methotrexate and trimetrexate as promising anti-malarial drug

“New uses of old drugs” concepts illustrated a burning example of Amlodipine and lacidipine, conventional antihypertensive drugs, inhibited *Leishmania donovani* infection *in vitro* and in BALB/c mice when administered orally. These 1,4-dihydropyridine derivatives functioned through dose-dependent inhibition of oxygen consumption, triggering caspase 3-like activation-mediated programmed cell death of the parasites [7]. Moreover, 1, 4-dihydropyridines derivatives containing diphenylpropyl and diphenylmethylazetidid groups at position 4 of their scaffolds showed significant antiprozoan activity including leishmania and trypanosoma cruzi apart from their hypotensive efficacy through Ca channel blocking action [50]. Bepridil, another hypotensive Ca<sup>+</sup> channel blocker exhibited anti-leishmanial activity in *L. chagasi* experimental model at effective therapeutic dose [51].

Sertraline, an antidepressant killed *L. donovani* promastigotes and intracellular amastigotes at (IC<sub>50</sub>s) of 2.2 and 2.3 mg/L, respectively. The drug was also effective in eliminating splenic (72%) and liver (70%) parasite loads in infected BALB/c mice through oral therapy. A sertraline-induced fall in cytoplasmic ATP levels and oxygen consumption rate in promastigotes suggests the involvement of an apoptosis mode of cell death in the treated parasites [6]. Another anticancer compound, tamoxifen demonstrated potential antileishmanial activity showing activity against *L. braziliensis* and *L. chagasi* parasites with IC<sub>50</sub> ranging 1.9 -2.4 μM and decreased 95-99% parasite loads in *in vivo* model. Thus it may be highlighted as promising leishmanicidal agent for the treatment of cutaneous and visceral leishmaniasis.[54]. Tricyclic antidepressant, imipramine were found to be effective as oral drugs in the treatment of visceral leishmaniasis in animal model by upregulation of proinflammatory cytokine like TNF α, IFN-γ and iNOS expression leading to intracellular amastigotes. [53]. One more tricyclic antidepressants, amitriptyline and chlorprothixene are most efficient in causing cell death of leishmania parasites by decreasing proline transport with IC<sub>50</sub> congruent 5 μM [54]. Phenothiazine related tricyclic antipsychotics and anti-allergic compounds are also powerful drug leads against trypanosomiasis and leishmaniasis by selective inhibition of trypanothione reductase [55].

An antiulcer compound, omeprazole significantly inhibited the growth of *Leishmania donovani*, the causative agent of visceral leishmaniasis by reducing more than 90% amastigotes burden in infected macrophages [56].

Tricyclic neuroleptics not only demonstrate anti-leishmanial, malarial and trypanosomal activity, but clomipramine, chlorpromazine like compounds were reported as potential anti-amoebic agents by showing inhibitory activity on cell proliferation and the lytic effects on *Entamoeba histolytica* parasites HK9 and HM1 trophozoites, which is responsible for intestinal or hepatic amoebiasis [57]. It is an interesting thing to mention that few calcium channel blockers like nifedipine and diltiazem or the sodium channel blocker quinidine were effective in reversing emetine drug resistance on the mutant amoeba protozoan parasites in the presence of very high concentrations of the tricyclic antidepressants. These drugs are performing such reversing of resistance by reducing the overexpression of a gene for an amoeba homolog of the mammalian P-glycoprotein. These drugs also decrease the emetine IC<sub>50</sub> on resistance strain [58].

Imipramine, clomipramine and desipramine, tricyclic neuroleptics have significant inhibitory effects on the growth of protozoan parasites like *Crithidia luciliae*, *trichomonas vaginalis* [59].

## 2.7. Antifungal potentiality of non-antibiotic marketed drugs

17-AAG, a geldenamycin derivative, initially was developed as potential anti-cancer drugs, but later on found to be useful as Hsp90 inhibitors of systemic candidiasis. It also, significantly improves the activity of fluconazole both *in vitro* [60]. Zhai et al. have recently stated that the combination of the anti-depressant sertraline, which emerges to target translation in yeast with fluconazole, declines fungal brain burden compared to fluconazole monotherapy in a mouse model of cryptococcosis [61].

Estrogen receptor antagonist, tamoxifen, identified as anti breast cancer drug, demonstrated significant antifungal activity in a mouse model of candidiasis through inhibition of calmodulin [62]. Miltefosine, an anti-cancer alkylphosphocholines derivative was held significant promise as novel orally available antifungal agents [63] and therapeutically potent against invasive fungal infections. It elicits its fungicidal effect via inhibition of cytochrome c oxidase (COX) 9, complex in the electron transport chain of the mitochondrial membrane and leading to disruption of mitochondrial membrane potential. This inhibition probably contributed to the miltefosine-induced apoptosis-like cell death.

Disulfiram, an anti-alcoholic drug has been further identified to be used for the treatment of the reversal of fungal drug-resistance and human fungal infection [64].

### 3. Conclusion

Literature reveals that most of the cases, existing old drugs[65] demonstrate their newer activity in smaller doses compared to their approved marketed pharmacological dose, that have used for current therapeutic use. So no clinical trial related to safety and toxicity issues, are required in phase 1,2 for launching into the market for reapplication towards newer disease remedial benefit. Thus such approaches save the time span and cost in the drug discovery process. Thus repositioning, redirecting, repurposing, reinvestigating and reprofiling of old marketed drugs for newer target of newer diseases would be a major land mark in drug discovery and development process in a short cut route.

Repositioned drugs have the advantage of decreased development costs and decreased time to market than traditional discovery efforts, due to availability of previously collected pharmacokinetic, toxicology, and safety data.[66] For repositioned drugs, as the clinical safety data, pharmacokinetics, and viable dose range are available at the start of a development project, the risks associated with clinical development are significantly reduced with fewer failures in the later stages [67].

Known drug compounds showed promise, while investigated for new uses to test in animal model, due to their affinity towards numerous enzyme and receptors presents in microbes. Our review suggests that several non antibiotic drugs are applied at human body to treat functional disorder oriented diseases such as cardiac malfunctioning, neurotic disorders, allergy, inflammation, cancer etc. But most surprising thing is that such old drug compounds elicited anti-microbial effect, may due to present of microbicidal pharmacophore scaffolds. These moieties may responsible for the binding with the enzymating proteins, growth factors present in microbes. In order to validate our hypothesis, we can present few examples of repositioning; where anti antipsychotics like chlorpromazine, Flupenthixol, Trifluoperazine showed anti-bacterial or anti protozoan activity could be due to the presence of chloro, fluoro phenothiazine ring. Furthermore, anti-hypertensive drug compounds like amlodipine, lacidipine and nifedipine contain aryl 1, 4 dihydropyridine moieties, which are responsible for anti-microbial effect, apart from their Ca<sup>+</sup> channel blocking hypotensive action, as supported by earlier reports [7]. Since, previous reports suggested that old drugs implemented therapeutic reuse at lower doses, compared to their FDA approved existing doses. Chances of toxicity could be less and no phase 2 and 3 clinical trials are required. Consequently time span and cost associated with drug discovery program could be avoided.

Drug repurposing is expected to not only add value to the product portfolio of the drug companies, but also to improve the capability of nonindustrial entities (academic and governmental) to bring "new" and inexpensive treatment options forward for a number of grave and neglected/orphan diseases.[68] Therefore, large-scale achievement of therapeutic and indication switching strategies in the future will provide an opening to unleash the potential of the pharmacopeia and escort a win-win situation for the public and private sectors and patients globally. We believe lot of researchers from corporate, academic institutions and pharmaceutical industries will get a boost to screen out blockbuster drugs from existing marketed molecules via repositioning and repurposing strategies [69]. Such unlock innovation can finally lead to better health for patients specially in case, while existing marketed anti-microbial drug fails to execute their action due to repetitive use oriented drug resistance.

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