Review Article

REPURPOSING OF DRUGS: EMERGING SCENARIO

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ABSTRACT

In recent times drug repurposing has gained interest over the traditional drug discovery due to reduction in time and cost of development of new drug. Drug repurposing approach has given promising drug candidates for various viral diseases like COVID 19, Ebola, Zika, Dengue, Influenza, HIV, Herpes, etc. On-target and off-target are the two basic strategies of drug repurposing. Macrolide, Artemisinin, Quinoline antiparasitic drugs are some of the drugs repurposed against cancer and drugs like thalidomide are repurposed against COVID-19 infection. Repurposing of veterinary drugs like ivermectin, levamisole and benzemidazole group of antiparasitic drugs are also under consideration. This review elaborates repurposing of antihypertensive drugs like angiotensin- converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARBs), β-blockers as anti- neoplastic drugs, anti-diabetic drugs against Alzheimer's disease, fluorophenyl benzimidazole (FPD) as antihypertensive drug, thalidomide against COVID-19 infection, levamisole as antineoplastic drug, benzimidazole as anti-cryptococcal drug and some other new drugs. Usage of in silico techniques and pharmacophore modeling strategies can further accelerate the process of drug repurposing. The drug repurposing strategies significantly minimize research and development costs, provide greater chances of success, shorter research time and lower investment risk.

Keywords: Drug repurposing, Anti-parasitic drugs, Anti-neoplastic drugs, COVID-19, Antihypertensive drugs, Antidiabetic drugs, *In silico* technique, Research and Development

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INTRODUCTION

Drug repurposing (DR) is also known as drug repositioning, drug re-tasking, drug re- profiling, drug rescuing, drug recycling, drug redirection and therapeutic switching. It is a process that involves the discovery of new pharmacological indications from old or existing drugs and the use of the newly

developed drugs to treat diseases other than the original or intended therapeutic use of the drug. It involves establishing new therapeutic uses for known drugs, including approved, discontinued, abandoned and experimental drugs (Ashburn and Thor, 2014; Dey, 2019).

Need for drug repurposing

Traditional drug development is a time-consuming, labor-intensive, costlier and high risk procedure. The novel approach of drug repositioning has the potential to be employed over traditional drug discovery programs by mitigating the high monetary cost, longer duration of development and increased risk of failure. Approximately 30% of the US FDA-approved drugs and biologics (vaccines) are repositioned drugs (Rudrapal *et al.,* 2020). Through drug repurposing, the patients can obtain medications at a much lower cost and more quickly. The drugs which are repurposed are those that have been abandoned because of incomplete clinical trials or failed on the post marketing surveillance. In drug repurposing, the early stages of clinical trials can be excluded because of the drug's effectiveness, safety and toxicity were already established, which in turn reduces their cost and time. In the traditional drug discovery process, it takes about 15 years for a novel drug to be developed before it can be sold whereas. It only takes 5 to 7 years to repurpose the known drugs (Chong and Sullivan, 2007).

Emerging trends in drug repurposing against viruses

Every day there is an increase in emerging viral infections but the targeted therapies for those emerging infections are not discovered. The drug repurposing approach has given many promising drug candidates for various viral infectious diseases like Ebola, ZIKA, dengue, influenza, HIV, herpes simplex virus, cytomegalovirus infections and various other infectious diseases. To develop new antiviral drugs quickly and to solve the difficulties in antiviral therapy, the drug repurposing technique is a reliable option (Mani *et al.,* 2019).

Comparison between traditional drug discovery and drug repurposing

De novo synthesis and the development of novel molecular entities (NME) are important conventional drug discovery. This process contains five stages: discovery and preclinical, safety evaluation, clinical research, FDA review and FDA post-market safety monitoring. It is an expensive, time-consuming technique that has a high failure rate. Drug repositioning, on the other hand, only has four stages: compound identification, compound acquisition, development and FDA post-market safety monitoring (Rudrapal and Chetia, 2016). In the most recent years, with the use of in silico methods and the usage of the structure-based drug design, the time and cost of developing new drugs have been greatly reduced and the probability of failure was also lowered (Agrawal, 2018; Kalita *et al.,* 2020).

Strategies of drug repurposing

On-target and off-target are the two basic strategies of drug repurposing. In on-target

drug repurposing method, a drug molecule with well-known pharmacological action is applied for new therapeutic indications. In this approach, the biological target of the drug is same, but the disease is different (Rudrapal and Chetia, 2016). Minoxidil is an example for repositioning, this medication prevents hair loss and was introduced as an antihypertensive due to its vasodilatory effects. As an antihypertensive drug, minoxidil has the ability to open potassium channels and dilates the blood vessels, allowing more oxygen, blood and nutrients to reach the hair follicles (Rudrapal *et al.,* 2020). On the other hand, in the off-target drug repurposing method, the pharmacological mechanism is unknown. Drugs act on new targets for new therapeutic indications. Therefore, both the target and the indication are new (Ashburn and Thor, 2014). For example aspirin (Colsprin), it has been traditionally used as NSAID in the treatment of pain and inflammatory disorders. It also acts as an anti-clotting factor by inhibiting the normal functioning of platelets (antiplatelet drug). It is, therefore, used in the treatment of coronary heart diseases. Another new use of aspirin has also been reported in the treatment of prostate cancer (Rudrapal *et al.,* 2020).

Methodologies of drug repurposing

The methodologies used in drug repurposing are divided into three general categories depending on the quantity and quality of the pharmacological, toxicological and biological activity information that is available. These are mostly I) drug, (ii) target, (iii) disease and therapy-oriented. 1). Drug-oriented method includes the evaluation of structural properties of drug molecules and biological activity. Using cell/animal experiments, this method is intended to find out whether the drugs possess biological effects. This kind of repositioning approach is based on conventional pharmacology and drug discovery principles, where studies are often carried out to establish the biological activity of pharmacological molecules. 2). Target-oriented method includes virtual high-throughput screening (vHTS) of drugs from drug libraries or compound databases, such as ligand based screening or molecular docking, followed by *in vitro* and *in vivo* high-throughput and/or high-content screening (HTS/HCS) of drugs against a specific protein molecule or an interest biomarker. Compared to drug-oriented method, this strategy has a significantly higher success rate in drug development since the majority of biological targets directly correspond to disease pathways (Napolitano *et al.,* 2013). Disease/therapy-oriented method is useful when there is more knowledge about the illness. The information about the illness may be provided by proteomics (disease specific target proteins), genomics (disease specific genetic data), metabolomics (disease specific metabolic pathways/profile), and phenotypic data (off-target mechanism, pharmacological targets, disease pathways, pathological conditions, adverse and side effects, etc.). More than 50 percent of the FDA-approved drugs were discovered using drug-oriented and target-oriented methods (Rudrapal *et al.,* 2020).

Repurposing of macrolide antiparasitic drugs for treating cancer

Macrolides are anti-parasitic drugs having both endo and ecto-parasitic actions. The primary mechanism of action is neuromuscular paralysis and death in parasites is achieved by increasing the concentration of inhibitory neuro-transmitter GABA and also by increasing the permeability of the neuron membrane to chloride ions (Geary, 2005). Avermectins and milbemycins are the major two primary macrolides, which have been used for a long time for anti-nematodal action. In addition to their anti-parasitic properties, macrolides also possess varying degrees of anticancer action.

The primary anticancer mechanism of macrolide drugs is apoptosis. Through the mitochondrial route, cell cycle arrest and blockade of the Ca^{2+} ion-activated Cl^- channels macrolides cause apoptosis. In addition to apoptosis, macrolides exerts their anti-cancerous effect by autophagy mainly by deactivating P21 activated Kinase (PAK1) and blocking stem cell genes. Macrolides correct the aberrant epigenetics of tumor cells through the interaction of the pairs of paired amphipathic alpha-helix 2 (PAH2) and Sin3 interaction domain (SID). Macrolides can reverse anti-tumor drug resistance by inhibiting the transcription of MDR (multiple drug resistance), serine/ threonine kinase 1 (MASTA1) and P-gp proteins which are normally responsible for drug resistance in anti-cancer chemotherapy (Li *et al.,* 2021).

Repurposing of benzimidazole antiparasitic drugs for treating cancer

Benzimidazoles are broad-spectrum antiparasitic medications with a structural resemblance to that of purines. Albendazole (ABZ), flubendazole (FLU), fenbendazole (FBZ), oxibendazole (OBZ) and febantel are the main examples of benzimidazoles. Benzimidazoles exert their antiparasitic action primarily by altering adenosine triphosphate (ATP) synthesis, sugar metabolism and tubulin binding to change the cell cycle (Lacey, 1988; Valdez *et al.,* 2002). These biological processes are also crucial in the progression of cancer, thus benzimidazoles exert their anti-tumor effect.

The main anti-cancerous mechanism of benzimidazole is by preventing the production of the hypoxia-inducible factor-1a (HIF-1a) and limiting the uptake of sugar via the glucose transporter (GLUT)/AMPK/P53 pathway, impairing energy metabolism and decreasing the tolerance of cancer cells to the hypoxic state. Benzimidazoles suppress microtubule polymerization, cause endoplasmic reticulum stress, encourage MAPK phosphorylation and cause apoptosis in cells. Benzimidazoles upregulates eva-1 homolog A (EVA1A) resulting in the accumulation of light chain 3B-II (LC3) and degradation of P62, and also blocking the signal transducer and activator of transcription 3 (STAT3) downstream signaling pathway. Additionally, benzimidazoles can promote antitumor immunity by decreasing the expression of programmed cell death protein-1 (PD-1), and preventing the buildup

of myeloid-derived suppressor cells (MDSC) (Li *et al.,* 2021).

Repurposing of artemisinin (ARS) and its derivatives in cancer

Artemisinin (ARS), a 1, 2,-trioxane extracted from the Chinese medicinal herb is best known as sweet worm wood has antimalarial activity. Number of ARS and its derivatives (ARTs), including dihydroartemisinin (DHA), artemether (ARM), artesunate (ART) and artemisitene (ATT) have emerged due to drug modification and synthesis technology (Li *et al.,* 2021). ARTs exert their anticancerous mechanism by inducing oxidative stress mainly by enhancing the level of ROS, DNA damage and also by cell cycle arrest. In addition, ARTs also cause ferroptosis by increasing the amount of unstable iron ions in cancer cells by controlling a number of iron-related proteins (IRP1/IRP2). ARTs strengthen the interaction between NK cells and cancer cells by enhancing the degranulation capacity of NK cells and also ARTs increase the potential of NK cells to destroy cancer. ARTs reduce negative regulatory factors (Treg cells and MDSCs) and increases IL-4 and IFN to stimulate T cell immunological response (Li *et al.,* 2021).

Repurposing of quinoline antiparasitic drugs in cancer

Similar to ARTs, quinolines also exert their anti-malarial action throughout the phases of the parasite's life cycle that occur in blood (Watkins, 1995; Nixon *et al.,* 2013; Miller *et al.,* 2016). Anti-cancerous effect of quinolines due to elevating the pH of the lysosome, results in a chain of events. By enhancing the tumor antigens, quinolines activate the immune system's response to fight against tumors. Quinolines inhibit autophagy by inhibiting the degradation of autophagy proteins. Quinolines cause apoptosis by inducing oxidative stress with the change in mitochondrial membrane potential, inhibiting the level of STAT3 phosphorylation in mitochondria and also by causing double-stranded DNA breakage in cancer cells. Quinolines increase the oxygen concentration in cancer cells by inhibiting the oxygen utilization in complex III of mitochondrial (Li *et al.,* 2021).

Therapeutic targets of the currently considered drugs for repurposing against COVID-19

Interferons help to retain corona virus in an antiviral state. Spike proteins of corona virus combine with the cellular angiotensin-converting enzyme (ACE2) receptor to enter the cell, and then ACE2 is down regulated. In this situation, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs) and statins may be effective since they upregulate ACE2 expression. Viral fusion is followed by endocytosis, during which viral structural proteins are lysed due to low endosomal pH but antimalarial drugs like chloroquine and hydroxychloroquine increase the pH and help to maintain an antiviral state. Functional RNA-dependent RNA polymerase (RDRP), is produced by proteolysis due to viral primary protease enzyme since the virus transcription and replication depend on

RDRP. Therefore, lopinavir, ritonavir, and darunavir are inhibitors of the major protease enzyme that may be effective against the virus. Remdesivir, favipiravir, ribavirin and arbidol are RDRP inhibitors that may be useful against coronaviruses (Singh *et al.,* 2020).

The role of levamisole as an effective immunomodulator

Levamisole is an antiparasitic drug that boosts cellular immunity and aids in autoimmune disease by normalization of the CD^{4+}/CD^{8+} ratio. Levamisole has no significant effect on the activation of T cells or natural killer (NK) cells (Schiller *et al.,* 1991). The primary job of dendritic cells (DCs), which are antigen-presenting cells, is to capture, process and deliver antigens to unprimed T cells (Banchereau and Steinman, 1998). Levamisole improves DC maturation and increases the expression of molecules such as CD80, CD83, and CD86 as well as major histocompatibility complex (MHC) molecules which further activates T lymphocytes (Cella *et al.,* 1997; Moore *et al.,* 2001; O'Sullivan and Thomas, 2002).

The role of levamisole as an anti-neoplastic activity

Levamisole inhibits angiogenic growth and induces cell apoptosis. Levamisole mainly inhibits the signaling of vascular endothelial growth factor causing clusters of undifferentiated endothelial cells to develop, thereby prevents proliferation of cancer cells (Friis *et al.,* 2013). The anti-cancer properties of levamisole are further explained by its capacity to cause endothelial cells to undergo apoptosis and thereby arrest growth. The levamisole also reduces retinoblastoma protein [pRb] which is a cell cycle regulator to its hypophosphorylated condition. This will inhibit E2F, a group of genes required for the production of transcription factors involved in DNA synthesis and cell cycle progression results in cell cycle arrest. Levamisole also causes stoppage of cell growth by increasing the synthesis of p21 protein, an inhibitor of cyclin dependent kinases required for cell cycle regulation (López-Marure *et al.,* 1997).

Repurposing of antihypertensive drugs as antineoplastic drugs

Angiotensin-Converting enzyme inhibitors (ACEI) and Angiotensin-Receptor Blockers (ARBs)

Captopril is an angiotensin-converting enzyme inhibitor (ACEI) that has been used extensively to treat a variety of cardiovascular conditions. By reducing the level of angiotensin II (Ang II), ACEI blocks the downstream signaling mediated by the angiotensin receptor type 1 (AT1R) on the renin-angiotensin-aldosterone system (RAAS) (Taler, 2018; Messerli *et al.,* 2018). Furthermore, ACEIs are activated by endopeptidases and block angiotensin-converting enzyme **(**ACE) and blocks the conversion of angiotensin-1-9 to angiotensin-1-7, which binds to MAS1 oncogene (MAS) receptors and produces opposite effects of AT1R (vasodilation, apoptosis, and antiproliferation) (Tipnis *et al.,* 2000; Ferrario *et al.,* 2005; Xia and Lazartigues, 2010; Tirupula *et al.,* 2014).

In addition to captopril, there are currently numerous ACEI available, including enalapril, benazepril, fosinopril, and others.

Aliskiren is the orally active first direct renin inhibitor that works by preventing the production of angiotensin and is produced when circulating renin interacts with angiotensinogen (Ang I). As a result of aliskiren, there will be lower circulatory concentration of Ang I and its product, Ang II. Apart from lowering blood pressure and vascular resistance throughout the body, aliskiren also lowers plasma renin activity (Bonanni and DallaVestra, 2012). In contrast to the usage of ACEIs and ARBs, aliskiren has shown to have a negative effect on individuals with diabetes or nephropathy. The increase in concentration of plasma pro-renin level secondary to aliskiren intake is directly associated with the increase in microalbuminuria (Bonanni and DallaVestra, 2012).

β-Blockers

Antihypertensive drugs mainly act by preventing endogenous catecholamines from acting on the autonomic nervous system's β-adrenergic receptor (Wiysonge *et al.,* 2012). Apart from blood pressure regulation, β-blockers also have a role in carcinogenesis, angiogenesis and tumor progression (Peixoto *et al.,* 2020). Propranolol is one β-blocker that prevents angiogenesis mainly by affecting the expression and activation of angiogenic signaling pathways like angiopoietin, vascular endothelial growth factor (VEGF), and hypoxia inducible factor. Additionally, propranolol has a biphasic response on vascular resistance, causing vasoconstriction and vasodilation at low and high dosages, respectively (Dezong *et al.,* 2014; Montoya *et al.,* 2019). Carvedilol, labetalol, and propranolol are a few examples of non-selective -blockers that are important in the treatment of cancer, as are selective -blockers like atenolol, nebivolol, and metoprolol. However, the majority of preclinical studies have focused on the propranolol effect (Pantziarka *et al.,* 2018).

Repurposing of ivermectin against Covid-19

Ivermectin is an antiparasitic drug with anti-viral potency. Single dose of oral ivermectin tablets (12 mg) every day for 3 days was given to hospitalized COVID-19 patients in limited clinical research, and it was found to reduce mortality and also shortened hospital stay. The mechanism by which ivermectin suppresses SARS-CoV-2 is by blocking importin α/β heterodimer, a nuclear importer of SARS-CoV-2 *in vitro*. The efficacy of ivermectin against COVID-19 was investigated in a number of randomized controlled studies (Mudatsir *et al.,* 2020).

Repurposing of thalidomide against Covid-19

Thalidomide a synthetic glutamic acid derivative was first sold in 1957 for medicinal purpose with FDA approval for the treatment

of multiple myeloma. At that time, thalidomide caused the catastrophe of congenital birth abnormalities in pregnant women. Over 10,000 infants were born with serious congenital malformations, such as stunted limb development, cleft lip and palate, deformed eyes and ears, and congenital heart disorders the usage of thalidomide was discontinued in pregnant women in 1961 (Khalil *et al.,* 2017). The FDA denied approval of thalidomide during COVID-19 crisis, since it may causes adult peripheral neuropathy (Matthews and McCoy, 2003). Theoretically, the main mode of action of thalidomide in reducing COVID-19 is by reducing inflammation. SARS-CoV-2-infected lung tissue exhibits deadly lung damage due to reduced immune response, increased inflammation, activated cytokine storm and severe oxidative stress. Thalidomide is known to inhibit the chemotaxis of neutrophils, cytokine storm, and its related oxidative damage. Thalidomide is also a known up-regulator for NK and T cells (Khalil *et al.,* 2020). Which might produce beneficiary effect against corona virus.

Repurposing of antidiabetic drugs in the treatment of Alzheimer's disease

All diabetic medications have indirect effects on the central nervous system by changing the levels of glucose and insulin in the blood. Main signaling pathway where insulin affects Alzheimer's disease is via the insulin receptor substrate 1 (IRS-1) serine/ threonine-specific protein kinases (AKT) pathway. It is possible that antidiabetic drugs originally intended for the treatment of diabetes could be especially helpful in re-establishing signaling through this pathway. Other drugs like metformin, leptin analogues (metreleptin), amylin analogues (pramlintide) and protein-tyrosine phosphatase 1B (PTP1B) inhibitors, may be helpful to restore insulin signalling through the IRS-1 AKT pathway and hence they might be a helpful in treating of Alzheimer's disease (Yarchoan and Arnold, 2014).

Repurposing of benzimidazole for anti-cryptococcal action

Anti-cryptococcal action of benzimidazole by interference with the cytoskeleton, plasma membrane, nucleus and capsule. Benzimidazoles significantly affect fungal intracellular proliferation rates (IPR) and prevent fungal escape through vomocytosis (de Oliveira and Rodrigues, 2021).

Repurposing of benzimidazole for vasodilatation

Fluorophenyl benzimidazole (FPD) relaxes the superior mesenteric arteries in a concentration-dependent manner mainly by preventing the contraction caused by angiotensin II. Fluorophenyl benzimidazole increases tissue levels of cyclic guanosine monophosphate (cGMP), block L-type calcium channels and K^+ efflux in aortic smooth muscle cells and results is relaxation (Iqbal *et al.,* 2021).

Some of the other examples for drug repurposing

Drugs	Mechanism of action old indication	Initial use	Repurposed use	Mechanism of action for new indication	References
Dexamethasone	Suppressing the migration of neutrophils and decreasing lymphocyte colony proliferation	Skin allergies, Asthma,	COVID-19	By inhibiting pro-inflammatory gene that encodes for chemokines, cytokines, cell adhesion molecules	(Horby *et al.,* 2021)
Lignocaine	Blockade of voltage-gated sodium channels	Local anesthetic	Antiarrhythmic drug	Treatment for ventricular arrhythmias by blocking voltage gated sodium channels	(Collinsworth *et al.,* 1974)
Amphotericin B	By binding to ergosterol in the fungal cell membrane, which leads to formation of pores and ion leakage	Antifungal	Visceral leishmaniasis	Loss of permeability barrier to small metabolites in promastigote cells	(Goldsmith and Perry, 2004)
Doxycycline	Blockade of protein synthesis	Antibacterial	Malaria	Blockade of protein synthesis in asexual erythrocytic stages of the malaria	(Tan *et al.,* 2011)
Atorvastatin	By blocking HMG-CoA reductase enzyme	Lipid-lowering drug	Sepsis	By increasing the vascular tonicity	(Singh *et al.,* 2017)
Spiramycin	By inhibiting the protein synthesis	Antibacterial	Toxoplasmosis	By inhibiting the protein synthesis	(Etewa *et al.,* 2018)
Tocilizumab	Act by preventing IL-6 mediated inflammation	Rheumatoid arthritis	COVID-19	Reducing the risk of inflammation	(Saki *et al.,* 2021)
Mavrilimumab	Anti-inflammatory action	Rheumatoid arthritis	COVID-19	Reducing the risk of inflammation	(De Luca *et al.,* 2020)
Baricitinib	Act by blocking JAK/STAT pathway	Rheumatoid arthritis	COVID-19	Act by blocking virus entry in to the cells	(Richardson *et al.,* 2020)

Ebselen	By inhibiting viral protease enzyme	HIV, Zika, Influenza virus	COVID-19	Reducing the risk of inflammation	(Haritha *et al.,* 2020)
Arbidol	By binding to haemagglutinin (HA) protein	Parainfluenza, Influenza, Hepatitis C	COVID-19	Blockade of trimerization of spike glycoprotein	(Nojomi *et al.,* 2020)
Melatonin	It scavenges reactive oxygen species and block transcriptional factors of pro-inflammatory cytokines	Anti-oxidant, Immunomodulatory role.	COVID-19	By activating T cell activation	(Cross *et al.,* 2021)
Teicoplanin	Inhibition of bacterial peptidoglycan sysnthesis	Anti-Staphylococcus	COVID-19	By inhibiting cathepsin L protease and cysteine protease	(Baron *et al.,*2020)
Spironolactone	Blocking the aldosterone dependent sodium potassium exchange site	Antihypertensive, Antiandrogenic, Potassium-sparing diuretic	COVID-19	By modulating ACE-2 expression	(Cadegiani *et al.,* 2020)
Sildenafil	By inhibiting PDE 5 enzyme	Vasodilator	COVID-19	Anti-inflammatory action	(Santamarina *et al.,* 2022)
Isoxazoline	Inhibition of GABA-gated chloride channel	Ectoparasitic drug	Human vector-borne diseases (phlebotomus, Zika, Malaria)	Hyper excitation and death of flea or tick	(Miglianico *et al.,* 2018)
Ronidazole	Inhibit DNA synthesis and induce DNA damage	Antiprotozoal drug	Clostridioides difficile	Bactericidal agent	(AbdelKhalek and Seleem, 2020)
Pyronaridine	Inhibition of DNA topoisomerase- 2 and induce DNA damage	Antimalarial drug	Echinococcus-granulosus	Kills echinococcus by stoppage of multiplication	(Li *et al.,* 2020)
Nitazoxanide	Interfering with the pyruvate ferredoxin oxidoreductase dependent electron transfer reaction in anaerobic energy metabolism	Antiparasitic drug	COVID-19	Activation of innate immune responses	(Mahmoud *et al.,* 2020)

CONCLUSION

Drug repositioning strategies are nowadays becoming more and more popular since they significantly minimise R & D costs, greater chances of success, shorter research time and lower investment risk. Use of in silico techniques and pharmacophore modeling strategies can further accelerate the process of drug repurposing. The creation of novel treatments based on already approved medications has recently taken on a new direction. Strategic drug repositioning has given innovation in identification of pharmacological compounds with unidentified therapeutic indications.

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