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A systematic review on Drug Re-profiling/Re-Purposing

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ABSTRACT *– Hardcore capability of drug repurposing has allowed rising population of diversified diseased patients to approach various medications with known safety profiles. In an ongoing scenario considering current pharmaceutical market, we have numerous drugs that are approved and repurposed by the U.S. Food and Drug Administration. Developing and bringing a novel drug molecule from the laboratory to a market requires a lot of investment in terms of money, efforts, and time. On the other hand, repurposing a drug holds the capability of bringing out best cures with harmless, ease availability and inexpensive quality. Sildenafil, Chloroquine, Metformin are some examples of repurposed drug used in multiple disease models. Despite numerous challenges, drug repurposing stood to be a core component to any comprehensive drug re-discovering strategies which has been planned to bring benefit to the patients suffering from a wide variety of dreadful ailments. In this review, we have discussed the various repurposed drugs in numerous types of cancer, deadly novel coronavirus (SARS-CoV-2) and some orphan diseases. This paper holds various examples of drugs which are still under clinical trial and have high chances of being approved as repurposed drugs benefitting humankind.*

Keywords: Drug repurposing, Strategies, COVID-19, Cancer, Orphan Diseases, Medicine, Pharmaceuticals

I. Introduction

Drug repurposing/drug repositioning/re-profiling/re-tasking can be defined as a process of finding a new pharmacological indication from different drugs which can be categorized as marketed, held back from being marketed for time being, pro-drugs, old, failed but can be used for therapeutic purposes[1]. It can be used as a blueprint which assist in spotting new uses for the drugs which are approved or are under investigation. This process is also known as Drug redirecting[2]. Several examples of repurposed drug are provided in the following part of this article to support written statements. Drugs like sildenafil and tadalafil prescribed to treat erectile dysfunction[3],[4] 8/29/2022 12:48:00 AMand thalidomide for leprotic patients[5] have shown huge success in health improvement. "Drug rescue" can be performed by various method, for example reverse docking[6]**.** It can be better understood by some drug examples like resveratrol[7]used in hyperoxia, ketamine used for multiple behavioral disorders, and others[8]. Well studied safety profiles of a drug molecule including various parameters like pharmacokinetics, pharmacodynamics, others help in reinforcing the new patient populations to a medication. This falls under the potential of Drug re-profiling[9]**.** Upcoming attestations assisting the novel use of pre-existing molecules have core of unexpected and focused findings[10]. The scholastic endowment towards development of numerous approaches is described in the figure of this paper as further discussed in proceeding sections. It assists in enabling systematic analysis of data for the generation of insights associated with drug repurposing[11]. It necessitates new remedial uses to discontinued, experimental drugs, approved, abandoned drugs. Drug repurposing also link itself with molecular docking in some aspects[12]. Evolution of existing drugs for avant grade targets is known as Drug re-tasking[13],[14]. Failure of certain drugs to be efficacious without any safety issue, in late-stage clinical trials, are explored further in new geographical markets[15]. New approaches to drug research and development are needed worldwide[16]. This led to the development of various systematic approaches with core virtuosity of pharma Industries in clinical development, in order to bring effective drugs to the patients[17]. Through drug repurposing traditional drug discovery can be complemented as it can alleviate the economical and time bound issues associated with novel drug discovery[18].

In the present scenario there is an urgent need to expand product pipelines with minimal risk issues. Various diseases which are threat to patient's health like cancer, newly evolved COVID-19, which is still evolving, and some orphan diseases allows expansion of drug repurposing necessary. Cancer is the abnormal growth of cells and is a major issue worldwide.

Global Statistics suggest that in year 2025 more than 20 million people will be diagnosed with cancer[19].

Era of SARS-CoV2 also known as COVID-19, with unclear mechanisms for infection is a dreadful and painful era experienced by human beings. Because of outnumbered death, drug repurposing is the only way to save people[20]**.** Well, cancer and COVID-19 are some of the familiar diseases when it comes to mechanism, infected patients, treatment, and death. Apart from other health degrading problems there are about 7000 rare diseases also called as orphan diseases. shockingly, only 6% of the rare diseases has treatment option available[21]. We have tried to briefly elaborate these problems in further parts of this paper. Drug repurposing do not always have positive outcomes but involves detailed investigation of a drug. We have tried to include few examples of repurposed drug in figure 2 of this paper with a brief elaboration in following sections.

Methodologies:

The information presented in this review is obtained from scientific literature databases such as PubMed, Google Scholar, Science-Direct, Scifinder, Used Key words are Drug repurposing, drug discovery, Cancer, orphan diseases, COVID-19, natural products, strategies, Food and Drug Administration. Approximately 500 units of literature are screened and information relevant to this review is considered.

A. De novo Drug discovery and Drug repurposing

De *novo* stands for new. Comparing drug re-profiling with traditional drug discovery program, a significant increase in time saving related to Research & Development has been observed. Finding a new drug molecule by this traditional approach is tedious and economically unsuitable[11].

The process of drug discovery can be divided into preclinical and clinical trials. Drug discovery process and in vivo testing of the drug in lab animals falls under preclinical trials[22]. These lab/industrial research, help scientist/clinicians/FDA in obtaining an idea of the expected mechanism of action along with potential side effects of that specific drug followed by its IC50. Sometimes pre-clinical trials can take several years for their completion[23],[24]. Phase I, II, and III requires healthy volunteers and unhealthy volunteers and numbers might vary based on the trial requirement for a particular disease for specific state of interest[15]. It is mandatory for drug approval process. For the drugs which are harmless and potent, data from preclinical and clinical trials can be compiled up in the form of new drug application (NDA). In phase IV, it is submitted to FDA for the approval for reviewal for monitoring and post-approval research[25]. Thus, in the process of new drug discovery, beginning to end might take around 17 years or more which is not same for drug repurposing[26]. *In silico* techniques involves the application of artificial intelligence with structure-based drug designing. For example: Ngidi et al. have explored silico drug repurposing using virtual screening technique revealing high potential drug against Fatty acid degradation protein D32 (FadD32) using 4 FDA approved drugs such as accolate, sorafenib, mefloquine and loperamide[27].

It has found to be used in the accelerated rate especially in recent years and might have towering scope in upcoming years[28]. Usually, to gain approval from FDA or European Medicines Agency re-purposed drug might require 3-12 years with 50–60% reduction in cost and should have records about clinical trial information[16],[29]. For a drug discovery 2 stages are mandatory, first in-silico screening and second stage involves both in-vitro and in-vivo screening. This helps in screening the proper targets for the drug with specificity and non-specificity of a drug molecule[30]. Experimental approaches can be considered more helpful in finding targets for the drugs as compared to computational approaches and can help find links between drugs and diseases in a reliable and credible order[31]. For an instance, Karuppasamy et al. have used in-silico approach to target MEK and PIM1 using two compounds DB012661 and DB07642, which can be the potential targets to explore in various cancers[32]. We have tried to explain the steps involved in drug repurposing with the help of figure 1.

B. Strategies for Drug repurposing

Going through various scientific literature we came to know that 30% of FDA approved biologics and drugs are repositioned drug[10]. Marked up developmental costs and static end results has encouraged advancement in interest focusing on drug repositioning especially in past few years[28]. Two major factors required for continuous progress in repurposing drugs includes bringing in new projects and compounds which possess potential for growth by designing varying strategies[33]. Different strategies concerning drug repurposing can be Target based, Knowledge based, Pathway based, Signature based, Phenotype based[34]. Target based involves high throughput screening, knowledge based involves information related to a drug molecule like chemical structure, side/adverse effect and others to speculate new and unrevealed targets[35], Pathways based involves the usage of various interactive network of signaling, metabolic and protein interaction pathway to establish right connection/link between disease or drug[15], Signature based for bringing in light the new off targets to approach inverse drug disease linking/connection profile, Target mechanism based involves the mechanism of discovering new mechanism of action of a drug[17], Phenotype

based have role in detecting genetic traits linked with diseases[36].

Strategies can be classified as On-target and off-target, in on-target the biological target of a drug is same with different disease like minoxidil[37]. Minoxidil was initially approved as hypotensive agent but being reported to induce hypertrichosis as side effect. It has been designed in the form of nano emulsion with a base of garlic oil and apple cider vinegar to enhance the delivery of the drug to produce better results[38] .Bimatoprost is also another example of the drug which has hair regrowth efficacy in androgenic alopecia and is worth exploring[39]. An off-target strategy, the pharmacological mechanism of a drug is unspecified thus involving innumerable drugs to act on new targets in hunt for therapeutic indications studying new effects like Aspirin[40]. Increasing diseases and disorders, have raised the bar for the requirement of new drugs. Although both computational approach and experimental approaches are related but if we must find a specific target then experimental approach is considered fruitful as compared to computational approach[41],[42]. Figure 3 of this paper represent computational approach for drug repurposing whereas numerous activities like phenotypic binding and various binding assays involved in experimental approach.

C. Various available drugs with Present status in Repositioning

Table 1 of this paper has a collection of various new drugs which are currently under clinical studies for drug repurposing studies. These all drugs were originally observed to serve a single purpose or other but are under clinical trial so that they can be repositioned and can serve to be more beneficial in diverse diseased conditions.

D. Pros and Cons

Everything has its own boon and bane so does the drug repurposing. Worth wise drug repurposing is explored in both pharmaceutical and biotech companies hence, non-stop progress is achieved. Drug repurposing provides quality with various other positive points. Risk associated with the failure is minored as focused drug goes through various trial phases and test for the approval with efficiency[43]. Repurposing a drug consumes less time as compared to the drug discovery process which needs around 17 years or more to be completed and might obtain both satisfactory and non-satisfactory outcomes[44]. From financial standpoint, drug repurposing seems to have much better outcome with less investments whereas drug discovery can demand high finance investment[2]**.** In drug re-purposing, risk associated with patients or volunteers participating in the study are reduced as various adverse and side effects of that drug has already been revealed with records. Hence, because of already established safety and pharmacokinetic profile risk and aftereffects can be further minimized[45]. To bring a drug into market may cost around few billions or millions[46]. In drug repositioning investors can save around 40% money in respect to the investment made in a drug discovery by picking shortest and fastest pathway of bringing a drug into market[22]. So far, we got to discuss advantages of drug repurposing but with advantages follow disadvantages as every coin has 2 sides. Hence, everything has its own positive and negative sides. Discussing access and commercial rights, companies can face some issues or challenges. Agreement between pharmaceutical companies is usually trust based[47]. Bias from institutional side or industrial side can be hindering for the establishment of product reputation in the market[48]. For a drug to be repurposed, we should be able to find the favorable and robust drug molecules so that it can assist in establishing the firm on the solid ground and not on the base made of sand[49]**.** At last, one of the major requirement and problem is financial investment, companies with low budget can't afford the expensive processes like drug repurposing.

E. Drug repurposing as a new emerging hope for several problems

1. a) New Hope for cancer

Cancer can be expounded as the abnormal cells division without any control and can invade nearby tissues which brings devastation to the health and the attacked body[50]. It can be metastatic and non-metastatic[51]. It can spread to other parts of the body through the blood and lymph systems[51]. It can be a Sarcoma, Leukemia, lymphoma, multiple myeloma, Central nervous system cancers (begin in the tissues of the brain and spinal cord) and others[25],[52]. Dreadful diseases like cancer necessitates the need for drug repurposing, so that an anti-cancer drug can be used in multiple cancers thus, with same drug we can provide new therapeutic approaches[53]. This strategy is not only cost effective but also have lifesaving tendency[54].

b) Repurposed natural drugs in cancer

Natural drugs are derived from natural sources. In this section we have tried to briefly focus on some drugs which have natural origin and can be used as anti-cancer agents after being repurposed. For an instance: Edible, and non- edible mushrooms can be used against cancers. To be more explicit, Mushroom belongs to fungus category and is shown to be effective against Histone deacetylases 7(HDACs). Histone

deacetylases (HDACs) are enzymes which play role in regulating gene expression. In-vivo studies demonstrated by Maruca et al. shows that ibotenic acid found in mushroom possess tendency to reduce cell viability on breast cancer cell lines[55]. Thymoquinone, a bioactive chemical constituent found in volatile oil of black seed herb (Nigella sativa, Ranunculaceae). This compound is known for its anti-inflammatory, anti-oxidative effect[56]

but now has been shown to possess anti-neoplastic effect both in-vivo and in-vitro[57]. Baicalein, a Chinese herbal medicine acts on multiple targets by binding and causing mismatches, thus induce double strand breakage, has been shown to be effective in colorectal adenocarcinoma cells[58]**.** Wortmannin derived from Penicillium funiculosum acts on multiple targets like myosin light chain kinase, phosphoinositide 3-kinase inhibits ataxia telangiectasia mutated and DNA dependent protein kinases, block double strand break repair, inhibits Fanconi anemia and is found to be effective in lung cancer, colorectal cancer ovarian cancer[59],[60]. Caffeine, a central nervous stimulant which usually reversibly block the action of adenosine on its receptor and now is found to inhibit ataxia telangiectasia mutated, ataxia telangiectasia and Rad3-related kinases and DNA dependent protein kinases, showing effectiveness in Bladder cancer, Non-Small-Cell Lung Cancer[59],[61]. Curcumin, an ayurvedic medicine suppresses nuclear factor-Kappa B, promote apoptosis and autophagy, inhibits Fanconi anemia and is effective against prostate cancer, melanoma, pancreatic cancer, renal cancer[62],[59], chloroquine against cancer stem cells trait in pre-malignant lesions[63]. Repurposing natural drugs makes cure easily available as these drugs are present in nature although sometimes difficult to synthesize but sometimes these can be better than synthetic drugs.

2.a) New hope for Newly emerging virus like COVID-19

COVID-19 is caused by a coronavirus called SARS-CoV-2[64]. A lot has been explored about COVID-19 and various companies have issued various drugs most of which are repurposed for an instance hydroxychloroquine[65], ivermectin, Remdesivir[66],[67]. Not so old time period when dreadful fear of this virus was at its peak because of its deadliness and uncountable deaths across countries, Re-exploring of the pre-approved FDA drugs was mandated to save lives[67],[68]. That's how we had vaccine breakthrough to deal with numerous on growing cases like Pfizer, Moderna[69]. Further, research is still going on and exploration never ends. In this part of the review paper, we have used table 2 to tabulate some drugs in positive hope for being repurposed.

b) Natural drugs repurposed for COVID-19

Various drugs of natural origin are under study, and some are approved because of urgent requirement in different parts of the world. For example: Chloroquine is an antimalarial drug, derived from Cinchona officinalis, Rubiaceae[70]. It has been approved in May 2020 from FDA to manage severe cases of COVID-19[66]. The main problem associated with this drug is their ability to cause heart related problems. MCG and Swiss firm Micelle technology are collaborating for a clinical trial to check the effectiveness of curcumin and artemisinin- based oral spray as a possible cure for COVID-19**.** Various natural compounds such as Celastrol[71], emetine, scutellarein, cepharanthine, caffeic acid derived from caffeine, tryptantherin, homoharringtone, griffithsin, quercetin has been shown to be effective in inhibiting Corona virus[72],[73]**.** Honey has been found to induce anti-viral activity and can prevent viral replications and is worth exploring further[66]**.**Plant molecules like Bismahanine, Coagulin N and K, Areca tannin A3, tannic acid, pseudo jervine, kamalachalcone C, Graecunin E, Taraxerol, stigmasterol, anisotin, adhatodine, beta-carotene, Eugenol, mangiferin, cis-Miyabenol C, Glycyrrhizic acid targets spike protein[66],[72] and are worth exploring cures for the treatment for COVID-19[74].There is increasing necessity and demand for the natural products in different parts of the world like Africa, Asia, USA exploring for fast, safe and better cure with minimal side effects to treat COVID-19 and spreading variants.

3.New Hope for Orphan Diseases

Orphan diseases are explicated as the rare diseases whose prevalence is very rare and are ignored thus, examples to be included can be Mad cow diseases[75], Fibro dysplasia ossificans progressiva (FOP) and adrenocortical carcinoma[76]. Drug repurposing in Orphan disease can be illustrated by some examples. First example of drug repurposing to cure orphan disease is sildenafil which was originally approved for Angina but got approved to be used in erectile dysfunction[3]. Second example involves Everolimus, initially used for preventing transplant rejection in solid organ but now approved by FDA for TSC related subependymal giant cell astrocytoma[17] ,cancer[77] and others[78]. Mechanism of action involves inhibition of mTOR. mTOR stands for mammalian target of rapamycin. It has been seen with the positive outcomes in facial angiofibroma[79], cardiac rhabdomyomas[80]. To make it more explainable we have introduced Figure 4 in this paper which briefly describes new incentives for repurposing drugs for orphan diseases.

4.Anti-cancer agents for COVID-19

In above section we have tried to briefly illustrate uses of some drugs that has been repurposed as anti-cancer and

against COVID-19. This section shows more of various anti-cancer agents which can be used as anti-COVID-19 drugs. For an instance: Tocilizumab, an anti-interleukin-6 receptor antibody has been shown to be used in Lung cancer[81], triple-negative breast cancer[82], cancer related cachexia[83]. According to documents initiated by F. Hoffmann-La Roche Ltd. Tocilizumab is shown to be studied in patients with severe cases of COVID-19 pneumonia[84]. Drug like Sarilumab, also known as REGN88 is a fully human anti-Interleukin 6R antibody which can be used as a single therapy agent or in combination study with drugs like aflibercept, a vascular endothelial growth factor blocker in breast cancer[85]. Studies promoted by Sanofi-Aventis Recherche & Développement has shown the use of sarilumab in hospitalized patients with COVID-19[86]. Monoclonal antibodies, an essential part of a cancer treatment can be used in an immunotherapy or targeted immunotherapy. Monoclonal antibodies like anakinra which is an Interleukin-1 antagonist and emapalumab, an anti-interferon gamma is used in anti-cancer treatment. It can be used as single or combination therapy agent to treat various cancers like meta static colorectal cancer[87], metastatic breast cancer[88], lung cancer[89], metastatic pancreatic ductal adenocarcinoma[90]. Swedish Orphan Biovitrum has shown intra-venous doses of anakinra and emapalumab to be effective in reducing hyperinflammation and respiratory difficulties in COVID-19 patients[86]. Other drugs which are given as the part of anti-cancer therapy like Remdesivir, Baricitinib has also been shown to be effective in COVID-19 patients 9[86].Above section of this part consist of example of anti-cancer drugs/ therapies which can be used in COVID-19, but this part briefly describes examples of some anti- COVID-19 drugs which can interact with anti-cancer agents and can reduce their efficiency. Firstly, Azithromycin, an anti-COVID-19 drug can interact with regorafenib, vinblastine leading to increased serum level of p-glycoprotein, increase toxicity and reduction in therapeutic effect[91]. Secondly, Chloroquine, an anti-COVID-19 agent can interact with doxorubicin, taxanes and trastuzumab leading to increase in plasma concentration, abnormality in conduction system[91]. Thirdly, Anakinra interacts with fluorouracil, durvalumab and can increase in immunosuppressive action and reduction in therapeutic effect[86]. Various other anti-COVID-19 drugs such as favipiravir, lopinavir, ritonavir, ribavirin, umifenovir can interact with enzalutamide, cytochromes and can reduce efficacy of anti-viral drugs[92].

II. Various Recommendations for Drug repositioning

There are uncountable opportunities accompanying numerous hurdles in the field of drug repositioning. Some of them are mentioned in above sections, and here we bring forth some crucial recommendations to bring a better understanding to the strategy of drug repurposing. Firstly, to have an integrative platform which can assist in data analysis[93]. User friendly formats which can be used by non-experts can boost the technological solution[94],[95],[96]. Secondly, pre-clinical and clinical data should be attainable in the improved fashion to avoid any confusion and hurdle from making progress[97]. Thirdly, uncomplicated, and quick access to clinical data for industry sponsored II-IV phases of clinical trial can allow research scholars to dig in and find out new opportunities in the field of drug repurposing[42],[98]. Fourth, to meet the uninterrupted need for the safety implications associated with repurposed drug to bring uncompromised outcome in favor of patient compliance[99]. Fifth and last, funding opportunities are required at most of the step involved in drug repurposing[100]. Funding plays a major role in the maintenance of resource libraries and various other technologies which assist the development of drug repurposing[46].

III. Future Prospects

Drug repurposing saves time, efforts and money when compared to drug discovery. With increasing demand of drugs, researchers and clinicians don't have 15-20 years to wait for a new drug discovery. Best recent example is COVID-19. Due to high number of deaths worldwide, increased heath devastation, drug repurposing is the best tool to be used and need further exploring to save various lives. Still, drug repurposing is the only hope for COVID-19 and its new variant in terms of finding immediate cure. Drug repurposing holds a strong hope and is the string holder for treating various infectious, deficiency, hereditary disease whether it's communicable or non-communicable. Hence, it's worth exploring.

IV. Conclusion

Some areas of drug repurposing are still unexplored to the core which means that there is still large room left for improvement. Various biological and networking system might be considered as important approaches to add benefits to drug repurposing process. For example, helping in unveiling a novel mechanism of action of a drug toward its target at molecular level/genetic level. Drug repurposing is a very systematic way of bringing importance to the innovations of drug discovery by exploring multifarious aspect of a molecule usage. Availability of various records and databases

assist in deep diving in the pool of hope and expertise in search of a new aspect which can be assigned to a drug, so that it can be titled as repurposed. Drug repositioning saves lot of money and time by cutting off R&D expenses and tedious journey by bringing a new purpose to a pre-existing drug. Continues efforts are required to make drug repurposing more efficient, rapid, and easy. Hence, it can be further improved to serve lives.

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