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DRUG REPURPOSING: SMART SOLUTION FOR CANCER

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ABSTRACT
The drug repurposing is the method of identifying the new medical use from the already existing or old or failed or investigational or FDA approved drug or pro-drug. This includes applicability of newly developed drugs to the treatment of diseases other than the drug of original or intended therapeutic use. Drug repurposing reduce the chances of risk and shorten the time duration to launch the drug in market at reduced the cost. In 2020, 10 million deaths were reported with the cancer, which is one of the leading cause of death across the globe. The aim of this study is to conduct a systematic review of drugs for which clinical trials for cancer repurposing are being conducted. The initial literature search on drugs repurposed for treatment of cancer was started with clinical trials registered in US based database (www.clinicaltrials.gov). Further literature search was conducted for individual drugs using various databases such as Pubmed and Google Scholar. The review emphasises the study of link between the drug and the mechanism by which its going to act for the disease and improve the recovery.The initial literature search retrieved seven drugs which are repurposed for the various cancers for instance metformin for prostate cancer, chemotherapy-induced peripheral neuropathy, ovarian cancer and leukemia, guanabenz for bone cancer, adalimumab for dupuytren's disease, chlorpromazine pill for malignant glimore, all trans retinoic acid for pancreatic adenocarcinoma, pitavastatin for breast cancer and mebendazole for liver cirrhosis. For clinical use of drugs for treatment of cancer further needs in-depth study integrating procedure and experimental strategies.

KEYWORDS:

1. INTRODUCTION
The drug repurposing is commonly known as the drug reprofiling, drug re-tasking, therapeutic switiching. It is defined as the process of identifying the new medical use from the already existing or old or failed or investigational or FDA approved drug or pro-drug and the applicability of newly developed drugs to the treatment of diseases other than the drug of original or intended therapeutic use.[1,2] The agents used for drug repurposing has well reported pharmacokinetics profile, safety dose and already passed the pre-clinical and clinical testing.[3,4] So the chances of risk is minimal and this can shorten the time duration to launch the drug in market as well as reduced the cost.[5,6] In 2020, 10 million deaths were reported with the cancer. It is leading cause of death across the globe. The lung cancer, colon and rectum cancer, liver cancer, stomach cancer and breast cancer are the most common cause of death.[7] The traditional approach of the drug development involves a lot of time and capital investment. The drug has to undergo various trials in order to evaluate the exact efficacy on human body. Thus the whole process involve 15 years to launch the drug in market for the use of cancer.[8] The aim of this study is to conduct a systematic review of drugs for which clinical trials for cancer repurposing are being conducted.

2. METHODOLOGY
The literature search on drugs repurposed for treatment of cancer was initiated with clinical trials registered in US based database (www.clinicaltrials.gov). Further literature search was conducted for individual drugs were registered for clinical trials in cancer using various databases such as Pubmed and Google Scholar. The filters such as drug name AND mechanism of action OR Drug side effects OR comparison with other drugs OR Machine deep learning CADD OR Artificial Intelligence OR pathways for repurposing were applied. Only articles with the preclinical and clinical data were included in this review.

3. RESULTS AND DISCUSSIONS
The initial search using US based clinical trial database reported 12 clinical trials being conducted for repurposing of drugs in cancer. These 12 clinical trials reported seven different drugs which are being evaluated

for cancer repurposing. Table 1 enlists name of drug, type of cancer and status of clinical trial. Out of these 12 clinical trials only 2 trials are being completed, 1 trial is being terminated and others are still ongoing in various stages. All the studies included were interventional studies.

To begin the research work, specific drugs were choose listed by clinicaltrial.gov by considering the fact that the drugs which are approved by the America is extensively studied with respect to all the parameters. Therefore, 'Cancer' and 'Repurposing' on the website of clinicaltrials.gov and 12 results were obtained. Further, the results were classified on the basis of status [Table1].

Table 1 Drugs registered for cancer repurposing clinical trials.

S. No.	Drug	Original use	Repurposed use	Allocation	Intervention model	Phase	Status
1.	Metformin	Diabetes	Prostate cancer	RCT	Parallel	2	Unknown
			CIPN	RCT	Parallel	2	Recruiting
			Ovarian Cancer	RCT	Single group	Early phase 1	Recruiting
			Leukemia	N/A	Single group	2	Not yet recruiting
2.	Guanabenz	Hypertension	Bone Cancer	N/A	Single group	Under study	Terminated
3.	Adalimumab	Rheumatoid arthritis	Dupuytren's disease	RCT	Parallel	2	Completed
4.	Chlorproma-zine pill	Antipsychotic	Malignant glimore	N/A	Single group	2	Recruiting
5.	All trans retinoic acid	Leukemia	Pancreatic Adenocarcinoma	RCT	Parallel	1	Completed
6.	Pitavastatin	Cholesterol	Breast Cancer	RCT	Parallel	2	Recruiting
7.	Mebendazole	Antihelmintics	Liver Cirrohosis	RCT	Parallel	N/A	Recruiting

CIPN: Chemotherapy-induced peripheral neuropathy; N/A: Not applicable; RCT: Randomised controlled trials

After the results were obtained Pubmed and Google Scholar was used to search the literature in which drug and repurposed indication. Total 1395 results were obtained (Figure 1). The articles related to mebendazole and liver cirrhosis were 351, pitavastatin for breast cancer 169, chlorpromazine and malignant glimore 8 articles, adalimumab and dupuytren disease 23, guanabenz for bone cancer 38, ATRA for pancreatic cancer 293, metformin and CIPN 24 articles, metformin and ovarian cancer and prostate cancer[gonad cancer] resulted 263 articles and metformin and white blood cells cancer resulted 226 articles. Further, to narrow down the data various filters were applied on the basis of type of article. The filters such as mechanism of action of drug, drug side effects, comparison with other drugs, machine deep learning CADD, AI, pathways of drug repurposing. By using the filter enlisted, the data were scrutinized and the number come down to 82. Only the article with the pre-clinical studies and clinical studies which can be cross referred with the clinical trials were preferred.

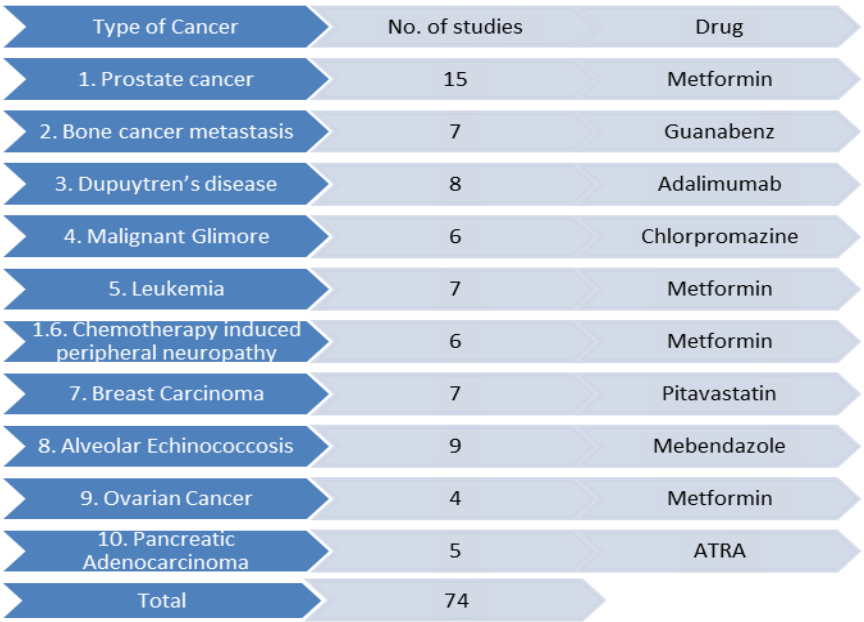

Figure 1: Studies reporting repurposing drugs for cancer.

3.1a Metformin and prostate cancer

The prevalence of prostate cancer is very high representing one-third of all new cancer cases each year. Prostate cancer is also reported as second ranked cause of cancer-related death in US.[9] Metformin, a biguanide is hallmark for its primary anti diabetic effect and is extensively researched.[10] In Europe, a plant named Galega officinalis (French lilac) was used to treat the diabetic condition whose key chemical active constituent was metformin.[11] Although the metformin is the hallmark of diabetes it's considered to be effective against the prostate cancer.[12] The recent studies have shifted the consideration of the drug as antidiabetic to anti-cancer drug and also proved to be effective.[13] The anti-cancer activity is highlighted by the diabetes specialists who observed the intake of metformin at lower dose for those patients who was at edge of developing prostate cancer.[14] Many studies have proved that the metformin markedly reduced cell migration and invasion in case of prostate cancer.[15] The effect of metformin was studied in the acidic environment which proved that it can successfully terminate.[16] The action is performed by the main two mechanisms. The first is the direct action which acts by directly acting on the tumour cell.[17] The effect is exerted by directly inhibiting the electron transport chain [ETC] of the mitochondria.[18,19] By inhibiting the ETC in mitochondria it's directly effecting the kerb cycle whose pathway is the lipid synthesis and beta oxidation which is important constituents of the metabolism of prostate cancer.[20] The insulin is important for the porsurvival effect with tumour cells and has high insulin receptor levels and metformin is able to lower the systemic insulin even in non-diabetic patients[21, 22] and subsequently leads to decrease in regulation of the phosphoinositide-3-kinase (PI3K) axis which is directly involved in the growth of the tumour cells.[23]

3.1b Leukemia and metformin

Leukemia is the result of transformation of the hematopoietic stem-progenitor cells [HSPCs]. The leukemia share its contribution of 2.8% among all cancer. The acute lymphoid leukemia [ALL] and acute myeloid leukemia [AML] results the proliferation of immature leukemic blasts which is stops at different stages of differentiation.[24,25] The metformin is the first line drug for the treatment of diabetes. The drug is the biguanide derivative which has proved its efficiency to act as the anti-cancer drug.[26,27] The drug stimulates the AMPK which causes the inhibition of mTOR which ultimately boost the autophagic response and regulates the disease progress. It's evident from the experiment conducted to study the cell growth in stem cells by using the metformin. The drug proved its ability to inhibit the growth of cells by stopping the cell cycle and induce the apoptosis which ultimately surged the cytotoxicity effect within the cell lines. Many laboratory reports suggested that the sensitivity of the tumour cells has increased during the chemotherapy when metformin is prescribed and apoptosis was detected in the cancer cell lines. Thus, the metformin proves its ability to be repurposed for the leukemia.[28-30]

3.1c Metformin and CIPN

Many neoplastic agents has the ability of double edge sword. They can prevent the cause but also induce side effects. The chemotherapy induced peripheral neuropathy is one of the major side effects which is faced by many patients.[31] The 30-40% of patients receiving chemotherapy face the peripheral neuropathy.[32] The intensity of degeneration depends upon the factors of dose administration during the therapy and the patient disease. The disease progress shows the symptoms of loss of sensitivity and pain in feet and hands. The CIPN is partially reversible and can damage the peripheral nervous system.[33] The experimental studies were conducted in the animal model using mice by inducing the peripheral neuropathy. The metformin was choosen to understand the effect for the CIPN. The metformin is the drug which is prescribed for the type – II diabetes. The drug has demonstrate its ability to act as anticancer drug . The cisplatin was responsible of increasing the sensational mechanism however the metformin prevents the sensational stimulation. The mechanism by which metformin act in case of CPIN is not clear but it likely to act by the mitochondria dependent cellular metabolism. The metformin act by increasing the activity of enzyme during mitochondrial fatty acid oxidation.[34,35] Many research was conducted on metformin which proved its efficacy to potentially reduce the loss due to peripheral nerve endings. This proves that the metformin has the potential activity to control CIPN.[36]

3.1d Metformin and Ovarian cancer

Ovarian cancer is fifth ranked cause of death due to cancer among women. It is projected by American Society of Cancer that in 2021, America will face 21,410 new cases of ovarian cancer and 13,770 women will die because of the ovarian cancer. The cancer is more prevalent in white women as compare to the African-American. The major cases are reported from the women of 63 years or more.[37] Metformin, the biguanide is well known recognised for its antidiabetic property. In various in-vivo and in-vitro experiments it has proven its anti-neoplastic activity. So it has gained popularity in the modern world of repurposing.[38] The in-vivo experiment on animal model, mice was conducted using the metformin to study the effect and mechanism. The researchers noticed that the treatment with metformin diminish the tumor burden. The researchers noticed that AMPK is activated by metformin and downregulate the pathway. This ultimately cause the antineoplastic effect of metformin.[39] The case control study was conducted with the motive to identify the effect of metformin in the ovarian cancer patients. The results were compared with the patients with ovarian cancer who did not received the metformin during the treatment. The results demonstrate the sign of improvement with metformin as the survival of the patient become better.[40] The study was conducted

in which the 341 ovarian cancer patients were studied, among which only 16 were suffering from type II diabetes and use metformin whereas, 28 despite being diabetic does not take metformin on daily basis and 297 were non- diabetic. The interesting thing to note that all the patients received the same anti-cancer therapy and the patients who were receiving metformin along with chemotherapy has better outcome as they reported the highest rate of survival.[41]

3.2 Guanabenz acetate and bone cancer metastasis

Guanabenz is well known for its action to control the elevated blood pressure by directly acting as central alpha 2-adrenoreceptor agonist and approved by FDA.[42] The drug is repurposed for its action on eukaryotic translation initation factor 2 alpha[elF2α]. during the time of nutrition deficiency, cell have to respond to the stress in order to preserve the energy. This gives the opportunity to tumor to grow.[43] So guanabenz acetate is the inhibitor of the GADD34 directly suppress the stress of the endoplasmic reticulum [ER] by inhibiting the elF2α which helps in the phosphorylation.[44] This causing the decrease in the functioning of elF2α of the Ras-related C3 or Rac1 pathway which increase the functioning of the activating transcription factor 4 [ATF4] which is one of the important factor to play a role in the osteoclastogenesis and downregulate the activation of the nuclear factor of activation T-cells, cytoplasmic 1 [NFATc1] which is a transcription factor that plays a major role in osteoclastogenesis.[45,46] Scholars conducted the research and found that the stress leads to activation of elF2α. The study investigate that the effect in the macrophages is observed particularly with guanabenz which induce anti-inflammatory response and reduce the expression of Egr2 and Csf2.[47] The study conducted by the Kazunori Hamamura, Nancy Tanjung, Hiroki Yokota evaluated that through regulation of ATF4 and NFATc1 the osteoclastogenesis is inhibited by the gunanobenz.[48]

3.3 Adalimumab and Dupuytren's disease

The dupuytren's disease targets 7% population in America. It's the one of the most common fibroproliferative disorder.[49] Because of uncontrolled activity of myofibroblast causes the fibrosis which is the hallmark of clinical character. The condition causes the irreversible curl of fingers towards the palm. The myofibroblast is the key element which is responsible for the matrix deposition and contraction in Dupuytren's disease.[50] Nanchahal and his team analysed the pathogenesis of the disease using human tissue. The study was performed to find the molecular and cellular mechanism behind the myofibroblasts, the substance responsible for the production and contraction of the matrix due to polymerization of intracellular intracellular α-smooth muscle actin.[51] The study reviled that the TNF is pivotal in converting the normal fibroblasts into the myofibroblasts and based on this evidence the clinical trials were planned with the anti-TNF therapy.[52] So the anti-TNF drugs were selected in which adalimunab was the potent drug to undergo the clinical trials. Adalimunab is the recombinant antibody. The human IgG1 monoclonal antibody comprises of light and heavy chain variable regions which is quite similar to naturally occurring human IgG1.[53] The original indication is used for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease. The adalimunab has long half-life of 10–20 days. Adalimumab act by binding to TNF-α leads to block its interaction with the TNF receptor p55 and p75 and neutralize the action of cytokine.[54,55] The study reported phase 2a randomised trial on the disease conducted on 138 patients treated by 40 mg adalimumab. This study reported adalimumab to be effective for the treatment. The adalimumab being an anti-tumour necrosing factor and proved to reduce the α-SMA and type I procollagen proteins.[56] Thus, the adalimunab can be nominated for the repurposing for the dupuytren's disease.

3.4 Chlorpromazine and Malignant Glimore

Malignant Glimore is an invasive brain tumour which is most common in adults with the average lifetime left to the adult is 2 years to live. The infilteration nature of the disease it affect the local brain cells and the surgery is not the ideal option for the same. If we consider the therapeutic option the, CNS being the highly secured area and not all the drugs have the capacity to act so the option reduce to the few drugs or the new therapeutic agents. The new therapy is the time and money consuming hence the drug repurposing emerged out to be the best option for medical staff to treat the disease.[57] The antipsychotic is choosen as the option because it share the property to penetrate into the blood brain barrier as well as the toxicity profile is known. Variety of pre-clinical tests were conducted and they proved their efficiency. The chlorpromazine is used to treat the psychiatric disorder from last 60 years. Because the CPZ has the ability to cut down the activity of mTOR so its selected for repurpose for glimore malignant. The CPZ reported its antineoplastic effect in many cancers and is repurposed for the same. The mechanism behind the action is still not understood. The proposed mechanism is that CPZ interfere and change the expression of the proteins which plays the significant role in cell cycle and the process of mitochondria. It is suspected that CPZ induces the cytotoxicity in the cell lines of U-87 MG glioma cells by inhibiting PI3K/AKT/ mTOR pathway by causing the autophagic death. In association with this, the CPZ prevents the cell entering the G2 phase of mitosis. CPZ act by inhibiting the enzyme of miotic kinase KSP/Eg5 which plays an important role in the division of the cell during its miototic phase. This causes the defective spindle division whichis monopolar and the defective division.[58,59,60] The experimental studies conducted demonstrated that the CPZ is effective in in-vitro studies against the disease when the CPZ is combined with the temozolomide both drugs have the capacity to reduce the cloning capacity and induce the cell death in the in-vitro study for GBM cell lines assayed. Because of the ability to demonstrate the

synergistic effect and inhibit the growth of GBM in cell lines the drug is selected for the repurposing.[61,62]

3.5 Pitavastatin and breast carcinoma

Stains are widely recognised for its ability to inhibit the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) which is involved in the biosynthesis pathway of choleaterol biosynthesis. So its prescribed in the treatment of hypercholesterolemia.[63] But now due to extensive research the category became the candidate for the repurposed drug for cancer. Many In-vitro and in-vivo studies noted that it exerts the apoptosis effect in the various cell lines including the result of breast cancer.[64] The breast carcinoma is the type of cancer particularly seen in the women and its chances increase with the increase in the age.[65] Pitavastatin which was created by Nissan Chemical Industries Ltd Tokyo, Japan and later developed by Koya Co. Ltd, Tokyo, Japan (the drug approved by FDA is now being studied for the repurposing for the breast cancer. The drug belongs to the category of the statin but has the potent pharmacokinetic profile hence elected for the breast cancer experiment. In case of breast cancer inflammatory cells plays significant role in the progression of breast carcinoma.[66] In the patients of breast cancer, the serum level of IL-6 is increases.[67] Further the inflammatory effect is due the IL-6 which is the tumor promoting as well as inhibitory effects thus known as pleuiotropic cytokine. So pitavastatin inhibit the gene expression activity of NF-κB by justifying With the Rho theory the interleikin -6 is inbihited which is indirectly involved in the production of the NF-κB. Pitavastatin at the concentration of 10 μMexerct the anti-inflammatory role in monocytic THP-1 cells through RhoA-dependent pathway. Thus the pitavastatin is considered as the potent candidate for the breast cancer and is under clinical trials.[68,69]

3.6 Mebendazole and alveolar echinococcosis

The benzimidazole is famous for its anthelmintic property in which mebendazole is the candidate as broad-spectrum drug. The drug was developed in the Belgium by Janssen Pharmaceutical, Research Laboratory, Beerse.[70] Liver cirrhosis is caused by the major injury of liver mechanically which could lead to necro-inflammation as well as fibrogenesis.[71] In the developing countries liver cirrhosis is the major health issue as it's the most common reason of death in Europe. According to the staistics, each year 5500 liver transplants surgeries are performed in Europe.[72] The antineoplastic activity of mebendazole was noticed when the experimental study was conducted, in which the efficiency of mebendazole was determined using the animal model of rat in which liver cirrhosis was induced by using the CCl4. The animal model revealed the result in decline in total collagen content and biosynthesis[73] In addition to this the other evidence proved the potency of drug against the alveolar echinococcosis. The alveolar echinococcosis is an intestinal parasite which when invade in liver cause malignant tumour.[74] The mice suffering from alveolar echinococcosis was experimented using the mebendazole which proved the chemolysis of the parasite.[75] The long-term treatment of mebendazole in animal model inhibit division which is essential for the survival of host. The treatment has the parasitotic effect on host.[76] Moreover, the case was reported in Switzerland where the patient suffering from the alveolar echinococcosis was treated for 13 years clinically with mebendazole and proved it as curative effect.[77] The studies proved that in humans the long-term treatment of methimazole for AE has ramified the survival rate as well as has lethal effect on parasite division.[78]

3.7 ATRA and Pancreatic Adenocarcinoma

The All-trans retinoic acid (ATRA) is the potential metabolite of the vitamin A. The major function is to help in cell growth and development of the cells.[79] It has potential effect as antineoplastic and use in chemotherapy. The compound demonstrated anti-cancer property in a number of cancer.[80] The ATRA is originally used in treatment of leukemia but is repurposed for the Pancreatic Adenocarcinoma. It is interesting to note that the studies of epidemiological demonstrate the relation of ATRA has the beneficial effect in Pancreatic Adenocarcinoma.[81] During the pre-clinical trial, ATRA with the standard drug combination was use in the model to target pancreatic stellate cells. The drug has the potential to suppress the growth of pancreatic ductal adenocarcinoma. The researchers use the orthotropic mouse model of pancreatic cancer to identify the role in PAK1 in response to tumour response. The PF-3758309 or genetic knockout causes the inhibition of PAK1 causes the upregulation of intra tumoral infiltration of CD3+ lymphocytes and splenic CD3+ and CD8+ lymphocytes. The combination of PF-3758309 and gemcitabine synergistically inhibited PDA cell growth in vitro and in vivo. The fact reviles the involvement of PAK1 have potential role in antitumor property.[82]

4 Future Perspectives and conclusions

The drug repurposing has a long history but most of which is based on discovery of drug molecules through chance observations. Currently, this drug repurposing is one the most promising measures for developing latest therapies mostly based on existing or approved medicines. The process of repurposing is a logical means of looking into more innovative ways of using the drug molecules already approved for use in different medical conditions.

The drug repurposing approach offers vital reduction in R&D prices, larger possibilities of success, shorter analysis time and lower investment risk. Considering all these benfits this approach is gaining a lot of popularity in pharmaceutical sector. This approach offers exponential benefits in terms cost, resources and time saving for scientists, R&D section of pharmaceutical companies and customers. The utilization of in-silico

techniques along with structure-based drug style (SBDD) and pharmacophore modelling methods and artificial technology will hasten the process of drug purposing. As these techniques are helpful in establishing the mechanism of action of drugs through investigating metabolic and signalling pathways, target specific mechanisms, gene expression profiling for many diseases including genetic disorders. Advances in genetics has led to availability of genomic and transcriptomic information which can be utilised further to uncover novel mechanisms of actions by drug target interactions at genetic and molecular level.

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