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DRUG REPURPOSING IN NATURAL PRODUCTS AND DERIVED COMPOUNDS: A PROMISING APPROACH

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Abstract

Drug repositioning is a pharmaceutical product technology flow that offers benefits to drug manufacturers along with patient-safer medicines. Several medications were repositioned effectively for targeting different indications. The pharmaceutical re-profiling is done with the main objective to establish strategies by using approved drugs and rejected drug candidates in the diagnosis of new diseases.Drug repositioning includes safety and adverse effects evidence from clinical trials that are already available and becoming increasingly attractive as it requires the use of less-risk substances such as already approved drugs, marketed products, discontinued drugs, shelved, and trial drugs with significantly lower average processing cost. There are many benefits of this strategy which include the shortened timeframe of drug development, best chances of completing Phase II or Phase III clinical trials, efficient design of dosage form and, of course, it will add value for products belonging to a business or laboratory inventory. Natural drug products are in use from ancient times which are promising candidates to be repurposed for curing diseases. In this review report, we presented an overview of the repurposing of herbal drug products including the process of current scenario of drug discovery and the opportunities and challenges which occur during the re-profiling of a natural drug product. It also summarises the subject of those herbal drug products on which drug repurposing is already done.

Keywords: *Challenges, herbal; natural products; repurposing; repositioning*

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1.Introduction

For thousands of years, nature has been an important source of pharmaceutical goods, with many valuable medicines being produced from plant sources. In general, plants have formed the basis for complex ancient pharmaceutical schemes, with earliest records, dated from about 2600 BCE, recording the uses in Mesopotamia of about 1000 plant-derived substances[1]. Natural products composed of a large proportion of existing drug agents in every field[2].

In the process of drug discovery, drug repositioning is anemerging area that discovers potential therapeutic targets for existing drugs. Drug repurposing is the process of reprofiling the existing drug for new use and it is gaining very much popularity these days,due to safety and pharmacokinetic studies for the repurposed drug molecule is already being conducted and it will take less time to purpose a drug for a disease and decrease overall cost [3] of the expensive drug development process.In short, with the help of drug repurposing process an existing drug can be developed for its different therapeutic use.

2. Approaches for drug repurposing

A product repurposing approach typically consists of three phases before the target medication is progressed through the development pipeline. These phases include:

I. Discovery of a candidate molecule for a specific purpose
II. Mechanistic analysis of the drug impact in preclinical models
III. Assessment of effectiveness in clinical trials in phase II.

With the rapid development of biology microarray techniques, various databases on drug and disease information such as DrugBank, ChemBank, OMIM, KEGG, and Pubmed have appeared and massive genomic databases such as MIPS, PDB, GEO, and GenBank have been created. This knowledge and data further fostered the rapid development of a variety of new computational approaches with significantly lower costs as well as fewer barriers(Xue et al., 2018). In this paper we gathered and compiled the recent information about the studies pertaining to the drug repurposing of the natural products and derived compounds.

3. Methodology

We tried to gather and record dispersed information from different sources relevant to natural product drug discovery in this study. A systematic literature search was conducted

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from various databases like PubMed, Science Direct, Google Scholar and Scopus to get knowledge about drug repurposing of different drugs on the basis of various keywords such as Repurposing, Repurposing + Natural, Repurposing + Plant, Repositioning, Repositioning + Natural, Repositioning + Plant and number of Web hits from different databases was recorded using Boolean information retrieval system utilizing keyword of the bioactive compounds with "AND" followed by “Repurposing” or “Repositioning” The detailed search strategy is presented in table 1. The last date of search was October 23, 2019.

Table 1: Table showing the search strategy for literature search on drug repurposing of bioactive natural products

S.No.	Search Engine	Search Keywords	Hits
1.	Pubmed	Repurposing	2,970
2.	Pubmed	Repurposing + Natural	167
3.	Pubmed	Repurposing + Plant	64
4.	Pubmed	Repositioning	12,261
5.	Pubmed	Repositioning + Natural	297
6.	Pubmed	Repositioning + Plant	140
7.	Pubmed	Drug Repositioning + Plant	57
8.	Google Scholar	Repurposing	92,200
9.	Google Scholar	Repurposing + Natural	40,900
10.	Google Scholar	Repurposing + Plant	17,200
11.	Google Scholar	Repositioning	4,33,000
12.	Google Scholar	Repositioning + Natural	1,48,000
13.	Google Scholar	Repositioning + Plant	51,100
14.	Google Scholar	Drug Repositioning + Plant	18,100
15.	Science Direct	Repurposing	9,240
16.	Science Direct	Repurposing + Natural	3,961
17.	Science Direct	Repurposing + Plant	1,893
18.	Science Direct	Repositioning	70,984

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19.	Science Direct	Repositioning + Natural	16,837
20.	Science Direct	Repositioning + Plant	5,491
21.	Science Direct	Drug Repositioning + Plant	1,426
22.	Scopus	Repurposing	4,504
23.	Scopus	Repurposing + Natural	231
24.	Scopus	Repurposing + Plant	95
25.	Scopus	Repositioning	18,948
26.	Scopus	Repositioning + Natural	486
27.	Scopus	Repositioning + Plant	219
28.	Scopus	Drug Repositioning + Plant	71

The number of web hits on Pubmed and Scopus was found to be 2,970 and 4,504 correspondingly on searching the keyword “repurposing” while it was 92,200 on Google scholar and 9240 on Science direct. While searching the keyword “Repurposing + Natural” there was a drastic decrease in web hits that is 167, 231, 40,900 and 3,961 on Pubmed, Scopus, Google Scholar, and Science Direct respectively.In addition to this, the web hits were 12,261, 18,948, 4,33,000 and 70,984 on searching the keyword “Repositioning” and number of hits were found to be 297, 486, 1,48,000 and 16,837 on searching the keyword “Repositioning + Natural” on Pubmed, Scopus, Google Scholar, and Science Direct respectively.

4. Results and Outcome

This study is based on the significance of drug repurposing in natural products and derived compounds. Drug repurposing is an emerging method used in pharmaceutical industries to explore the existing drug candidates for novel therapeutic uses. This first part of the literature-based study is done to explore the possible potential of drug repurposing methods in natural products and natural products derived compounds as there is no comprehensive review is available till date on drug repurposing of natural products to the best of our knowledge.

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One of the most complex scientific fields of contemporary drug discovery encompasses several different scientific disciplines. Drug discovery has been a target- and mechanism-agnostic approach for many years, which was often fuelled by serendipity dependent on ethnobotanical expertise[4].Using the high throughput screening (HTS) method, a large number of compounds screened with the discovered target, synthesized through combinatorial chemistry, are named hits for their biological activity. Quantitative Structural Activity Relationships (QSAR) arealso of immense significance in the discovery of new drug candidates or analogues [5]. The specific measures in finding new drugs for specific diseases are presented in figure 1.

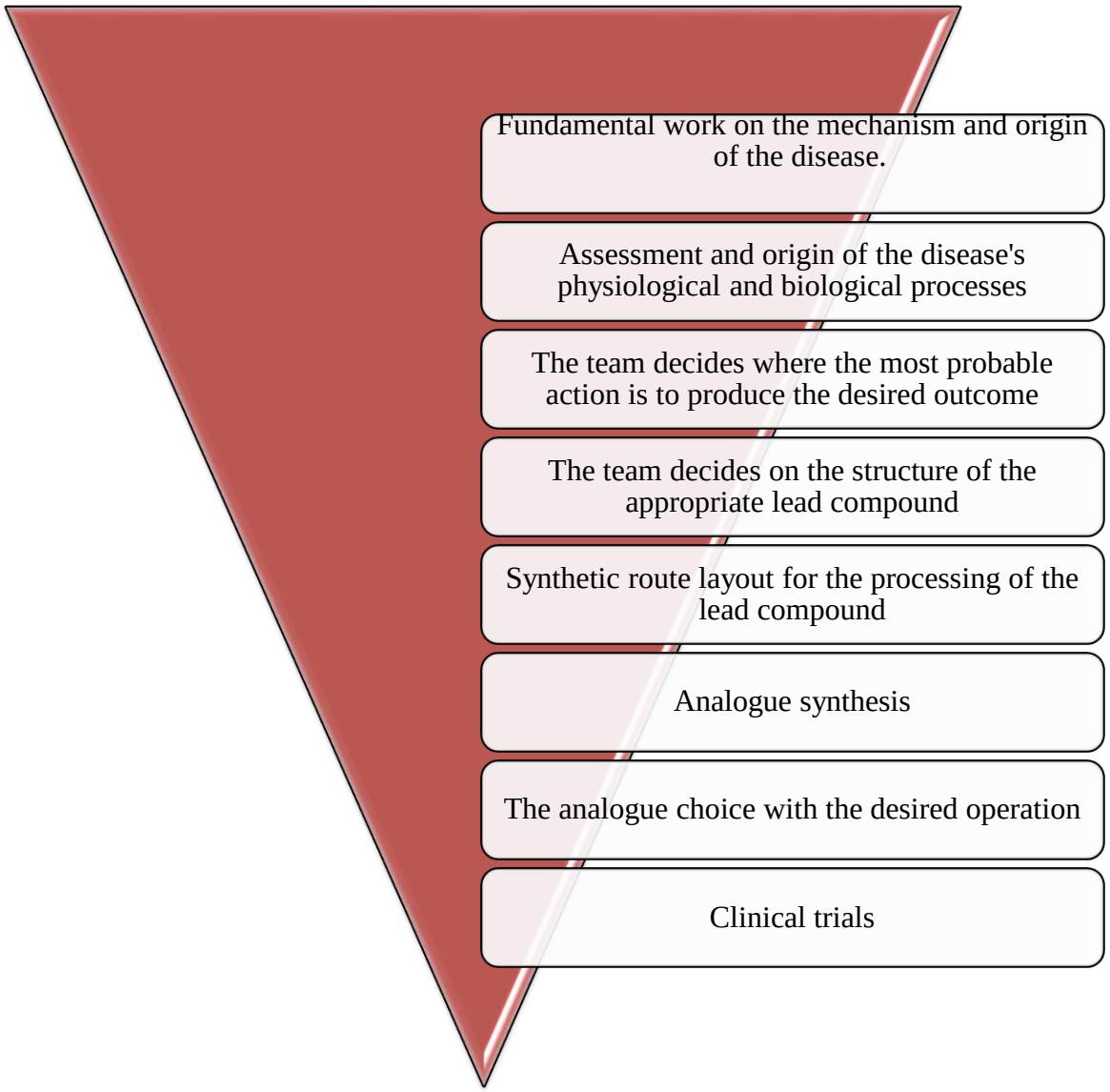

Figure 1: Specific measures in finding new drugs for specific diseases

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Drug repurposing is a safe and successful way of accelerating the processes of drug discovery and development compared to de novo approaches to drug discovery. Drug repurposing uses drugs and medicines licensed by the FDA that failed in clinical trials with detailed information on possible safety, structure, and pharmacology[6].Sildenafil for angina was repurposed for erectile dysfunction in the mid-2000s and thalidomide was also repositioned to multiple myeloma for morning sickness. The success created a great interest in repurposing, which resulted in many repurposing focused start-ups being formed[7]. After development of the repositioning hypothesis clinical tests of the suggested methods, a commercially feasible target material profile could develop for a candidate in search of finding compounds with the required characteristics can done. This search also involves a public review and subscription-based sources of information. Pharmaceutical repositioning removes most countries'price bottlenecks. Developing a new product using a pharmaceutical repositioning technique costs just $1.6 billion, although the conventional approach costs $12 billion.

In the United States, only 20 to 30 new chemical companies are accepted annually, and each effective new chemical entities (NCE) (NCEs: drugs not containing a previously approved active ingredient) takes an estimate of US$ 1.78 billion and 13.5 years from discovery to launch. Although measurements of the expense of drug discovery differ, it is important to note that these figures still do not compensate for product failures. Since only 11 percent of the drugs investigated in clinical trials are finally approved, the actual cost of drug development is significantly higher than the estimates published[8].

Typical drug development approaches usually involve five phases: preclinical or testing, security evaluation, clinical research, FDA approval, and post-market compliance surveillance by the FDA. In product repositioning, however, there are only four steps: compound recognition, compound acquisition, production, and post-market security monitoring of the FDA. Due to the rapid growth of knowledge in bioinformatics and big data in biology, drug repositioning significantly reduces the time cost of the drug development process. Researchers need only 1-2 years to identify new targets for drugs and on average 8 years to develop a repositioned drug. In addition, the investment required for drug repositioning in research and development is lower than that required for traditional strategies[9].

4.1. Drug repurposing in natural products: opportunities

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Over thousands of years, bioactive natural products have been used, with instances from the beginning of recorded history[10]. Preclinical methods used to identify potential candidates for medications include target-based sampling, phenotypic screening, natural product alteration, and physiological approaches[11]. The In-silico ethnopharmacology approach could be used to elucidate the molecular basis of the therapeutic activity of Ayurvedic medicinal plants and drug repurposing[12].

Due to the low toxicity and synergistic effect of herbal medicines they are a very attractive source of new active compounds. Traditional herbal medicines have been used for a long time, including various natural compounds found in plants.Despite many medication repositioning trials, most of them concentrated on identifying possible signs for existing drugs rather than herbal compounds[13].Repurposing strategy offers various advantages over the development of a given indication of a completely new drug. First and perhaps most prominent, the risk of failure is lower as the repurposed drug has already been found to be sufficiently safe in preclinical models and humans if early-stage studies have been completed with less probability of failure, at least from a safety point of view. Second, fewer investment is needed, although this will vary significantly based on the candidate's stage and development process. Third, the time frame of drug development may be shortened, as most of the preclinical analysis, risk evaluation and, in some instances; the design of formulation will have already been achieved[14].

Plant-based systems continue to play a vital role in medicine, and there have been detailed evidence of their use by different cultures. In 1985, the World Health Organization (WHO) reported that about 65% of the world's population depended primarily on herbal pharmaceutical products for their primary health care, although plant products did play a significant role, and so far more indirect role in the health care systems of the rest of the population, mainly residing in developed countries[1].

Traditional medicinal plants have a higher structural diversity, highly bioavailable and because of their low toxicity, herbal medicines are a very attractive source of new active compounds in the process of drug discovery.Approximately 420,000 plant species are currently estimated to occur in nature and more than 248,000 higher plant species have been reported, and medicinal properties are recognized from these 12,000crops. Moreover, from a pharmacological and phytochemical point of view, less than 10% of all plants are examined.

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In some cases, without any alteration, a natural product like taxol can become a medical product[15, 23].

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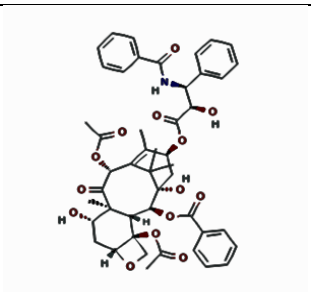
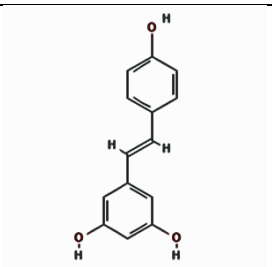
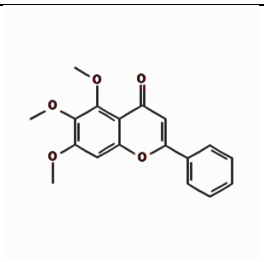
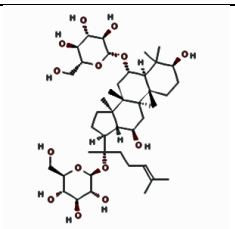
4.2 Drugs on which repurposing studies are done so far

After the extensive literature search it has been observed that efforts were made for repurposing of many of the natural compounds and derived products. The details of the natural products-based drugs on which repurposing studies were done are presented in **Table 2.**

Table 2. Details of the natural products-based drugs on which repurposing studies were done

S.N	Name of the natural products	Chemical structure	Disease/Studied for	Reference
1.	Taxol		Breast cancer	[16]
2.	Resveratrol		Anticancer	[17]
3.	Mosloflavone/5,6,7-trimethoxyflavone-resveratrol		Anti-inflammatory (MAPK inhibitor)	[18]
4.	Ginsenoside		β-hemoglobinopathies	[19]

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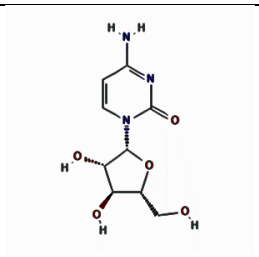
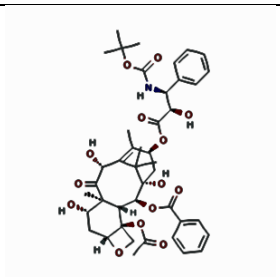
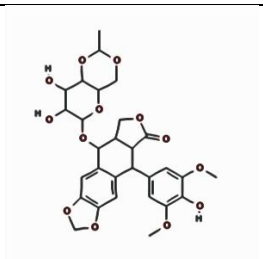
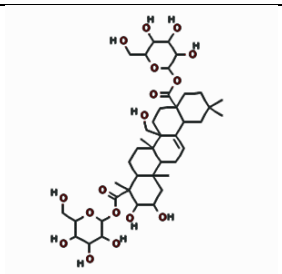
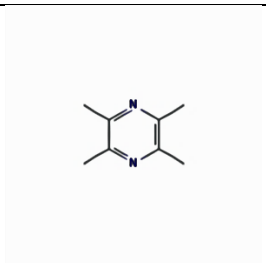
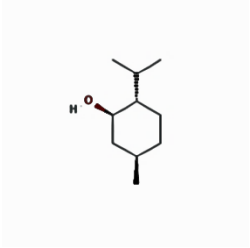
5.	Cytarabine		Lymphoma	[20]
6.	Docetaxel		Anticancer	[21]
7.	Etoposide		Breast cancer	[22]
8.	Ginseng		Topoisomerase I inhibitor	[23]
9.	Tetramethylpyrazine		Postoperative Tissue Adhesion	[24]
10.	L-Menthol		Cancer therapeutics	[25]

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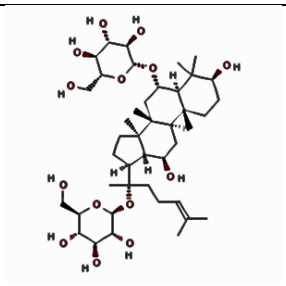
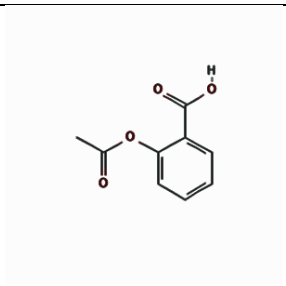
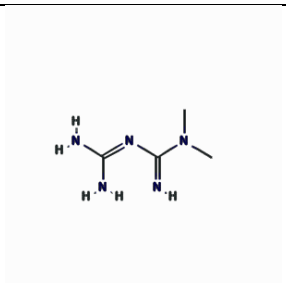
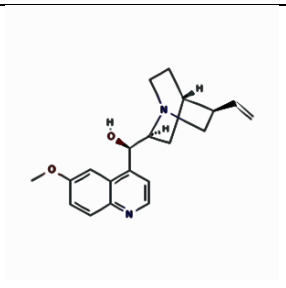
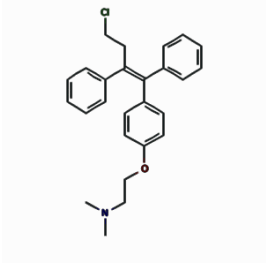
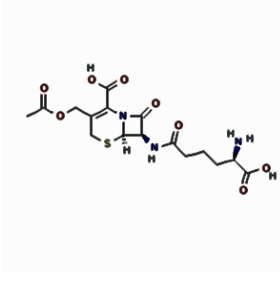
11.	Ginsenoside		Microbial enzyme.	[26]
12.	Aspirin		Pancreatic cancer	[27]
13.	Metformin		Tuberculosis	[28]
14.	Quinine		Against dengue virus	[29]
15.	Toremifene		Oral Bacterial Infections	[30]
16.	Cephalosporin		Pro-senescent radiosensitizers	[31]

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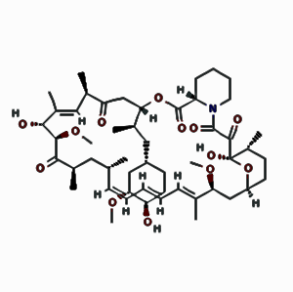
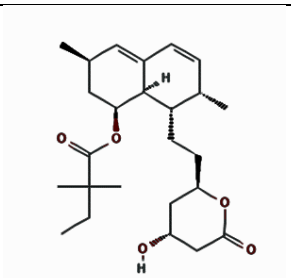
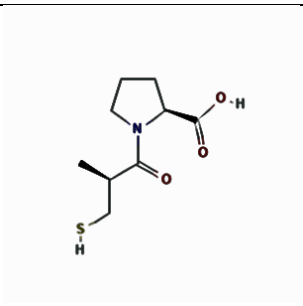
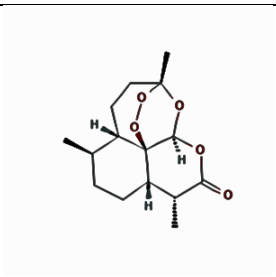
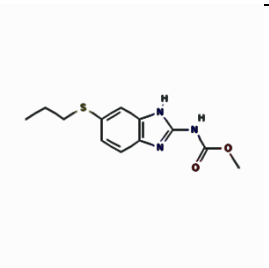
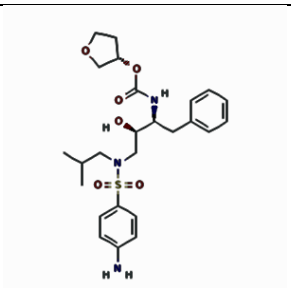
17.	Sirolimus		Inflammatory Dilated Cardiomyopathy	[32]
18.	Simvastatin		Prostate Cancer Mortality	[33]
19.	L-Captopril		Inhibitor of DapE enzyme	[34]
20.	Artemisinin		Anti-mycobacterial	[35]
21.	Albendazole		Chemotherapeutic agent	[36]
22.	Amprenavir		Extracellular signal-regulated kinase-2 inhibitor	[37]

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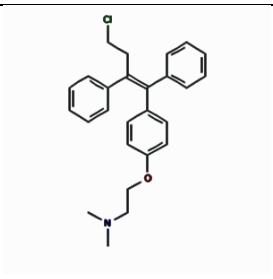
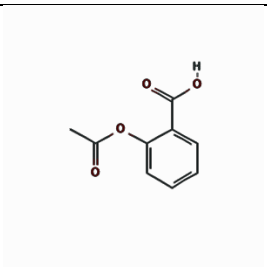
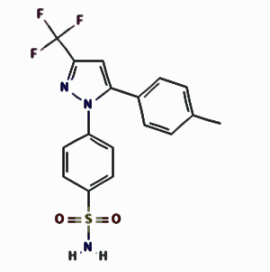
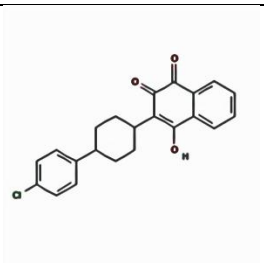
23.	Toremifene		Oral Bacterial Infections	[38]
24.	Aspirin		Anti-Cryptococcus	[39]
25.	Celecoxib		Topical antimicrobial agent	[40]
26.	Atovaquone		Cancer stem cells.	[41]

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4.8 Challengesin drug repurposing of natural products

The obstacles around drug discovery arise from the commercial and regulatory levels. However, a molecule requires much more than just possessing strong pharmacological features to be commercially viable. If the intellectual property around the compound are expired or near to be expired, there may be no reason to do work on an alternate meaning, as there would be no benefit from it[42].Just like any other discovery, a repositioning initiative needs a capital investment, and it is extremely difficult to convince management to spend in properties that were previously unsuccessful[43].

Timeline achievement: repurposing old drugs for novel indication requires several factors such as dosing scheme and route of administration in order to achieve the significant benefit for the new indication[6].Pharmaceutical repurposing targets at different groups of individuals with specific medical disorders, so it is important to predict potential adverse reactions, allowing a thorough analysis of each outcome [6].

5. Conclusion and future directions

Repurposing is considered as one of the most promising solutions to develop drugs for different diseases in less time than developing a new molecule. Several initiatives are taken to encourage product recycling and repurposing and it offers useful and valuable opportunities to pharmaceutical companies and the academic world to rediscover new and innovative medical technologies and create opportunities for care in specific diseases such as cancer, nervous system disorders and cure of rare diseases. Natural product repositioning will provide several benefits in curing different clinical conditions as they are safer and shows synergistic action than the synthetic molecules. Despite many advantages and opportunities of repositioning of drug product it often comes with some challenges which are needed to be overcome for successful drug repurposing.

In this this part one of the report we have gathered the details about the repurposing status on the natural product based bioactive compounds. The project will also be taken further as a part 2 of the work in that the mechanistic attributes of these drugs (and also some other recent natural products) will be taken into the consideration.

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