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Drug repositioning: Progress and challenges in drug discovery for various diseases



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ABSTRACT

Compared with traditional de novo drug discovery, drug repurposing has become an attractive drug discovery strategy due to its low-cost and high efficiency. Through a comprehensive analysis of the candidates that have been identified with drug repositioning potentials, it is found that although some drugs do not show obvious advantages in the original indications, they may exert more obvious effects in other diseases. In addition, some drugs have a synergistic effect to exert better clinical efficacy if used in combination. Particularly, it has been confirmed that drug repositioning has benefits and values on the current public health emergency such as the COVID-19 pandemic, which proved the great potential of drug repositioning. In this review, we systematically reviewed a series of representative drugs that have been repositioned for different diseases and illustrated successful cases in each disease. Especially, the mechanism of action for the representative drugs in new indications were explicitly explored for each disease, we hope this review can provide important insights for follow-up research.

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1. Introduction

Drug discovery and development is an expensive, time-consuming, and risky business. The average cost of bringing a new drug to the market is estimated at \$ 1.24 billion [1]. As shown in Fig. 1, traditional drug development strategies are roughly divided into four stages: drug discovery, preclinical studies, clinical trials, and post-marketing safety monitoring. Due to regulatory requirements regarding safety, efficacy, and quality in animal research and clinical trials, the time required to develop a new drug is approximately 12–17 years [2]. However, drug repositioning process significantly saves the development time. It only costs researchers approximately 3–12 years to develop an old drug for new treatment (Fig. 1). Furthermore, the cost of drug repositioning is much lower than traditional drug development. This strategy provides many research institutions with opportunities to develop drugs with less investment. Therefore, in order to speed up the drug development process, lower the risk of failure and reduce costs, pharmaceutical companies have adopted drug repositioning as an effective alternative.

In recent years, it can be seen from Fig. 2 that the investment in drug research and development is increasing, however, the number of approved drugs is still limited. Thence, people are increasingly interested in drug repositioning due to a variety of factors. The purpose of drug repositioning is to determine new indications for old drugs, which can be divided into the following categories: (i) Drugs that have been successfully marketed. (ii) Drugs with no specific indications and safety problems in clinical trials. (iii) Drugs

that are terminated due to budget and other reasons. Compared with traditional drug discovery, drug repositioning may allow compounds to skip to Phase II, thereby reducing time to market and lowering investment costs. In addition, since clinical data are available at the beginning of a development project, the risks associated with further development are greatly reduced [3]. Another great advantage of drug repositioning is that many cases have been proven to be sufficiently safe in preclinical trials. Besides, for an approved drug, not only preclinical information but also clinical profiles are also available, which accelerates the development of drug discovery [4]. A crucial purpose of drug repositioning is to find new drug-disease relationships. Multiple methods have been developed to achieve this goal, including computational methods, biological experimental methods, and the combination of both [5]. With the open-source of many drug-related databases, this advancement has accelerated the development of a computational approach. At the same time, the mixed approach that combining biology and computational method greatly improves the efficiency of drug repositioning while reducing costs. Drug repurposing strategy should avoid hasty proof-of-concept. Instead, a detailed and comprehensive plan should be proposed, and the information obtained in the previous development cycle should be used to appropriately simplify the work. When conducting pre-clinical research, drug pharmacology and dose intensity need to be considered. Early development must not bypass scientific inspections [6]. Besides, drug repositioning faces some major challenges. For example, if the initial clinical trials do not meet current regulatory requirements, new Phase I trials may be needed to

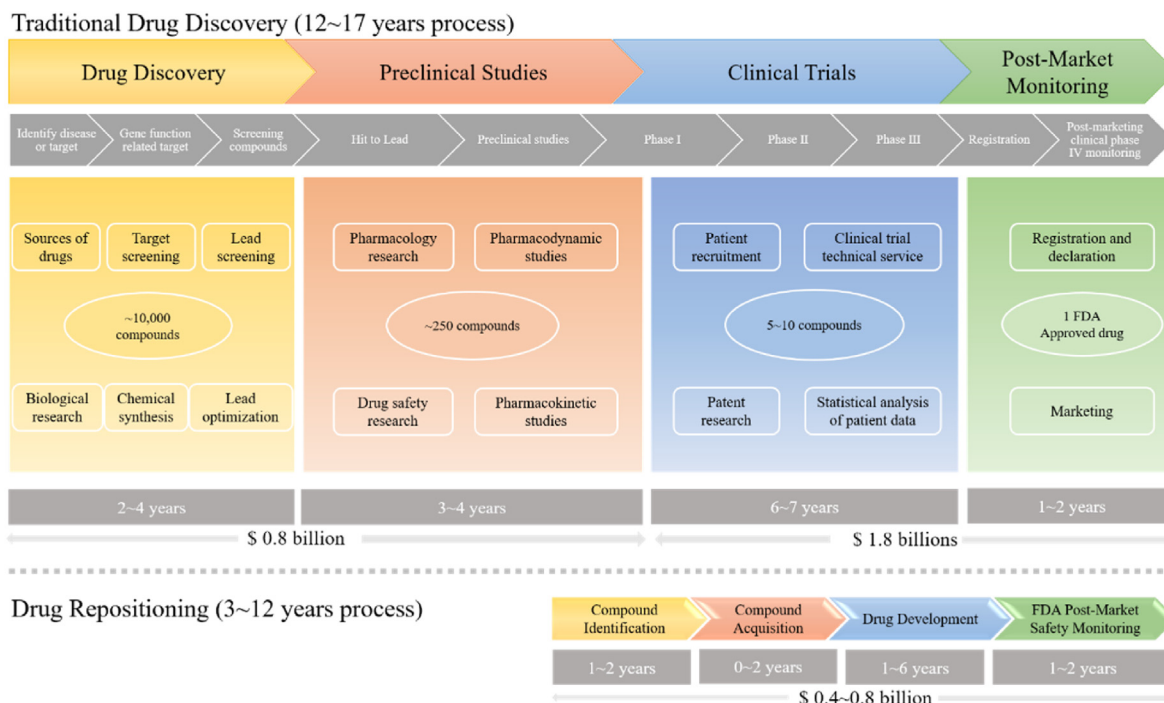


Fig. 1. Comparison of traditional drug development and drug repositioning process.

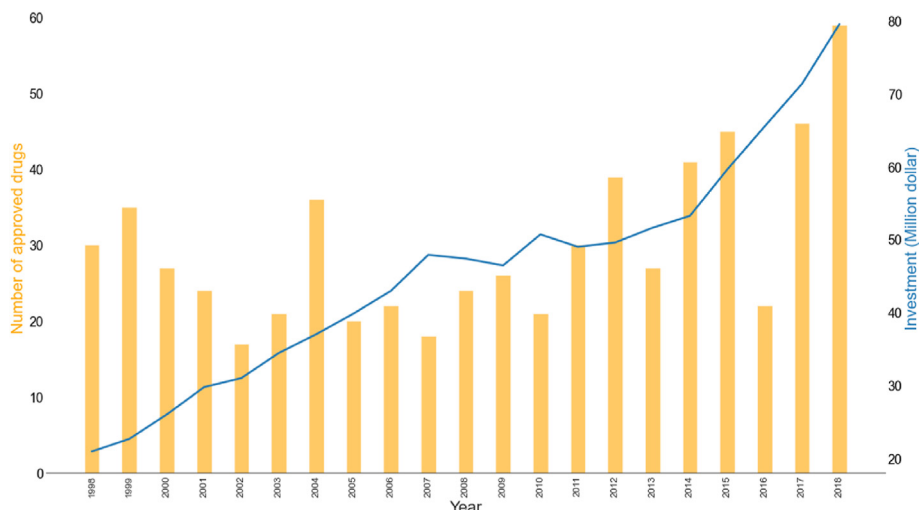


Fig. 2. The number of approved drugs and investment by the FDA from 1998 to 2018.

complete the data. Most successful cases are derived from an understanding of pharmaceutical pharmacology or clinical efficacy following a retrospective analysis of the original indications of the drug. These repositioners have weaker intellectual property protections that will reduce companies' return on investments. A majority of drug repositioning applications are based on positive clinical or epidemiological observations or discovering efficacy *in vivo*. With the rapid development of computing methods and data explosion, the mixed advantages of drug repositioning will become more prominent.

In this perspective, we systematically summarized several applications and notable strategies of drug repositioning in different types of diseases, including neurological diseases, cancer, microbial, and virus infections. As for neurological disease, we reviewed 9 potential candidates that can be repurposed in the treatment of Alzheimer's disease. These drugs, including Carmustine, Bexarotene, Tamibarotene, Imatinib, Valsartan, Nitrendipine, Liraglutide, Acitretin, Minocycline, had been approved with specific indications. Although they are old drugs, one important consideration is that the safety depends on the indication. Any change of dosage or route of administration will need a re-examination of the drugs. For oncological diseases, all reviewed drugs except ciglitazone and clofibrate are approved drugs. These two are experimental compounds that require further study than old drugs. Due to lack of safety and toxicity data makes the late stages of development for a repositioned drug considerably important. For antimicrobial repurposing sections, all reviewed drugs are approved drugs. It should be noted that, flupenthixol and thioridazine are withdrawn drugs. Flupenthixol caused a relapse in all patients and observed a significant weight decrease in clinical [7]. Thioridazine was withdrawn worldwide in 2005 due to its association with cardiac arrhythmias. Even if the adverse effects of such drugs lead to the eventual withdrawal from the market, this does not prevent their research in drug repurposing. In the antiviral repurposing review, emricasan, Suramin, emetine, CVL218, PJ-34, and Beclabuvir are categories in the investigational group. These compounds required complete evaluations of mechanism, dosage, formulation, and safety. We also focused on the current major challenges of drug repositioning and provide some suggestions for accelerating the application of drug repositioning.

2. Neurological diseases

In recent years, identifying relevant drugs for neurological disorders is still an important task in drug development. Compared with *de novo* drug discovery, drug repositioning is more cost-effective and time efficient. This approach has achieved significant success in neurological diseases. Alzheimer's disease (AD) is the most common disease that belongs to neurodegenerative disease. It is a collective term for loss of memory and other cognitive abilities that seriously affect daily life. It is predicted that the number of patients suffering with AD will reach 74.7 million by 2030 and 131.5 million by 2050 [8]. Reducing the risk of dementia is a priority task in the work of the World Health Organization (WHO).

AD was first described by the German psychiatrist Alois Alzheimer in 1907 [9]. When conducting a pathological study of the brain tissue of patients with dementia, it was found that there are two types of lesions in the brain of AD patients, senile plaque (SP) and neurofibrillary tangles (NFTs) [10]. SP is composed of β -amyloid, and NFTs are caused by abnormal phosphorylation of tau protein [11]. Amyloid precursor protein (APP) exists on the surface of neurons. Under normal circumstances, APP is broken down by enzymes on the surface of neurons and releases β -amyloid protein. Many β -amyloid proteins are assembled into insoluble fibers to eventually produce SP [12]. When neurons communicate, signals are transmitted from the soma to the synapse. These signals are transmitted through microtubules, which are stabilized by normal tau proteins. The tau protein appears abnormal during AD, destroying the normal structure of the microtubules, so the neuron's skeleton can no longer be maintained and falls apart [13]. The abnormal tau protein aggregates in neurons to form filaments. Because there is no backbone support, neurons degenerate, connections between neurons are lost, tau protein is abnormally accumulated, and eventually neurons die. As shown in Fig. 3, the coexistence of these two lesions is necessary for the occurrence of AD, but which lesion occurs first is still being studied. In fact, reducing SP is not enough to eradicate AD, and the relationship between β -amyloid and tau protein is not clear [13]. Therefore, the exact molecular mechanism leading to dementia remain the focus, and the relative importance of different pathological entities as

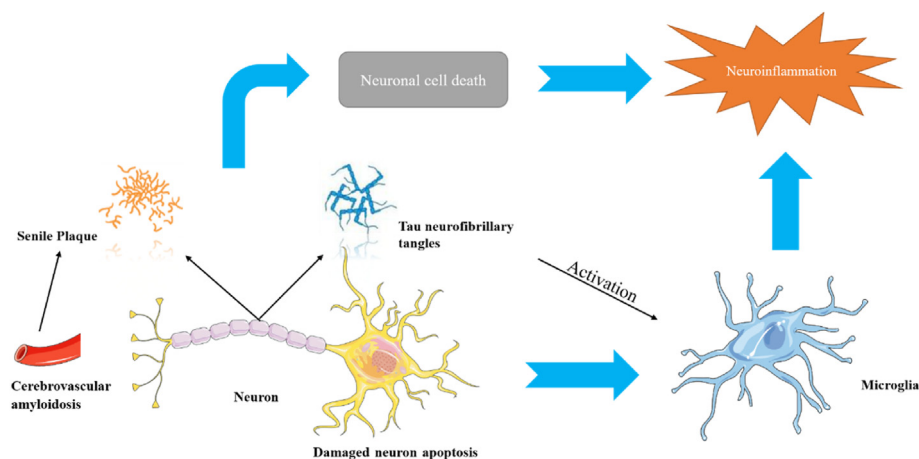


Fig. 3. Potential pathological process of Alzheimer's disease [15].

drug substrates remains controversial [14]. Even though there are currently four approved drugs for treating AD, we still need to establish an understanding of the pathogenesis of the disease to develop more candidates.

Studies have shown that there is a significant relationship between hypertension and Alzheimer's disease [16,17], but the relationship between the two is much complicated. At present, because the pathological mechanism of AD is still unclear and only stays in the theoretical stage of mechanism research [18], there is no specific method for the treatment of AD. Thus, the studies suggest that only some cognitive improvement drugs can treat AD. Anti-cancer drugs showed a great therapeutic effect on AD. Clinical statistics show that breast cancer patients undergoing chemotherapy have a reduced risk of developing AD in old age [19]. The reason for this phenomenon perhaps is shared signaling pathways, thus providing credibility for the role of anticancer drugs in AD [20].

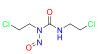
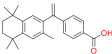
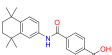
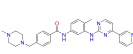

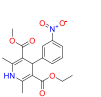
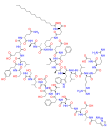
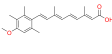
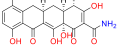
2.1. Drugs repositioned on Alzheimer's disease

Carmustine (Table 1) was approved by the FDA for the treatment of brain cancer and was found to be effective for AD. As an alkylating agent, **carmustine** induces cross-links bases pair in DNA [21]. It inhibits cancer cell replication by hindering the normal replication process of DNA [22]. Drug repositioning study reveals that **carmustine** mainly regulate APP to reduce amyloid- β (A β) aggregation [23]. Compared with the control group in the neural experiment, **carmustine** significantly reduced the normalized level of A β in the cells [23]. The experimental conclusion summarizes that long-term use of **carmustine** at a non-toxic dose may reduce the production of A β to achieve the purpose of treatment for AD. In addition, **carmustine** interacts with secretase independently, which can avoid side effects caused by off-target. This increases the safety of the drug in the treatment of AD. **Carmustine** acts on different targets demonstrating that the drug repurposing strategy is on the basis of polypharmacology. **Bexarotene** (BEXA) (Table 1) is a Retinoid X Receptor (RXR) agonist that increases apolipoprotein E (ApoE) expression and microglial phagocytosis. It was approved by the FDA for the treatment of cutaneous T-cell lymphoma (CTCL). The mechanisms of anticancer are inhibition of cell cycle progression, inhibition of angiogenesis and metastasis [24]. In 2016, Krishna and colleagues found that **BEXA** can restore cognitive function by reducing cholesterol and A β [25], this result indicates that **BEXA** become an important drug for the treatment of AD. The primary mechanism of action is that RXR participates in the formation of ApoE-related lipoprotein particles and promotes the

degradation of A β . Agonists of these receptors also promote phagocytosis by microglia and macrophages. The research indicates that BEXA acts on specific targets but repurposes different diseases settings. **Tamibarotene** (Table 1) is a retinoic acid receptor (RAR) agonist, and it was approved in Japan for the treatment of acute promyelocytic leukemia (APL) [26]. Since **Tamibarotene** is a synthetic retinoid, it can regulate the immune system and reduce inflammatory cytokines and chemokines, which control the excess stimulation of astrocytes and microglia around Ab plaques. **Tamibarotene** is reported to have fewer side effects than other retinoids, so it is considered a promising drug candidate for the treatment of AD. Reported results strongly implied that **tamibarotene** could result in impaired β -secretase cleaving and lowering A β production [27]. **Tamibarotene** controls multiple target genes involved in the pathology of AD. Mechanisms of action for the drug revealed that the repurposing strategy is related to polypharmacology. **Acitretin** decreases the expression of STAT1 and STAT3-dependent signaling which interferes with the JAK pathway [28]. In a transgenic mouse model of AD, retinoids led to increased ADAM10 expression. Therefore, the systematic retinoids especially **acitretin** present a valuable therapeutic strategy for the treatment of AD. It should be noted that, compared with the placebo group, **acitretin** is generally safe and well-tolerated in clinical trials [29]. This result preliminarily proves that the **acitretin** seems to be an ideal candidate drug for the treatment of AD. Since **acitretin** acts on multiple targets pertaining to multiple disease pathways, the repurposing strategy is on the basis of polypharmacology. **Imatinib** (Table 1) is a selective tyrosine kinase inhibitor. It is also the first-line drug for the treatment of chronic myeloid leukemia [30] and gastrointestinal stromal tumors [31]. Studies have shown that **Imatinib** can be used to treat Alzheimer's disease [32] due to interferes c-Abl/p73 signaling pathway and decreasing the tau protein phosphorylation in hippocampal neurons. The repurposing strategy is also related to the polypharmacology of the drug. However, **Imatinib** has been proven to effectively reduce the production of A β in vitro and in animal models, it is not obviously in humans, so further research is needed.

Antihypertensive drugs can significantly reduce the accumulation of amyloid- β . Attempting to choose some antihypertensive drugs as neuroprotective agents can achieve the purpose of treating AD because the neuroprotective and cognitive functions of AD may be mediated through related mechanisms of angiotensin receptor blockers (ARB) and calcium channel blockers (CCB) associated with hypertension. **Valsartan** (Table 1), an angiotensin receptor blocker, blocks the vasoconstrictor and aldosterone-secreting effects of

Table 1
Drug repurposing examples and their mechanism of action in Neurological Diseases.

Target	Structure	Drug	Drug Class	Proposed Mechanism	Original Indications
DNA/RNA		Carmustine	Anti-cancer	Cultured cells overexpressing APP	brain tumors, multiple myeloma, Hodgkin's disease and non-Hodgkin's lymphomas.
Retinoic acid receptor RXR-alpha/beta/ gamma		Bexarotene	Anti-cancer	Stimulate the expression of apolipoprotein E	cutaneous T-cell lymphoma (CTCL)
Retinoic acid receptor alpha/beta		Tamibarotene	Synthetic retinoid	Reduce significantly the insoluble A β levels	Investigated for treatment in leukemia
Tyrosine-protein kinase ABL1		Imatinib	Anti-cancer	Inhibit GIST cell proliferation	malignant gastrointestinal stromal tumors
Angiotensin receptor blockers (ARBs)		Valsartan	Anti-hypertensive	Block AT1 or processing of angiotensin II	hypertension to reduce the risk of fatal and nonfatal cardiovascular events
Calcium channel blockers		Nitrendipine	Anti-hypertensive	Calcium antagonists	mild to moderate hypertension
GLP1 analogs		Liraglutide	Type II diabetes	GLP-1 analogue; Activating GLP-1 receptor insulin secretion	diabetes and intended for weight loss
Retinoid therapy		Acitretin	Severe psoriasis and dyskeratosis	Induce apoptosis of primary human keratinocytes	severe psoriasis in adults
Tetracycline antibiotics		Minocycline	Broad-spectrum antibiotics	Bind to a position of ribosome 30S subunit and inhibiting protein synthesis	inflammatory lesions of acne vulgaris

angiotensin II in hypertension treatment. A drug-related study found that **Valsartan** significantly reduces the accumulation of AD β -amyloid in a mouse model. This drug received attention in AD treatment because **Valsartan** alleviates the deterioration of A β -mediated cognitive ability even if it is administered less than two times a dose for the treatment of hypertension [33]. In 2014, Yang et al. found that **Valsartan** could ameliorate cognitive decline by regulating the expression and activity of AChE, and reduce oxidative damage by decreasing the level of MDA in cortex and hippocampus [34]. This finding further supports the potential strategy of **Valsartan** in the treatment of AD based on polypharmacology. Hypertension is one of the risk factors for dementia, while anti-hypertensive drugs with different mechanisms have different effects on dementia [35,36]. Previous studies have found that calcium channel blockers seem to be most effective drugs. **Nitrendipine** (Table 1), a second-generation calcium channel blocker, is used for the treatment of hypertension by inhibiting the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes. The possible explanation for **nitrendipine** in AD treatment is to block the uncontrolled calcium influx into the neurons. This repurposing case indicates that nitrendipine exerts a specific mechanism of action in different diseases settings. It has also been shown to be particularly beneficial and safe in hypertensive patients with a high risk of dementia [37]. The relationship between hypertension and dementia is not yet known, so further research is needed.

Liraglutide (Table 1) is a glucagon-like peptide-1 (GLP-1) receptor agonist in type II diabetes treatment. Given that the connection between AD and central insulin signaling is gradually recognized, **Liraglutide** has also been proven to have a neuroprotective mechanism [38]. Liraglutide interferes Phosphoinositide

3-kinase/mitogen associated protein kinase (PI3K/MAPK) dependent pathways by binding to glucagon like peptide-1 receptor (GLP-1R) to increase the presence of A β transporters in cerebrospinal fluid [39]. Because **Liraglutide** is currently approved for the treatment of type 2 diabetes, so it acts like a shortcut in the treatment of AD. **Minocycline** (Table 1), an anti-inflammatory tetracycline compound, binds to the bacterial 30S ribosomal and inhibits protein synthesis. Reports have established the presence of inflammatory markers in AD patients' brains. **Minocycline** could exert anti-inflammatory effects through the blood-brain barrier and has neuroprotective effects. Studies have shown that **Minocycline** prevents the deposition of A β and the death of neurons [40], and protects hippocampal neurogenesis in the presence of A β [41]. The repurposing strategy is on the basis of specific mechanism of action but repurpose for different diseases settings. Unfortunately, clinical trials have shown that **Minocycline** has different efficacy at different doses compared with placebo. The results of clinical trials show that high doses have no obvious benefit. Besides, the cognitive function of mild patients was not improved after accepting **Minocycline** treatment. Therefore, **Minocycline** needs further research in drug repositioning.

Although some of the drugs discussed here appear to be good candidates for further research, it is uncertain whether any of them will succeed as successful therapies for Alzheimer's disease and a more systematic approach is needed to screen approved drugs and analyze epidemiological biological and clinical data to identify new potential candidates for repurposing in Alzheimer's disease. It is also important to consider the optimal stage of the disease for treatment based on the mechanism of action of new indications and thus to determine whether the trial should target early-clinical Alzheimer's patients [42].

2.2. Representative cases of drug repositioning in other neurological diseases

One of the most representative cases of drug repositioning in neurological disease comes from galantamine. **Galantamine** is a phenanthridine alkaloid isolated from *Galanthus caucasicus* in 1947 [43]. After a few years, its structural characteristics were obtained and used for surgery and anesthesia. **Galantamine** was mainly used as a cholinesterase inhibitor in the 1960s to treat diseases such as polio and muscle atrophy. Because its activity is better than pyridostigmine but weaker than neostigmine, it has not attracted widespread attention [44]. Another reason that hinders the development of **galantamine** is its extremely low synthesis efficiency as **galantamine** is more difficult to synthesize than other analogs. Research in the 1990s [45] found that **galantamine** can improve memory dysfunction in mice, and it is speculated that it may be effective in treating AD. Later, it was confirmed that **galantamine** can specifically bind to the active site of acetylcholinesterase, thereby improving the function transmission of cholinergic nerves, improving the cholinergic energy in the brain of AD patients, and improving cognitive ability [46]. In 2001, the FDA approved the registration of **galantamine** for the treatment of mild to moderate AD [47]. **Galantamine** does not improve the daily activities of untreated patients with severe AD. The dual-mode action of **galantamine** (AChE inhibition and allosteric nicotinic receptor modulation) develops new therapeutic strategies. The dual mechanism is shown in Fig. 4a. This case is also considered a polypharmacological strategy due to its drug repurposing target inconsistent with the original target.

Galantamine binds to presynaptic and postsynaptic nicotinic acetylcholine receptor (nAChR) on cholinergic neurons but different with acetylcholine (ACh) [48]. The response of nAChR to ACh will be enhanced, when **galantamine** and ACh bind to their respective binding sites at the same time. Activation of nAChR promotes the release of neurotransmitters that are important for memory [49]. Therefore, regulating nAChR has important clinical benefits in AD, including improving memory function. In addition, **galantamine** inhibits the utilization of ACh by inhibiting AChE. Compared with butyrylcholinesterase, **galantamine** is 50 times more selective for AChE. This high selectivity mat improves the tolerability. **Galantamine** has been proven efficient in the

symptomatic treatment of Alzheimer's disease patients [50].

Amantadine is an antiviral drug synthesized in the 1950s and approved to prevent and treat the symptoms of influenza A infection. Subsequently, **amantadine** was used to develop treatments for neurological disorders [52]. The drug repositioning of **amantadine** was accidentally discovered during the case observation of a patient in 1968 [53]. Experimental data linked its mechanism of action to the antagonist effect of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors [54].

Parkinson's disease (PD) is performed by the loss of dopaminergic neurons causing a decrease in dopamine levels [55]. **Amantadine** is a non-competitive antagonist of the NMDA receptor, which stimulates dopamine release and prevents dopamine reuptake (Fig. 4b). Subsequently, it was discovered that **amantadine** modulates the activity of glutamatergic corticosteroid and subthalamic-pallidal pathways, which is the core mechanism for the development of dyskinesia in PD [56]. In 1973, **amantadine** was the first drug approved by the FDA for the treatment of dyskinesia in PD. In 2017, the extended-release formulation was approved for use in the treatment of levodopa-induced dyskinesia [57]. The drug is currently only used to treat Parkinson's disease in the United States. This successful case provides a new treatment strategy and provides novel polypharmacology directions.

3. Oncological diseases

In the past decades, significant work has been done in search of novel methods for the treatment of cancer. However, cancer is still one of the leading causes of death worldwide. The consideration method in drug development does not only include de novo design but also search approved known molecules used in a non-oncological situation [58]. The explosive growth of a great number of cancer genome data and the gradual disclosure of internal high-throughput screening data by pharmaceutical companies have made in silico drug repositioning more convenient. More than 200 non-cancer drugs have been shown to have anticancer activity. A typical example of this is propranolol, which is often used as a blood pressure lowering drug and has since been proven to be effective in relieving tumors in combination with other cancer treatment strategies. The scientists of the Dana-Farber team used the PRISM molecular barcode method to select 4518 drugs from the

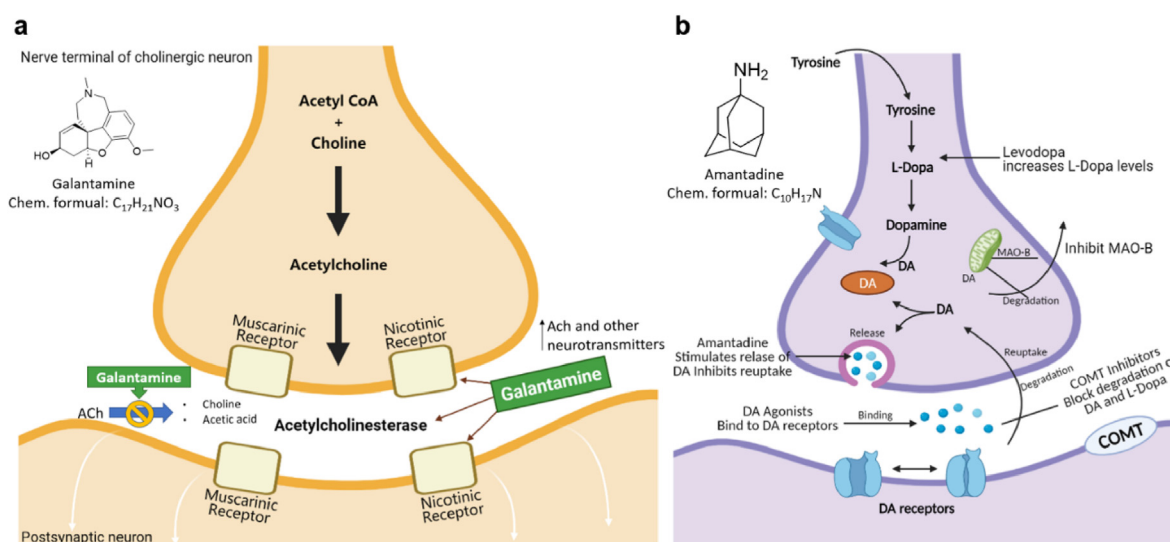


Fig. 4. a. Galantamine targets two sites of action: Nicotinic receptors and Acetylcholinesterase. b. Amantadine stimulates dopamine release and prevents dopamine reuptake. COMT = Catechol-O-transferase; DA = dopamine; MAO = monoamine oxidase (Source-Medscape) [48,51].

Drug Repurposing Center for screening. The screening targets covered 578 cell lines of 24 tumor types. Surprisingly, a great number of non-oncology drugs can selectively inhibit cancer cell line subsets [59]. Some of these drugs even discovered cancer targets that were not previously involved [59]. Researchers found that the mechanism of action of most anti-cancer drugs is mainly through the replacement of proteins. This study found that some drugs do not only block proteins but instead activate or stabilize protein-protein interactions [59].

3.1. Colorectal cancer (CRC)

Colorectal cancer is the second leading cause of cancer death worldwide, mutations in the TP53 gene are the leading cause of colorectal cancer [60]. The p53 protein is encoded by the TP53 gene [61]. p53 can not only promote the repair and survival of damaged cells but also promote the permanent removal of irreparable damaged cells through apoptosis or autophagy [62]. Therefore, the complex regulation of p53 can prevent tumor incidence and progression [62]. With the development of genomics and screening of existing drugs, it has been discovered that non-oncology drugs have shown anticancer activity [63,64]. **Chlorpromazine (CPZ)**

(Table 2) is mainly used to treat psychiatric diseases by blocking postsynaptic dopamine receptors in cortical and limbic areas of brain. Studies have found that the apoptosis of tumor cells induced by **CPZ** depends on the expression of p53 [61]. Therefore, **CPZ** offers potential for the treatment of CRC and provides effective research ideas for drug repositioning due to polypharmacology. Dehydroepiandrosterone (**DHEA**) (Table 2) is a major C19 steroid produced by the adrenal. It has been reported that **DHEA** can significantly inhibit 1,2-dimethylhydrazine-induced colon tumors in BALB/c mice [65] in 1984. The mechanism of action for **DHEA** is to reduce the number of abnormal crypt foci (ACF) induced by azoxymethane (AOM) to achieve the purpose of treatment. The results of acting on different targets should make a wary of side effects. **Orlistat** (Table 2) is a fatty acid synthase (FASN) inhibitor for obesity management, which works by inhibiting the absorption of dietary fat. In 2011, a study by Zhuang et al. found that **orlistat** can inhibit the growth of colorectal cancer by arresting the cell cycle in the G1 cycle and activating the apoptosis of caspase-3 [66]. Additionally, orlistat inhibited inflammation, hyperplasia, and tumor progression through NF- κ B activation [67]. Since fatty acid synthesis plays an important role in the survival of cancer cells, fatty acid synthase may be a potential target for cancer treatment. The

Table 2
Drug repurposing examples and their mechanism of action in Colorectal Cancer.

Target	Structure	Drug	Drug Class	Proposed Mechanism	Original Indications
D2 dopamine receptor		Chlorpromazine (CPZ)	Antipsychotic agent	Tumor cell apoptosis induced by p53 expression	For the treatment of schizophrenia to control nausea and vomiting;
Estrogen receptor		Dehydroepiandrosterone (DHEA)	Over-the-counter dietary supplements	DHEA has a chemopreventive effect on colon cancer precursors	Indicated for the treatment of lupus, depression, adrenal insufficiency, cervical cancer
Fatty acid synthase		Orlistat	Treat obesity	Inhibit pancreatic lipase	Indicated for obesity management including weight loss and weight maintenance
(H ⁺ , K ⁺)-ATPase enzyme		Pantoprazole	Gastric protection	Prevent the final step in gastric acid production	Treatment of gastroesophageal reflux disease associated with a history of erosive esophagitis
Pyruvate dehydrogenase kinase		Dichloroacetate (DCA)	Treat brain cancer	Inhibit the enzyme pyruvate dehydrogenase kinase	Used for the treatment of warts and cauterization
Estrogen receptor		Raloxifene	Reduce the risk of breast cancer	Mediate anti-estrogen effects on breast and uterine tissues	Indicated for the prevention and treatment of osteoporosis
Cytochrome P-450-dependent enzymes		Itraconazole	Against Histoplasmosis; Blastomycosis; Cryptococcal meningitis; Aspergillosis	Lead to impaired ergosterol synthesis	For the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients
VEGF/VEGFR2		Tanshinone IIA	Treatment of coronary heart disease; angina; myocardial infarction	Interfere with the tumor cell cycle, promote tumor cell apoptosis, and inhibit tumor cell invasion and metastasis.	Used to treat patients suffering from myocardial infarction (MI), angina pectoris, stroke, diabetes, sepsis
5-Hydroxytryptamine receptor 2A		Fluspirilene	Chronic schizophrenia	Guanine nucleotide binding to G protein triggers signal transduction and regulates the activity of downstream effectors.	Used for schizophrenia

polypharmacological properties of **orlistat** provide new ideas for drug repurposing. **Pantoprazole** (Table 2) is an irreversible proton pump inhibitor (PPI), and it was used for the treatment of gastroesophageal reflux disease. Since PPIs are commonly effective in cancer patients, studies investigating drug repositioning are particularly important for therapy. Zeng et al. found that **pantoprazole** can effectively inhibit TOPK, highly expressed in multi types of cancers, especially in colorectal cancer cells [68] via virtual screening. Thus the polypharmacological properties of **pantoprazole** provide novel directions to different diseases therapy. **Dichloroacetate (DCA)** (Table 2) is a specific inhibitor of pyruvate dehydrogenase kinase (PDK). It increases pyruvate flux into the mitochondria by inhibiting the PDK, promoting glucose oxidation. As early as 1956, Otto Warburg observed that cancer cells inherently depend on glycolysis to produce chemical energy [69]. PDK inhibitors can attenuate the effect of glycolysis to promote the oxidative phosphorylation of mitochondria and inhibit the growth of colorectal cancer cells [70]. This case indicates that repurposing strategy is related to a similar mechanism of action but applies in different diseases settings. Non-hormonal compounds are binding to estrogen receptors that could produce beneficial effects on the skeletal system without adverse effects on other tissues. These compounds were called selective estrogen receptor modulators (SERM). **Raloxifene** (Table 2) is a SERM that the FDA approves to treat and prevent postmenopausal osteoporosis in women. Through research on the prevention of different types of colon cancer, it was discovered that **raloxifene** may act as an ER- β antagonist to achieve the purpose of preventing colon cancer [71]. The death of patients due to tumor recurrence is also a major obstacle in cancer treatment. A reasonable explanation is that the cells continue to exist and enter the cell cycle after the induced stimulation during the dormant period. Comparison of different tumor cells disclosed that dormant colorectal cancer (CRC) cells are chemo-resistant [72]. Therefore, it is hoped that drugs can interfere with the dormant state to kill cancer cells to prevent cancer recurrence completely. The repositioning strategy is related to mechanisms of action in different diseases settings. **Itraconazole** participates in compound synthesis and detoxification via hydroxylation reaction and inhibits cytochrome P450 (CYP) enzymes [73]. CYP enzymes are important for the biosynthesis of sterols, which are vital components of fungal cell membranes. In 2018, Simon et al. reported that the broad-spectrum antifungal drug **itraconazole** (Table 2) could switch dormant cells into global senescence. This evidence supports the therapeutic potential of **itraconazole** in CRC [74]. Pre-clinical validation studies indicate that **itraconazole** interference Wnt signaling pathway inhibition and tumor growth arrest [75]. The drug repurposing strategy is related to itraconazole polypharmacology. **Tanshinone IIA (Tan IIA)** (Table 2), as a member of the major lipophilic active constituent isolated from the root of Chinese medicinal herb, can mediate the apoptosis of colorectal cancer cells. **Tan IIA** is the most abundant diterpene quinone in *Salviae miltiorrhizae* and used to treat cardiovascular disease. **Tan IIA** protects cardiomyocytes from ischemia and hypoxia injury by inhibiting the expression of miR-1 through the p38-MAPK signaling pathway [76]. Sayilaxi et al. proved that **Tan IIA** reduces the viability of CRCs by promoting the lysis of mitochondria [77]. Furthermore, Researches reveal that **Tan IIA** inhibits the growth of cancer cells by stimulating autophagy in MEK-ERK-mTOP pathway [78]. The repurposing strategy indicates that **Tan IIA** acts on multiple targets pertaining to multiple diseases pathways. p53-MDM2 protein-protein interaction plays a key role in almost all tumor cells [79]. The identification of inhibitors of p53-MDM2 from the approved drugs library could increase the successful rate of anticancer drug discovery. The antipsychotic drug **fluspirilene** (Table 2) as a virtual screening drug has been shown to

be an effective p53-MDM2 small molecule inhibitor [80]. Experimental results show that **fluspirilene** can significantly inhibit the growth of cancer cells including CRCs. **Fluspirilene** exerts a specific mechanism of action in different diseases settings, providing novel insight for drug repurposing.

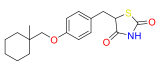
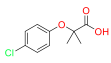
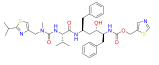
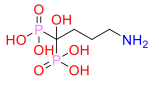
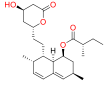
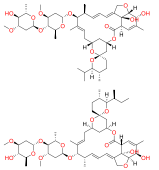
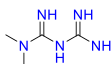
3.2. Ovarian cancer

Malignant tumors of the ovary are one of the common malignant tumors of female reproductive organs [81]. Epithelial cancer is the most common among malignant ovarian tumors. The incidence of ovarian malignant tumors ranks third in gynecological tumors, but the mortality rate is the first, so it poses a serious threat to women's lives. For the treatment of ovarian cancer, platinum-based combined chemotherapy is currently used in clinical practice. Niraparib, Rucaparib, and Olaparib are targeted drugs for ovarian cancer.

Peroxisome proliferators-activated receptors (PPARs) are ligand-activated receptors in the nuclear hormone receptor family, and its three subtypes have been discovered including PPAR α , PPAR β/δ , and PPAR γ [82]. PPAR α plays an important role in regulating inflammation and tumorigenesis. The activation of PPAR- β/δ can enhance fatty acid metabolism, while the activation of PPAR- γ can cause insulin sensitization and enhance glucose metabolism [83]. Previous studies have shown that [84,85] ligands that activate PPAR γ can be used as effective therapeutic strategies to inhibit ovarian cancer. Anti-tumor drug repositioning mainly starts from the research of mechanism. It is hoped that the method of drug repositioning can not only achieve the effect of treating ovarian cancer, but also obtain a certain preventive effect.

Ciglitazone decreases differentiation and angiogenesis in human umbilical vein endothelial cells to exert an anti-hyperglycemic effect. **Ciglitazone** (Table 3) is a highly selective agonist of PPAR γ and improves insulin sensitivity. In vivo studies have found that **ciglitazone** can inhibited glucose uptake in ovarian cancer cells and decreased expression of glucose transporter-1 (GLUT-1) [86]. Based on mechanistic studies, the polypharmacology of **ciglitazone** is beneficial for drug repurposing. **Clofibric Acid (CA)** (Table 3) is a ligand of PPAR α , and used for the treatment of hyperlipidemia. In 2007, a study revealed that **CA** can be used to inhibit the growth of human ovarian cancer [87]. Studies have found that the main mechanism is that **CA** can induce the expression of carbonyl reductase (CR) in ovarian cancer cells, thereby reducing the level of PGE2 and inhibiting the expression of VEGF, leading to the inhibition of angiogenesis and ultimately inducing tumor cell apoptosis [87]. Another study found that compared with the control group, the group that received **CA** can effectively treat peritoneal cancer caused by ovarian cancer without damaging the organs [88]. The action of **CA** on multiple targets associated with multiple disease pathways demonstrates that its drug repurposing strategy is based on polypharmacological properties. **Ritonavir** (Table 3), an HIV protease inhibitor, cleaves both structural and functional proteins to inhibit the formation of infectious virions to produce the antiviral effect. When the body's innate immune system is weakened, it increases the risk of solid tumors. Researchers found that **ritonavir** can inhibit the apoptosis of a variety of tumor cells [89,90]. **Ritonavir** inhibits cancer cells from exerting anti-tumor effects by depleting G1 cyclin and mediating G1 cell cycle arrest of ovarian cancer cells [91]. **Ritonavir** synergistically inhibits AKT to increase the efficacy of cell apoptosis. Therefore, it is recommended that **ritonavir** be used as an enhancement drug for the treatment of ovarian cancer. The drug repurposing strategy is based on specific mechanism of action for different diseases settings. Inhibiting mevalonate pathway has an inhibitory effect on the growth of ovarian cancer cells, so it is also a novel strategy to consider drugs

Table 3
Drug repurposing examples and their mechanism of action in Ovarian Cancer.

Target	Structure	Drug	Drug Class	Proposed Mechanism	Original Indications
PPAR γ		Ciglitazone	Never used as a medication	Inhibit ovarian cancer cell growth	Ciglitazone may potentially be used in ovarian hyperstimulation syndrome
PPAR α		Clofibrilic Acid	Regulate blood lipids	Inhibit angiogenesis and induce apoptosis	Clofibrilic acid is a biologically active metabolite of the lipid-lowering drugs
HIV protease		Ritonavir	HIV infection	Inhibit cell cycle and induce apoptosis	Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.
Farnesyl pyrophosphate synthase		Alendronate	Anti-osteoporotic drugs	Inhibit mevalonate pathway	Indicated for the treatment and prevention of osteoporosis
Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase		Lovastatin	Anti-dyslipidemia drugs	Inhibition of mevalonate pathway	Indicated to reduce the risk of myocardial infarction, unstable angina in individuals without symptomatic cardiovascular disease
Yes-associated protein 1 (YAP1)		Ivermectin	Anti-parasitic agent	Inhibit cell proliferation	Ivermectin cream is indicated for the treatment of inflammatory lesions associated with rosacea
5'-AMP-activated protein kinase subunit beta-1		Metformin	Diabetes	Lead to a decrease in insulin resistance and a clinically significant decrease in plasma fasting insulin levels	Indicated as an adjunct to diet and exercise to increase glycemic control

targeting this pathway for the treatment of ovarian cancer [92]. **Alendronate** possibly inhibits the mevalonate pathway to inhibit bone resorption for the treatment of osteoporosis. **Alendronate** (Table 3) showed a concentration-dependent inhibitory effect on SKOV3 cells. Studies have found that **alendronate** attenuates the activation of Rho by inhibiting the mevalonate pathway, thereby inhibiting the migration of ovarian cancer cells [93]. Either in vivo or in vitro evaluations have shown the inhibitory effect of **alendronate** on the growth of ovarian cancer cells [94]. The drug acting on single target but repurpose for different diseases settings. Statins are usually used as drugs that inhibit the mevalonate pathway to treat hypercholesterolemia [95]. Also, it can cause specific apoptosis of tumor cells [96], and it has been shown that the combination of statins and traditional chemotherapy strategies can improve the efficacy of targeted tumors [97–99]. Statins used to treat cardiovascular disease through inhibit the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA). It has been proposed and proved that inhibition of the HMG-CoA may against cancer. **Lovastatin** is an HMG-CoA reductase inhibitor, and it works by reducing the production of cholesterol. **Lovastatin** (Table 3) may lead to cell cycle progression and cell proliferation by affecting the cholesterol biosynthesis pathway, thereby mediating antineoplastic effects [100]. The specific mechanism of action for **lovastatin** provides drug repurposing strategy. **Ivermectin** (Table 3) may inhibit LPS-induced production of inflammatory cytokines for the treatment of inflammation [101]. **Ivermectin** inhibits the proliferation of cancer cells by regulating a variety of signal pathways. It mainly blocks cell cycle progression and promotes apoptosis by blocking KPNB1 [102]. Besides, **ivermectin** can also inhibit the growth of ovarian cancer by targeting molecules in the energy metabolism pathway [103]. This evidence is sufficient to prove that **ivermectin** has great potential for the treatment of ovarian cancer. The case also proved that ivermectin acts on multiple targets pertaining to multiple diseases pathways.

Metformin (Table 3) is the first choice for treating diabetes in clinics by lowering hepatic glucose output, and the discovery that **metformin** can inhibit the growth of cancer cells in vivo and in vitro has aroused great interest from scientists. Studies have shown that **metformin** can reduce cancer mortality [104–106]. Many different studies on the mechanism of action of **metformin** were performed. When cisplatin was used in combination with metformin, as the concentration of **metformin** increased, the half-maximal inhibitory concentration of cisplatin on the ovarian cancer CP70 cell line decreased significantly. In addition, in an apoptosis experiment of ovarian cancer epithelial cells, it was found that **metformin** can induce the apoptosis of OVCAR-3 and OVCAR-4 cell lines that depend on adenosine phosphate active protease (AMPK) and inhibit cancer cells. Although there are many studies on the anticancer mechanism of metformin, it is still in the experimental stage, and its safety and effectiveness are still to be explored. Mechanism studies proved that the repurpose strategy is based on polypharmacology.

3.3. Melanoma

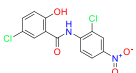
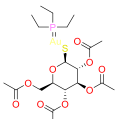
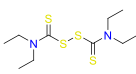
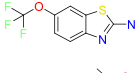
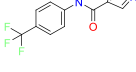
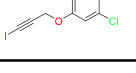
Melanoma is a malignant tumor that develops from melanocytes that originate in the nerve ridge. Melanoma is a very deadly skin cancer that starts in melanocytes. Ultraviolet (UV) light radiation from sunlight and the number of melanocytic nevi is the main environmental risk factors for melanoma skin cancer development [107]. In the past, the main treatment strategies for malignant melanoma were surgery, radiotherapy, and chemotherapy. Nowadays, there are currently some drugs on the market that can be used to treat melanoma, but it is still difficult to treat melanoma because of drug resistance and high metastasis. Through the study of melanoma signaling pathways, it has been found that STAT3 plays an important role, so it is proposed to use STAT3 inhibitors as potential anti-melanoma compounds [108]. Besides, some drugs have

anticancer activity against a variety of solid tumors, including melanoma. James et al. [109] developed a method based on knowledge graphs to find high-quality melanoma drug candidates. This method uses a more systematic biological graph probabilistic analysis to improve the quality of drug screening, and finally screened 25 candidate drugs for the treatment of metastatic melanoma. Riedel et al. [110] obtained haloprogin by screening the FDA-approved drug library. The synergistic effect of this drug and the organometallic drug RAPTA-T can effectively kill cancer cells. Currently, it is mainly used in the development of melanoma drugs.

Niclosamide (Table 4) is a drug approved by the FDA to treat parasitic infections [111]. The mechanism of action for eradicate tapeworm infections via diminishing the potential of the inner mitochondrial membrane to inhibit oxidative phosphorylation to Ref. [112]. [113]. Besides, the molecular mechanism investigation indicates that **niclosamide** exhibits anticancer activity by suppressing STAT3 phosphorylation [114]. Mahdi Hatamipour et al. encapsulated **niclosamide** in nanoliposomes and showed anti-tumor activity against melanoma in vivo [115]. Due to the poor solubility and low bioavailability of **niclosamide** hindered its clinical application [116], it is hoped that its application in cancer can be ameliorated through preparation. **Niclosamide**, which acts on multiple targets about multiple disease pathways, provides a drug repurposing strategy. FDA approves **auranofin** for the treatment of rheumatism. Studies speculated that it induces heme oxygenase 1 (HO-1) mRNA, an inducible heme-degrading enzyme with anti-inflammatory properties. Because protein kinase C (PKC) plays a key role in the function of melanoma cells, the PKC inhibitor **auranofin** is considered as a potential treatment for melanoma. Experiments revealed that **auranofin** inhibits melanin synthesis by reducing the activity of intracellular tyrosinase [117]. The drug repurposing strategy is on the basis of polypharmacology. FDA approved **disulfiram (DSF)** (Table 4) in 1951 for the treatment of alcohol addiction via inhibiting all the identified aldehyde dehydrogenase isoforms. **DSF** showed metal-dependent anti-tumor activity in the 1970s [118]. The report showed [119] that **DSF** inhibited cell line proliferation and induced apoptosis of melanoma cells in the presence of free copper, so it was identified as one of the effective compounds that preferentially reduce the proliferation of

melanoma subtypes. **DSF** induces apoptosis by reducing the mitochondrial membrane potential [120]. In this case, the drug repurposing strategy of **DSF** is related to polypharmacology. Drug resistance is a vital issue in the treatment of tumor drugs. When **DSF** is combined with copper, it shows that it can inhibit drug resistance-related targets, so **DSF** is considered to have great development potential. **Riluzole** (GRM1 blocker) (Table 4) is used to treat amyotrophic lateral sclerosis (ALS) [121]. Early studies have found that ectopic expression of glutamate receptor 1 (GRM1) in melanocytes can transform into melanoma. Therefore, **riluzole** is proposed as an effective drug for the treatment of melanoma [122]. It inhibits the metabolic activity of melanoma by blocking the signal transduction of mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathways. Although **riluzole** is well tolerated [123], further clinical test results are needed. Drug repurposing strategy of **riluzole** is related to polypharmacology. **Leflunomide** (Table 4) was approved by the FDA in 1998 for the treatment of rheumatoid arthritis (RA). **Leflunomide** is a dihydroorotate dehydrogenase (DHODH) inhibitor [124–126]. Besides, reported studies reveal that **leflunomide** exerts the effects via inhibiting the transcriptional elongation of genes that are required for melanoma growth [127]. Since **leflunomide** is effective against a variety of cancer cells and required different concentrations. It is necessary to continue to investigate the safest dose for the treatment of melanoma. The repurposing strategy is related to the polypharmacology properties. Through the screening of FDA-approved drugs, it was identified that **haloprogin** (Table 4) interacts with RAPTA-T to synergistically kill cancer cells [128]. **Haloprogin** possibly treats Tinea infections via inhibiting oxygen uptake and disrupting yeast membrane structure and function. On the other hand, combination treatment can be administered in very low concentrations and efficiently inhibit melanoma growth. In the mouse model, **haloprogin** shows superior to standard drugs for the treatment of melanoma. However, whether the combination drugs can inhibit the spread of melanoma needs further research. Although the mechanism of action is unknown, the drug repurposing strategy is suspected to be related to polypharmacology due to different targets.

Table 4
Drug repurposing examples and their mechanism of action in Melanoma.

Target	Structure	Drug	Drug Class	Proposed Mechanism	Original Indications
STAT3		Niclosamide	Anti-helminthic drug	Induce the apoptosis of melanoma cells	For the treatment of tapeworm and intestinal fluke infections
AKT		Auranofin	Rheumatoid Arthritis	Increase reactive oxygen species (ROS) levels and apoptosis	Used in the treatment of active, progressive or destructive forms of inflammatory arthritis
Aldehyde dehydrogenase		Disulfiram	Inhibit the enzyme acetaldehyde dehydrogenase	Affect the intermediate metabolism of alcohol	For the treatment and management of chronic alcoholism
Glutamate		Riluzole	Lou Gehrig's disease	Anticonvulsant	For the treatment of amyotrophic lateral sclerosis
Mitochondrial enzyme dihydroorotate dehydrogenase		Leflunomide	Rheumatoid Arthritis	Reduce the cell viability of melanoma cells	For the management of the signs and symptoms of active rheumatoid arthritis (RA)
Unknown		Haloprogin	Antifungal agent	Inhibit the absorption of oxygen and destroy the structure and function of the yeast membrane	Used to treat fungal (Tinea) skin infections

3.4. Represented cases of drug repositioning in cancer

During the 1950s–1960s, **thalidomide** was widely used as an antiemetic for pregnant women, and it caused tens of thousands of malformed babies. However, **thalidomide** combined with dexamethasone can treat multiple myeloma (MM). MM is an incurable malignancy of terminally differentiated B-cells accounting for approximately 1–2% of all human cancers [129]. **Thalidomide**, a synthetic derivative of glutamic acid, is an oral immunomodulatory therapeutic drug. Its activity as a single agent in refractory or relapsed MM was first reported in 1999 [130]. According to reported researches, the anti-angiogenesis effect is mediated by inhibition of VEGF and β fibroblast growth factor (FGF) [131] (Fig. 5). Besides, **thalidomide** inhibits production of MM growth factors including IL-6, TNF- α , and vascular endothelial growth factor (VEGF) [129]. It can also block the G1 growth of MM cells. Although the exact mechanism of **thalidomide** in the treatment of multiple myeloma is not completely understood and its anti-angiogenic effect is only part of the means of its anti-myeloma activity, the treatment results for multiple myeloma are particularly impressive.

4. Antimicrobial repositioning

The current speed of discovery of antibiotics is much lower than the peak period of 1940–1960 [133]. The main reason is that antimicrobial resistance has weakened the speed of antimicrobial development. Antimicrobial resistance is a serious global problem, new drugs, and novel treatments are urgently needed to improve this situation [134]. As with other drugs, de novo antibacterial discovery is a long and arduous process, which not only requires time and cost but also has very high safety and toxicity risk [135]. Due to its effectiveness, drug repositioning has made substantial progress in the development of alternative drugs for the treatment of bacterial and fungal infections over the past decade. And it has become one of the major strategies for the drug development of pharmaceutical companies. Recent research has found that bithionol, a drug previously used to treat parasitic infections in horses, is being reused to kill antibiotic-resistant bacteria, including Methicillin-resistant *Staphylococcus aureus* (MRSA), a common hospital-acquired infection. This is a successful case in which scientists are addressing resistance by exploring drug repositioning.

S. aureus infection can cause osteomyelitis. The current clinical challenge is mainly its relapse and drug resistance [136]. Existing

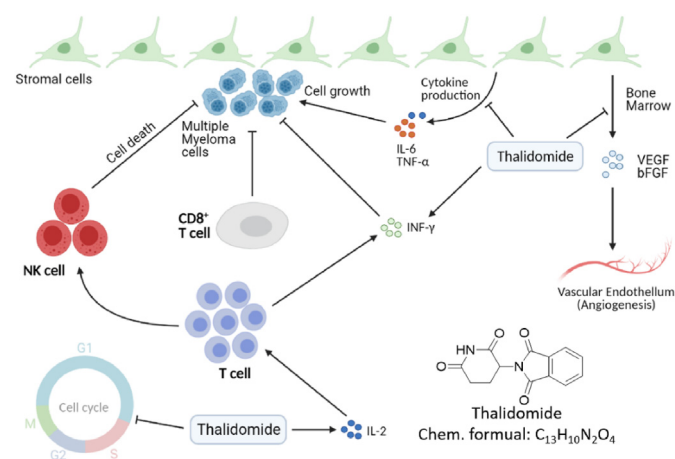


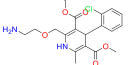
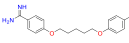
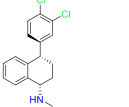
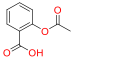
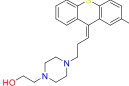
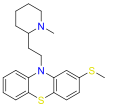
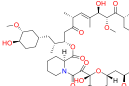
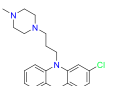
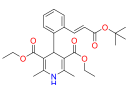
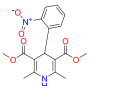
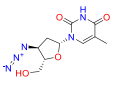
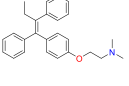
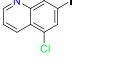
Fig. 5. The pharmacological mechanisms of thalidomide. Thalidomide arrests multiple myeloma (MM) cells in the G1 phase by inhibiting adhesion of MM cells to bone-marrow stromal cells [132].

drugs cannot eradicate small-colony variants (SCV), so drug repositioning is needed to find new drugs to treat chronic infections. Through high-throughput screening from FDA-approved drug libraries, four drugs were finally identified as having bactericidal activity against SCV [137], with the most obvious effect of sitafloxacin. In addition, many non-antibacterial drugs have been reused for bacteria and fungi. For example, the antidepressant azathioprine has anti-biofilm activity against *E. coli* [138]. The activity of anthelmintics against Gram-positive and Gram-negative bacteria and fungi has been reported [139,140]. Mazumdar et al. [141] found that cardiovascular drug **amlodipine** (AML) (Table 5), if combined with existing antibacterial drugs, may overcome the resistance of existing drugs. **AML** exerts antihypertensive and antibacterial effects by inhibiting voltage-gated calcium channels and β -lactamase [142], respectively. Therefore, drug repurposing strategy is related to the polypharmacology of drugs.

The drug repurposing strategy has obvious advantages in the combined treatment of antimicrobial drugs. **Pentamidine** (Table 5) is suspected to interfere of critical functions in DNA, RNA and protein synthesis [143]. Through screening, it was found that **pentamidine** can be combined with antibacterial drugs to treat multidrug-resistant Gram-negative infections. The mechanism of action studies reveal that **Pentamidine** altered the integrity of the outer membrane of *E. coli*, providing a physical basis for this synergy [144]. Different mechanisms of action demonstrate that the drug repurposing strategy of **pentamidine** is related to polypharmacology. However, whether the laboratory results can be successfully converted into clinical results needs further research. **Sertraline** (Table 5) is an antidepressant which belongs to selective serotonin reuptake inhibitors (SSRIs). The combination of **sertraline** and amphotericin B has a synergistic effect on *Alternaria alternata*. Zhai et al. reported [145] that **sertraline** exhibits a unique effect on cryptococcosis by interfering with translational inhibition of protein synthesis. Costa Silva et al. proved that SSRIs promote apoptosis and reduce the biological activity of *C. albicans* by changing the integrity of the mitochondrial membrane [146]. The antifungal activity on a variety of fungi makes **sertraline** promising as an antifungal drug. Due to the lack of antibiotics that can be used to treat methicillin-resistant *S. aureus* (MRSA), an alternative therapy continues to be found. It proved that sertraline acts as SSRI but repurposed for different diseases settings. **Aspirin** relieves pain and reduces fever mainly due to decreased prostaglandins and TXA2. However, **aspirin** (Table 5) plays an anti-staphylococcal effect by inhibiting the expression of alpha-toxin and matrix adhesion genes [147]. The differences of targets demonstrated that the repurposing strategy is related to polypharmacology. Others proved that although **aspirin** is less effective than ordinary antibiotics, it can exert a synergistic effect as an adjuvant for MRSA [148]. **Flupenthixol** is a powerful antagonist of both D1 and D2 dopamine receptors [149]. Recently, it is found that **flupenthixol** reduces the proton pump activity of *S. aureus* by decreasing the transmembrane potential. Different targets and mechanisms of action indicate that the repurposing strategy is related to polypharmacology. In view of the increasing number of pathogenic organisms with multidrug resistance, combination therapy may prove to be the best option.

Thioridazine (Table 5) was a typical antipsychotic drug act on Dopamine D2 and D1 receptor in its early period, and it was stopped using in 2005 due to adverse cardiac reactions [150]. **Thioridazine** proved to be sensitive to methicillin-sensitive *S. aureus* (MSSA), Enterococcus, and *M. tuberculosis*, the mechanism of action is suspect the inhibition of membrane-bound enzymes [151]. Although **thioridazine** has lost its role in the treatment of psychosis, it still has great potential in antifungals. Different mechanisms of action in different targets indicate that drug repurposing may provide a strategy for developing

Table 5
Drug repurposing examples and their mechanism of action in antimicrobial applications.

Drug	Structure	Drug Class	Repurposed Indication	Initial Mechanism	Original Indications
Amlodipine		Cardiovascular	Antibacterial	Act on vascular smooth muscle to lead to a reduction in peripheral vascular resistance	Hypertension. Coronary artery disease. Angina
Pentamidine		Antiprotozoal	Antibacterial	Inhibition of protein and RNA synthesis and antagonism of receptors	For the treatment of pneumonia
Sertraline		Antidepressant	Antifungal	Inhibition of CNS neuronal uptake of serotonin (5HT)	Used for the treatment of major depressive disorder (MDD)
Aspirin		NSAIDs	Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Target cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2)	Pain, fever, and inflammation
Flupenthixol		Antipsychotics	Antibacterial	Antagonizing dopamine actions	Used for maintenance therapy of chronic schizophrenic patients
Thioridazine		Antipsychotic	Methicillin-resistant <i>Staphylococcus</i> (S.) aureus	Block dopamine (DA) receptors	For the treatment of schizophrenia and generalized anxiety disorder
Rapamycin (TOR)		Potent immunosuppressant	Antifungal; Antineoplastic	Selectively block the transcriptional activation of cytokines thereby inhibiting cytokine production	Used to treat lymphangi leiomyomatosis
Prochlorperazine		Antipsychotics	Antibacterial	Block D2 dopamine receptors in the brain	Indicated for the symptomatic treatment of severe nausea and vomiting
Lacidipine		Cardiovascular drug	Gram-positive and Gram-negative	Dilating peripheral and coronary arteries, reducing peripheral vascular resistance	Indicated for the treatment of hypertension either alone or in combination with other antihypertension agents
Nifedipine		Cardiovascular drug	Gram-positive and Gram-negative	Interfere with cell biosynthesis	Indicated to treat vasospastic angina and chronic stable angina
Zidovudine		Antiretroviral drug	Synergistic effects with polymyxin	Prevent the formation of phosphodiester linkages	Used in combination with other antiretroviral agents for the treatment of human immunovirus (HIV) infections.
Tamoxifen		Breast cancer	Antifungal	Estrogen receptor antagonist	Indicated to treat estrogen receptor-positive metastatic breast cancer in adults
Clioquinol		Antiseptics	Antifungal	Act as a zinc and copper chelator	Used for the treatment of various intestinal diseases

antimicrobial drugs. Signaling pathways that activate mitogen-activated protein kinase (MAPKs) elicit many of the responses due to changes in environmental conditions and other stimuli. These pathways were first elucidated in the unicellular eukaryote *Saccharomyces cerevisiae*. The MAPK pathways of yeast among the understood signal transduction have greatly improved our knowledge about the functions and regulation of these pathways. Also, these studies provide guidelines for drug repurposing [152]. Subsequently, Immunosuppressants often lead to reduced immune function in the treatment of autoimmune diseases, accompanied by fungal infections. Therefore, research on the antifungal activity of

immunosuppressants has been increased. **Rapamycin** (Table 5), a serine/threonine protein kinase inhibitor, directly regulates protein synthesis, cellular proliferation and lipid metabolism. On the other hand, **rapamycin** has a synergistic effect with amphotericin B in a limited dose [153]. The drug exerts its antibacterial effect mainly by retarding cell-cycle progression at the G1/S transition. Although **rapamycin** cannot be used as an antibacterial drug in clinical trials, it is still a potential antibacterial drug due to its target. The advantage of this repurposing strategy is combination therapy due to act on different targets. **Prochlorperazine** mainly works on D2 dopamine receptors and is used for the treatment of anxiety and

schizophrenia. In vitro screening shows that **prochlorperazine** has strong antibacterial activity in *Bacillus* and *Enterobacter* [154]. Especially, it was found to reduce the proton motive force of *S.aureus* by reduction in the transmembrane potential [155]. **Prochlorperazine** biased towards adjuvants for combined use against multiple fungi in the subsequent development process. **Lacidipine** (Table 5) is a powerful third-generation calcium channel blocker used to treat hypertension [156]. In 2007, it was found through in vitro screening that the drug has essentially antibacterial effects on *S. aureus* and *V. cholerae* [157]. The primary mechanism may be the combination of **lacidipine** and conventional antibacterial drugs to cause structural modification or enhance its antibacterial effect [157]. The mechanism of antibacterial action of **lacidipine** needs further study. **Nifedipine** (Table 5) is L-type calcium channel blocker. In the experiment, it showed promising antibacterial activity against *Cryptococcus*, *Candida* and yeast. The compounds screened to have antibacterial effect belong to dihydropyridines, so it is believed that the antibacterial effect is mainly related to its structure. Experimental results show that the antifungal effect of the calcium channel blocker (CCB) involves the regulation of Cch1-Mid calcium channels [158]. Although nifedipine belongs to non-dihydropyridine CCB, it belongs to L-type CCB [159]. Mechanism studies suggest that **nifedipine** repurposes in different disease settings. **Zidovudine** (Table 5) is used to treat HIV due to its anti-retroviral activity [160]. *K. pneumoniae* lacks effective treatment drugs due to multi-drug resistance. It has recently been proposed that the combination of **zidovudine** and polymyxin B shows excellent antibacterial efficacy and minimizes the resistance to polymyxin [161]. **Zidovudine** was activated in bacteria by thymidine kinase (TK), and interference in DNA resulted in DNA chain termination. The repurposing strategy of zidovudine has been demonstrated in different diseases settings [162].

FDA-approved small-molecule compound library was screened for ESKAPE pathogens, of which ebsele (EB) and 5-fluoro-2'-deoxyuridine (FdUrd) have improved mouse survival rate in lethal models of septicemic MRSA infection. The results indicate the potential of these drugs to treat resistant bacterial infections [163]. In addition, Breger et al. identified 15 drugs with antifungal activity [164]. In recent years, several different methods have also been derived to find new indications for the rapid location of old drugs. Arielle et al. [165] developed a high-throughput assay that ultimately identified 75 drugs by screening generic drug libraries. **Tamoxifen** (Table 5) initially targets estrogen receptor that is prevalent in receptor-positive breast cancers. But the drug also affects neutrophils and produces neutrophil extracellular traps (NETs), a mesh of proteins that kill bacteria. The 'off-target effects' could have critical clinical implications. Another method is to screen based on the specific effective structure of antibacterial drugs to find potential antibacterial drugs. Ejim et al. [166] proposed screening from approved drug libraries, and obtained six non-antibacterial drugs, which enhanced the activity of Mexicycline against a reference *Pseudomonas aeruginosa* strain. Bacterial resistance is accompanied by a gradual decrease in treatment options, and multiple aspects need to be taken to address the issue of global antimicrobial resistance. In short, the combination of drug repositioning of antimicrobials and the rapid development of new drug mechanisms can reduce the abuse of antimicrobials or reduce the constant threat of antimicrobial resistance. It is through different approaches that humans can cope with the challenges posed by antimicrobial resistance.

4.1. Represented cases of drug repositioning in antimicrobial repositioning

Fungicides are broad-spectrum chemical agents that inactivate

microorganisms. When bactericides are used on living tissues, they are often referred to as antiseptics [167]. **Clioquinol** was produced as an antiseptic and sold as an oral intestinal acaricide in 1934 for the treatment of various intestinal diseases [168]. In the early 1970s, it was withdrawn from the market due to its association with subacute myeloid optic neuropathy (SMON) [168]. Alsterholm M et al. investigated antibacterial activity of a combination of **clioquinol** and corticosteroids against *Calbicans*, *E.coli*, *S.aureus*, *S.epidermidis* and *Streptococcus pyogenes* [169]. Among all topical skin drugs, 3% **clioquinol** has the strongest antifungal activity. Based on reported researches, it is believed that **clioquinol** can be a promising formulation in topical epidermal mycosis [167]. It can also be used in combination with systemic antifungal agents to reduce the occurrence of drug resistance and enhance efficacy. It has a broad antifungal spectrum and has moderate to strong activity among common pathogenic fungi. In addition, studies have shown that **clioquinol** does not exhibit an antibacterial effect by directly binding ergosterol to exhibit plasma membrane instability. Through in-depth study of the mechanism, it is shown that **clioquinol** can act on the cell wall more effectively than other derivatives to exert antibacterial effects [170]. Therefore, reasonable structural modification can speed up the development of antifungals and enhance the application.

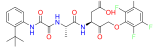
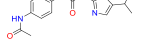
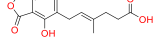
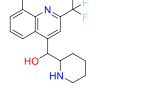

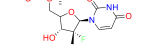
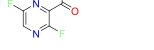
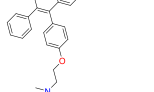
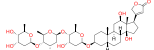
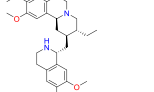
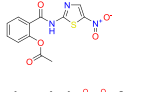
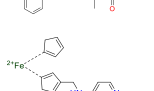
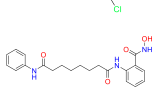
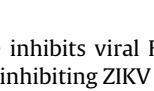
5. Antivirus repositioning

Influenza virus infection has become a serious worldwide health problem due to its infectivity. The virus was first discovered in tobacco plants. Researchers have discovered that diseases in tobacco plants are transmitted through a vector called tobacco mosaic virus. Over the past few decades, scientists have successfully developed dozens of antiviral drugs against viral proteins or host factors. Antiviral drugs could be divided into three main categories, including anti-DNA virus drugs, anti-RNA virus drugs, and anti-retroviruses drugs. The virus needs to enter the cell before replicating, eventually causing the virus to become infected. Although there are both vaccines and antiviral drugs, some genes of viruses constantly change and antiviral resistance emerges. Due to this, it is urgent to develop efficient antivirals.

Although Zika virus infection shows mild or even asymptomatic symptoms, there is currently no effective treatment. For similar public health events, traditional drug development processes are complex and time-consuming. Protein-targeting drugs may have limitations, hope to find new indications for existing drugs [171]. Barrows et al. [172] identified 24 potential anti-ZIKA viruses' drugs through screening. Xu et al. [173] also systematically identified **emricasan**, an oral caspase inhibitor, as a highly effective anti-ZIKA drug. Although the FDA-approved drugs show good safety and pharmacokinetics, they have been proven to affect the fetus, which means clinical trials are essential [172]. Drug targets network analysis can be used to identify important genes in the infection pathway in the screening process.

In 2014, the large-scale ZIKA virus (ZIKV) outbreak in Brazil caused global health problems. Mechanism studies have found that ZIKV infection leads to increased caspase-3 activation, which in turn leads to cell death [174]. **Emricasan** (Table 6) is the first caspase inhibitor tested in human which is used to protect liver cells from excessive apoptosis. **Emricasan** exerts antiviral effects by reducing neuronal cell death and inhibiting the activity of caspase-3, which is induced by ZIKV. The repurposing strategy is based on the same target but repurposing for different diseases settings. **PhA-690509** (Table 6) as an investigational drug for cell cycle-dependent kinase (CDK), inhibits all three ZIKV strains in a dose-dependent manner. As one of the first drugs to be screened and proven to have antiviral activity against ZIKV, **PhA-690509** as well

Table 6
Drug repurposing examples and their mechanism of action in antiviral applications.

Drug	Structure	Drug Class	Repurposed Indication	Mechanisms	Original Indications
Emricasan		Nonalcoholic steatohepatitis (NASH)	ZIKV infection	Anti-cell-death	Investigated for treatment in hepatitis (viral, C), liver disease
PhA-690509		Cyclin-dependent kinase A inhibitor	ZIKV infection	Inhibit caspase-3 activity in SNB-19 cells	Anti-cancer
Mycophenolic acid		Immunosuppressant	ZIKV infection	Inhibit an enzyme needed for the growth of T cells and B cells	For the prophylaxis of organ rejection in patients receiving allogeneic renal transplants
Mefloquine		Chloroquine resistant or multidrug resistant falciparum malaria	ZIKV infection	Asexual red blood cell type killing Plasmodium falciparum; Plasmodium vivax (killing blood proliferator)	Against chloroquine-resistant forms of Plasmodium falciparum
Suramin		African trypanosomiasis and onchocerciasis	ZIKV infection	Block the replication of a variety of viruses	For treatment of onchocerciasis
Sofosbuvir		Chronic hepatitis C	Inhibit ZIKV RNA polymerase	Against hepatitis C virus (HCV).	Used in combination therapy with other antiviral medications to treat HCV infected patients
Favipiravir		Influenza	Against Ebola Virus	Inhibit RNA dependent RNA polymerase (RdRp) activity of influenza virus	Used to treat cases of influenza that were unresponsive to conventional treatment
Toremifene		Metastatic breast cancer	Against Ebola Virus	Overexpression of NPC1 inhibits virus invasion	For the treatment of metastatic breast cancer
Cardiac glycosides		Chronic cardiac insufficiency	Anti-HCMV	Drugs interfere with host pathways where viruses are carried away	manifest and chronic cardiac insufficiency
Emetine		Anti-parasitic drugs	Anti-HCMV	Direct killing of amoeba trophozoites	severe invasive amoebiasis
Nitazoxanide		Anti-parasitic drugs	Anti-HCMV; Anti-Influenza	Inhibit RNA and DNA virus replication	For the treatment of diarrhea in adults and children caused by the protozoa Giardia lamblia
Manidipine		Anti-hypertensive drug	Anti-HCMV	Block the entrance of extracellular calcium into the cell	For the treatment of hypertension
Ferroquine		Antimalarial	Anti-HCV	Inhibit the formation of β -hemin	Antimalarial drug candidate
Suberoylanilide hydroxamic acid		Anticancer	Anti-HCV	Catalyze the removal of the acetyl moiety from the lysine residues of proteins	For the treatment of cutaneous T-cell lymphoma

as niclosamide inhibits viral RNA replication and finally achieves the purpose of inhibiting ZIKV infection [173]. Due to both DNA and RNA viruses modifying CDK function to favor viral replication, it plays a prominent role in viral infections. The study demonstrates that the repurposing strategy is related to the exact mechanism in different diseases settings. **Mycophenolic acid (MPA)** (Table 6) was used as an immunosuppressant in the early stage to prevent dengue infection [175]. **MPA** depletes guanosine nucleotides and inhibits their proliferation, thereby suppressing cell-mediated immune responses and antibody formation [176]. Through the

screening of cells that are susceptible to the ZIKA virus, it is found that **MPA** shows the most effective antiviral effect on ZIKV [177]. The mechanism of the drug's effect may be due to targeting the ZIKV replication process [177]. In addition, the safety of **MPA** makes it a potential drug for the treatment of the ZIKA virus. Research studies indicate that the drug repurposing strategy of **MPA** is related to specific mechanism of action but repurpose for different disease settings. Mefloquine inhibits merozoite invasion and proteins interactions involved with nutrient uptake to exert an anti-malarial effect. **Mefloquine** (Table 6) was identified that has an

effective anti-dengue virus and anti-ZIKA virus activity by virtual screening [178]. Different from the wet experimental screening method, **mefloquine** was obtained by calculating the electrostatic potential map of the compound through molecular modeling, and the antiviral activity was tested by experiment [178]. Since this drug has shown adverse events of anxiety or hallucinations in clinical trials, **mefloquine** needs to be tested in vivo to further evaluate its safety. Also, its detailed mechanism of action remains to be further studied. **Suramin** (Table 6) is an anti-parasitic drug initially, and it was more recently shown inhibition on multiple viruses. After the outbreak of ZIKV, it is believed that it can be used to treat ZIKV infection. **Suramin** inhibits the early stage of the replication and affects the entry of the virus, thereby reducing the proportion of cells infected by ZIKV. The intervention of **suramin** will not only affect the synthesis of viral RNA but also reduce the infectivity [179]. The results verify that the repurposing strategy is on the basis of different diseases settings. The FDA approved **sofosbuvir** (Table 6) in 2013 to treat chronic hepatitis C virus (HCV), and it is also the first drug that treats certain HCV without the need for interferon therapy [180]. Like the mechanism that initially achieves therapeutic effects by sofosbuvir, it mainly reduces the number of viral infections by restraining viral replication [181]. The drug repurposing strategy with specific mechanism but repurpose for different diseases settings. **Sofosbuvir** is well tolerated and safe in its original pharmacological effects, and these advantages can support its development as an anti-ZIKV drug. **Favipiravir (T-705)** (Table 6) is an RNA polymerase inhibitor that works on influenza. Although **favipiravir** is well tolerated in the Ebola virus disease, it does not show strong antiviral activity. **Favipiravir** acts as the primary mechanism of anti-influenza or antiviral drugs through selective and potent inhibition of RNA-dependent RNA polymerase (RdRp) of RNA viruses [182]. Experimental studies have shown that the infectivity of the virus gradually decreases with increasing doses [183]. Although **Favipiravir** exhibits a dose-dependence, the Pharmacokinetics (PK) and tolerability of relevant doses need to be studied to determine the best dosing regimen of **favipiravir**. **Toremifene** (Table 6), selective estrogen receptor (ER) modulators, is used to treat certain breast cancers. **Toremifene-Mefloquine-Posaconazole** is a group of drugs that can effectively block the entry of Ebola [184]. The main mechanism of action may be direct binding to the internal fusion loop region of Ebola virus glycoprotein (GP). These three drugs achieve a synergistic effect by inhibiting Niemann-Pick C1 (NPC1) protein, Acid sphingomyelinase (ASM) activity, and Nicotinic acid adenine dinucleotide phosphate (NAADP)-stimulated lysosomal calcium release [184]. Drugs used to treat EBOV lost potency due to low activity. The combined method can not only prevent the development of drug resistance but also reduce the dosage of each drug. Polypharmacology of toremifene provides the potential for drug repurposing. Pregnant women and people with weakened immune systems are often threatened by human cytomegalovirus. **Cardiac glycoside (GC)** (Table 6) is a type of glycoside compound that can enhance myocardial contractility. It inhibits the $\text{Na}^+ - \text{K}^+ - \text{ATPase}$ on tissues to increase intracellular Ca^{2+} concentrations to promote inotropy and bradycardia [185]. **GC** has recently been shown to have anti-cancer and antiviral activities [186]. As a typical cardiac glycoside compound, digoxigenin can effectively inhibit HCMV at a concentration of nanomolar level [187]. Studies have found that cardiac glycosides may inhibit HCMV replication by regulating transcription and translation. Therefore, it is recommended to explore its significance on the combination treatment in subsequent development. Different mechanisms of action on different targets lead to drug repurposing strategies. **Emetine** (Table 6), an FDA approved drug for the treatment of amoebiasis, blocks protein synthesis in both mammalian and parasitic cells. The combination of **emetine** and Ganciclovir

synergistically inhibits murine cytomegalovirus (MCMV) in a mouse model, but its anti-HCMV activity significantly reduced in vitro. Unlike emetine inhibiting RNA and DNA virus replication, another experiment indicates that **emetine** disrupts the interaction between MDM2-p53 and MDM2-IE2 induced by HCMV and exerts antiviral effects. The case of drug repurposing for emetine is related to polypharmacology. Studies have found that the dose of **emetine** used to treat antiviral is far lower than the standard dose, and it does not show toxicity [188]. The advantage of **emetine** as a potential candidate drug for anti-HCMV is that it adopts a new type of host-dependent antiviral mechanism and has higher safety, whether it is a single drug or a combination drug. **Nitazoxanide** (Table 6) initially acts on pyruvate-flavodoxin oxidoreductase for the treatment of diseases caused by other protozoa or helminths. It was later proved that it has effective activity against a variety of RNA and DNA viruses, including influenza and a variety of viruses [189]. Nitazoxanide has been regarded as a broad-spectrum antiviral drug due to inhibit the replication of several RNA and DNA viruses [190]. The drug repurposing strategy is on the basis of specific mechanism but repurpose for different diseases settings. **Manidipine** (Table 6) is used as a calcium channel blocker for the treatment of hypertension. Human cytomegalovirus (HCMV) is a widespread herpes virus, and congenital HCMV infection is one of the causes of fetal death [191]. The IE2 protein of HCMV is an important regulator of viral and host cell gene expression [192]. Studies have shown that **manidipine** explicitly inhibits the replication of HCMV by interfering with the IE2-dependent activation of the viral E gene [193]. Mechanisms studies demonstrated that the repurposing strategy for **manidipine** is related to polypharmacology. **Ferroquine (FQ)** (Table 6) is used for treating malaria may due to inhibit β -hematin formation. Recently, it is investigated as a novel HCV inhibitor. The study of its antiviral mechanism found that the entry stage of HCV is an attractive stage for virus intervention [194]. Ferroquine not only inhibits the binding of HCV into target cells, but also inhibits RNA replication, and finally exhibits antiviral activity independent of genotype. In addition to single-agent antiviral studies, the combination of **FQ** and interferon (IFN) or HCV NS3/4A protease inhibitor also showed a synergistic antiviral effect. The different mechanism of action for **FQ** provide drug repurposing strategy. Ayami Sato et al. found that **suberoylanilide hydroxamic acid (SAHA)** (Table 6), an HDAC inhibitor for T-cell lymphoma, was used as a promising anti-HCV drug. **SAHA** inhibits the replication of HCV in OR6 cells without cytotoxicity [195]. **SAHA** is an effective drug for the treatment of HBV-negative hepatocellular carcinoma (HCC) patients, but **SAHA** should be used with caution in HBV-positive HCC patients [196]. **SAHA** is effective in drug repositioning strategy due to their pharmacological activities in multiple targets.

The coronavirus SARS-CoV-2 is the pathogen of COVID-19. Coronavirus belongs to the Coronaviridae family. COVID-19 is currently the seventh known coronavirus that can infect human, the remaining six are HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV, and MERS-CoV [197]. Due to its high replication rate, it has rapidly spread around the world [198]. With the rising number of confirmed cases, the World Health Organization announced that COVID-19 has become a public emergency of international concern. The main clinical symptoms of confirmed cases are fever, cough, dyspnea, and vomiting [199]. The receptors of SARS-CoV-2 and SARS-CoV are both angiotensin-converting enzyme 2 (ACE2), and mucosal cells contain many ACE2 receptors. The virus could continue infecting new hosts by generating numerous copies of its genome and packaging them into virions. Finally, the capsid and RNA are composed to generate new virus particles and released out of the cell to infect new cells [197]. COVID-19 is a serious respiratory disease. Since there are no drugs

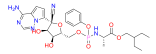
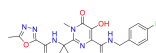
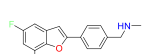
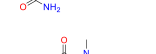
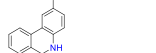
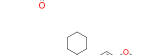
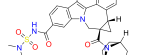
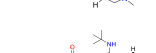
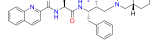
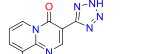
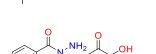
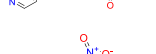
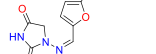
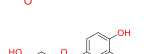
to treat the virus, drug repurposing is an existing effective response strategy.

Rameez et al. [200] identified **raltegravir**, **paritaprevir**, **bictegravir**, and **dolutegravir** as anti-SARS-CoV-2 by targeting 3C-like protease (3C_lpro) and 2'-O-ribose methyltransferase (2'-O-Mtase) of potentially therapeutic drugs. Chen et al. [201] applied the development of SARS-CoV enzyme-specific inhibitors to SARS-CoV-2 and obtained 16 candidate drugs through virtual screening. Among them, the antiviral drugs Eplclusa and Harvoni have

inhibitory effects on HCV. Zhou et al. [202] used web-based drug repositioning methods to quantify the interaction between drugs and targets, and identified 16 potential anti-human coronaviruses (SARS-CoV and SARS-CoV-2) drugs. Table 7 summarizes drugs screened by different methods or for different target proteins as potential drugs for further research.

Remdesivir is a nucleoside analog with antiviral activity and the first drug approved by the FDA for the treatment of COVID-19. Previous reports have shown that **remdesivir** has a variety of

Table 7
Drug repurposing examples and their mechanism of action in COVID-19 applications.

Drug	Structure	Drug Class	Repurposed Indication	Initial Mechanisms	Original Indications
Remdesivir		Antiretroviral	COVID-19	Inhibit action of RNA polymerase	Used to treat RNA virus infections
Raltegravir		Anti-HIV	COVID-19	Act on HIV integrase and prevent HIV replication	For the treatment of HIV-1 infection in conjunction with other antiretrovirals.
CVL218		PARP1 inhibitor	COVID-19	Against SARS-CoV-2 replication. Anti-inflammatory effect	Broad spectrum anticancer agent
PJ-34		PARP1 inhibitor	COVID-19	Reduce RNA binding, which prevents viral replication	Anticancer agent
Beclabuvir		Anti-HCV	COVID-19	Bind to thumb site 1 of the hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase	Antiviral drug for the treatment of HCV infection
Saquinavir		HIV protease inhibitor	COVID-19	Bind to active sites of HIV-1 and 2 proteases	For the treatment of HIV-1 infection
Pemirolast		Bronchial asthma	COVID-19	Inhibit the antigen-induced release of inflammatory mediators	For the prevention of itching of the eyes
Isoniazid Pyruvate		Tuberculosis	COVID-19	Not clear	Isoniazid pyruvate is a metabolite of isoniazid
Nitrofurantoin		Urinary tract infection	COVID-19	Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates	Used to treat acute uncomplicated urinary tract infections
Eriodictyol		Antioxidant	COVID-19	Active the expression of critical transcription factors	Used for antiallergenic, antimicrobial, anticancer, and antioxidant
Ribavirin		Antiretroviral drug	COVID-19	Inhibition of influenza virus RNA polymerase	Indicated for the treatment of chronic Hepatitis C virus
Teicoplanin		Glycopeptide antibiotic	COVID-19	Stop genomic viral RNA release and viral replication cycle	For the treatment of bacterial infections caused by susceptible microorganism
Bortezomib		Treat multiple myeloma and mantle cell lymphoma	COVID-19	Reversible inhibitors of chymotrypsin like activity of 26S proteasome in mammalian cells	Used for the treatment of adult patients with multiple myeloma or mantle cell lymphoma
Flurazepam		Anticonvulsant	COVID-19	Inhibition of limbic system on the control of brainstem reticular structure	For short-term and intermittent use in patients with recurring insomnia and poor sleeping habits

antiviral activities in vitro [203–205], including SARS-CoV [206] and MERS-CoV [207]. **Remdesivir** is a diastereomeric mono-phosphate phosphoramidate prodrug that inhibits viral RNA polymerase. Its active analog enters and accumulates in the cell. Consistent with other antiviral mechanisms of action, it exerts anti-SARS-CoV-2 activity by inhibiting RNA-dependent RNA polymerase. However, the WHO recommended publishing that **remdesivir** did not significantly improve the survival rate and hospitalization of patients. Therefore, its clinical effectiveness and safety need to be further evaluated. **Raltegravir** is an antiretroviral drug used in the treatment of HIV-1 infection. It impedes the insertion of HIV-1 DNA into the host cell genome. Subsequently, raltegravir was identified as a potentially effective drug against the main protease (Mpro) of SARS-CoV-2 based on a computational method [200]. Since Mpro is essential to the life cycle of the virus, it is recognized as the best drug discovery target [208]. Raltegravir was screened against Mpro and RdRp. The drug exerts an antiviral mechanism of action that is consistent but repurposed in different disease settings. Although the computational approach can speed up the process of drug repositioning, it still needs further evaluation in vitro and in vivo. The method based on machine learning predicts that poly ADP-ribose polymerase 1 (PARP1) inhibitor **CVL218** is an effective drug against coronavirus and has been experimentally verified in vitro [209]. Researchers speculated that CVL218 might target the N-terminal domain of SARS-CoV-2 to impede viral replication. They also emphasized that PARP inhibitors may inhibit the replication of coronavirus. Clinical studies of non-cancerous diseases have proved that PARP1 inhibitors treat acute lung diseases caused by SARS-CoV-2 infection [210]. **PJ-34** is the first-generation PARP1 inhibitor. Past studies have shown that PARP1 inhibitors play a central role in inflammatory injury and related diseases, especially in inflammatory diseases of the lung [211]. In particular, **PJ-34** can target the N-terminal domain of the coronavirus nucleocapsid (N) protein and reduce the RNA binding ability, thereby inhibiting virus replication [209]. This is also the basic research that **PJ-34** is considered to be an effective antiviral drug [212]. The method of describing the interaction between drugs and viral targets based on the knowledge map also confirmed that **PJ-34** might have anti-SARS-CoV-2 activity. But further clinical verification is needed. The repurposing strategy of CVL218 and PJ34 is based on specific mechanisms of action but repurposes for different diseases settings.

Beclabuvir is a non-nucleoside NS5B polymerase inhibitor of the RdRp of the hepatitis C virus (HCV) [213]. Both SARS-CoV-2 and HCV are + ssRNA viruses. Thus, an attempt was made to identify effective SARS-CoV-2 inhibitors by screening RdRp inhibitors. **Beclabuvir** was identified as a potential drug for the treatment of SARS-CoV-2 through virtual screening of approved drugs [213]. It had been proved that beclabuvir can efficiently bind to RdRp of the SARS-CoV-2. In this case, drug repurposing strategy is based on specific mechanism of action but apply in different diseases. Molecular docking predicted **saquinavir** is an anti-SARS-CoV-2 drug, and its binding mode is highly similar to the Mpro ligand N3 [214]. **Saquinavir** binds to the active site of the HIV-1 and HIV-2 proteases to prevent the cleavage of viral polyproteins. *In silico* study demonstrated that **saquinavir** inhibited 3CL^{P_{ro}} activity in SARS-CoV-2 [215]. In addition, in vitro studies have shown that low-dose **saquinavir** can alleviate the replication of SARS-CoV-2 [216]. Although the calculation method still has certain limitations and required experimental verification, this method speeds up drug discovery and provides a guiding role for the experiment [217]. In the early period of the COVID-19 outbreak, in order to find effective treatment as soon as possible, Nicholas Dean Smith used to screen compounds at the interface between S protein and human ACE2 receptor by virtual screening. Results show that **pemiroloast** has the strongest binding affinity [218]. Besides, the higher-ranking

compounds include **isoniazid pyruvate**, **nitrofurantoin**, and **eriodictyol**. Among them, **pemiroloast** is used to treat chronic asthma through inhibiting the antigen-induced release of inflammatory mediators [219]; **isoniazid pyruvate** is a metabolite of isoniazid [220]; **nitrofurantoin** is used to treat urinary tract infections via reduced bacterial flavoproteins to reactive intermediates, and **eriodictyol** is used to treat asthma via activates the expression of transcription factors in a dose-response manner [221]. Although a preliminary ranking of small molecules can be performed through large-scale virtual screening, the compounds obtained based on calculations need to be experimentally verified. The specific mechanism of action should be studied for the development of fully effective and safe COVID-19 drugs. **Ribavirin** is a guanine analog. The antiviral activity not only interferes with polymerase, but also directly inhibits the production of natural guanosine by inhibiting inosine monophosphate dehydrogenase directly, thereby reducing the viability of the virus [222]. Studies have reported [223] that the current three-drug combination (**interferon beta-1b** + **lopinavir-ritonavir** + **ribavirin**) is the safest and effective, but more clinical trial data are necessary. Drug repurposing mainly aims to enhance drug efficacy through combination therapy. There are interactions between ribavirin and multiple domains of SARS-CoV-2 infection. The reduction of TMPRSS2 expression by **ribavirin** can be explained as the mechanism of action against SARS-CoV-2. The repurposing strategy is related to specific mechanism of action but repurpose in different type of virus. **Teicoplanin** is an antibiotic used to treat staphylococcal infections. It exerts antibacterial activity by binding to lipid substrate, resulting in inhibition of bacterial peptidoglycan synthesis [224]. This drug has shown activity against a variety of viruses [225,226]. **Teicoplanin** blocks the virus replication by blocking the protease that mediates the cleavage of the viral S protein [227]. A recent retrospective report showed that the mortality rate of the **teicoplanin** group was more reduced than the control group [228], but there was no statistically significant difference. In this case, the drug repurposing strategy is based on polypharmacology properties. After evaluating the antiviral activity of several HIV-1 protease inhibitors against SARS-CoV-2 in vitro, researchers found that **nelfinavir** showed the lowest EC₅₀ value and the highest selectivity index (SI). Thus, it is considered as a candidate for the treatment of COVID-19 [229]. Li et al. reported that **nelfinavir** is active against SARS-CoV-2 in Vero E6 cells, and it displayed multi targets properties through docking results [230]. The drug repurposing strategy of **nelfinavir** is based on the virtual screening of antiviral drugs. The specific mechanism of action needs further study. Researchers from the Tokyo National Institute of Infectious Diseases subsequently reported that the combined use of **nelfinavir** and cepharanthine showed satisfactory results [231]. But the research is currently only in vitro testing, and further research is needed.

5.1. Represented cases of drug repositioning in antiviral applications

One of the representative cases of drug repositioning in antiviral is the use of **Chloroquine (CQ)** to treat ZIKA. **CQ** is a commonly used anti-malarial drug, which has important clinical significance. Besides, **CQ** is also used to treat rheumatoid arthritis and other autoimmune diseases. It has been proven that **CQ** can reduce ZIKV-related morbidity and mortality [232]. One of the main challenges of ZIKV is congenital fetal malformations caused by an infection in pregnant women. **CQ** has a long and successful history, and there is no clear evidence that it can cause fetal harm when used to prevent malaria [233]. Therefore, **CQ** is recommended for the prevention and treatment of ZIKV. **CQ** hinders the fusion of flavivirus envelope

protein and endosomal membrane by affecting endosomal acidification. Cell proteases are essential for the lysis of flavivirus precursor membrane (prM) protein during virus excretion. This transition is pH-dependent, and changes in intracellular pH may cause the release of fewer infectious virus particles [234].

Furthermore, studies have shown that **CQ** can inhibit SARS CoV-2 replication in Vitro, but it has not shown obvious advantages in vivo. It is currently proposed that the antiviral mode of action may intervene life cycle of the virus. Another suggested mechanism is to inhibit quinone reductase 2 [235], which is necessary for sialic acid, while coronaviruses are abundant in sialic acid [236]. Recent antiviral studies have shown that **CQ** interferes with the glycosylation process of the cellular receptor ACE2 to inhibit SARS CoV-2 from entering cells [237]. It is necessary to pay attention to the G6PD activity in the blood of patients in clinical trials. The use of **CQ** in patients with G6PD deficiency may bring high-risk adverse reactions [238].

6. Conclusion

Drug repositioning has become a successful drug discovery strategy due to reduced costs and faster approval procedures. Many successful examples have also shown the great potential of this method in practice. Drug repositioning has multiple advantages, including safety, money-saving market potential advantages, and return on investment potential. It is known that the safety of existing drugs reduces the risk of drug discovery, and this advantage fetches up shortcomings of drug development due to safety failures. As the cost of repositioning is much lower than the de novo drug development, it provides a new strategy for non-profit organizations and academic centers. The repositioned drug Thalomid and its derivatives have brought more than 2.8 billion U.S. dollars in revenue (<https://ir.celgene.com/investors/default.aspx>), this result also proves the return-on-investment potential of drug repositioning. Although drug repositioning significantly reduces the time and cost associated with the drug development process, the limitations of its application should not be underestimated. A majority of the cases only stay in experiments in vivo and in vitro. Thus, drug repositioning could be improved in many different ways. For example, computational approaches can predict new indications for old drugs and learning their intrinsic features simultaneously, which can help us to identify potential candidates and greatly improve screening efficacy by computational methods.

The rapid growth of disease and drug-related data sets in recent years has also brought rapid development to computational drug repositioning, especially structure-based drug repositioning. Strategies like machine learning and knowledge-based mapping such as network pharmacology can more accurately analyze the internal relationship between drugs and targets, thereby obtaining more meaningful information. Considering the sudden global major public health event such as COVID-19, computational drug repositioning is one of the most feasible strategies. To better understand the role of different methods in drug repositioning, and provide methodological guidance for future public health emergencies, we recommend combining experimental and computational approaches to improve the efficiency of drug repositioning. In this article, we reviewed new mechanisms of action for drugs on common diseases including neurological diseases, cancer, microbial, and virus infections. The opportunities for drug repositioning are of great potential. Although different drugs adopt different identification approaches for repositioning, most of them stay before phase II clinical trial, which is still far away from markets. A better way is to combine multiple approaches both computationally and experimentally for different situations and exploring specific mechanisms, providing novel insights and helping identify candidates for new treatment.

Notes

The authors declare no competing financial interest.

CRediT authorship contribution statement

Yi Hua: Writing – original draft. **Xiaowen Dai:** Data curation. **Yuan Xu:** Data curation. **Guomeng Xing:** Data curation. **Haichun Liu:** Data curation. **Tao Lu:** Writing – review & editing. **Yadong Chen:** Writing – review & editing. **Yanmin Zhang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

AD	Alzheimer's Disease
WHO	World Health Organization
SP	Senile Plaque
NFTs	Neurofibrillary Tangles
APP	Amyloid precursor protein
BEXA	Bexarotene
RXR	Retinoid X Receptor
CTCL	T-cell lymphoma
DHEA	Dehydroepiandrosterone
RAR	Retinoic Acid Receptor
ApoE	Apolipoprotein E
ARB	Angiotensin Receptor Blockers
CCB	Calcium Channel Blockers
SERM	Selective Estrogen Receptor Modulators
GLP-1	Glucagon-Like Peptide-1
nAChR	Nicotinic Acetylcholine Receptor
ACh	Acetylcholine
NMDA	N-methyl-D-aspartate
PPI	Proton Pump Inhibitor
PD	Parkinson's Disease
ACF	Abnormal Crypt Foci
AOM	Azoxymethane
FASN	Fatty Acid Synthase
DCA	Dichloroacetate
PDK	Pyruvate Dehydrogenase Kinase
CRC	Colorectal Cancer
Tan IIA	Tanshinone IIA
PPARs	Peroxisome Proliferators-Activated Receptors
CA	Clofibrilic Acid
CR	Carbonyl Reductase
YAP1	Yes-Associated Protein 1
AMPK	Adenosine Phosphate Active Protease
PKC	Protein Kinase C
DSF	Disulfiram
ALS	Amyotrophic Lateral Sclerosis
MAPK	Mitogen-Activated Protein Kinase
PI3K	Phosphatidylinositol 3-Kinase

DHODH	Dihydroorotate Dehydrogenase
MM	Multiple Myeloma
NPC1	Niemann-Pick C1
NAADP	Nicotinic Acid Adenine Dinucleotide Phosphate
ASM	Acid Sphingomyelinase
FGF	Fibroblast Growth Factor
VEGF	Vascular Endothelial Growth Factor
SCV	Small-Colony Variants
AML	Amlodipine
SSRIs	Selective Serotonin Reuptake Inhibitors
MRSA	Methicillin-Resistant <i>S. aureus</i>
CCB	Calcium Channel Blocker
SMON	Subacute Myeloid Optic Neuropathy
ZIKV	ZIKA Virus
CDK	Cycle-Dependent Kinase
MPA	Mycophenolic Acid
HCV	Hepatitis C Virus
PK	Pharmacokinetics
FQ	Ferroquine
SAHA	Suberoylanilide Hydroxamic acid
HCC	Hepatocellular Carcinoma
ACE2	Angiotensin-Converting Enzyme 2
3Clpro	3C-Like Protease
PARP1	Poly ADP-ribose Polymerase 1
RdRp	RNA-dependent RNA polymerase
prM	precursor Membrane
CQ	Chloroquine
G6PD	Glucose-6-Phosphate Dehydrogenase

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