Repositioned Drugs for Inflammatory Diseases such as Sepsis, Asthma, and Atopic Dermatitis

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Abstract

The process of drug discovery and drug development consumes billions of dollars to bring a new drug to the market. Drug development is time consuming and sometimes, the failure rates are high. Thus, the pharmaceutical industry is looking for a better option for new drug discovery. Drug repositioning is a good alternative technology that has demonstrated many advantages over *de novo* drug development, the most important one being shorter drug development timelines. In the last two decades, drug repositioning has made tremendous impact on drug development technologies. In this review, we focus on the recent advances in drug repositioning technologies and discuss the repositioned drugs used for inflammatory diseases such as sepsis, asthma, and atopic dermatitis.

Key Words: Drug repositioning, Inflammatory disease, Sepsis, Asthma, Atopic dermatitis

INTRODUCTION

Since the early 1990s, drug repositioning has evolved and generated considerable interest, especially during the last 10 years. Bringing new drugs to the market using conventional drug discovery technologies is a time-consuming and expensive process, due to which many drug companies have turned towards drug repositioning (Sekhon, 2013). Another major factor that has led to an increased interest in drug repositioning is the high failure rate of new drugs. Drug repositioning provides a promising avenue to identify better and safer treatment options without the full cost or time required for *de novo* drug development (Ashburn and Thor, 2004; Chong and Sullivan, 2007; Tobinick, 2009; Sleigh and Barton, 2010; Phelps, 2011; Sardana *et al*., 2011). Discovery of novel drug targets is another big challenge in the drug development process. In the treatment of diseases more than 400 proteins are used as drug targets and many known drug targets are involved in multiple pathologies (Sekhon, 2013). Historically, researchers came to know about drug repositioning due to some unexpected discoveries during late stage clinical trials or post-approval steps. One such classic example is sildenafil that was unsuccessful in its development as a new drug for common hypertension but became immensely successful as a drug for male erectile impotence and was later established as a drug to treat pulmonary arterial hypertension (Sekhon, 2013). Research is ongoing to find alternate uses of existing approved or generic drugs to treat many diseases (Fig. 1).

Drug repositioning can be defined as finding new uses of existing drugs that are outside the scope of the original indication (Jang *et al*., 2016). Since the last decade, drug repositioning has gained increased importance due to the enormous rise in the cost of new drug discovery (O'Connor and Roth, 2005; Chong and Sullivan, 2007). Many researchers are applying repositioning strategies to discover novel therapeutic applications of known drugs, since 90% of the new drug candidates fail in the early stages of safety and efficacy tests during *de novo* drug discovery. For the development of drugs, various target protein and drug characteristics, based on chemical structures and the properties of ligands and receptors, have been used to identify new targets for existing drugs (Jang *et al*., 2016). According to the Keiser hypothesis, structurally similar chemicals have comparable properties, including biological activities (Keiser *et al*., 2009).

The docking method is a common strategy used in drug repositioning. This method focuses on the physical interactions between drugs and targets (Zahler *et al*., 2007; Kinnings *et al*., 2009; Chang *et al*., 2010). This method mainly deals
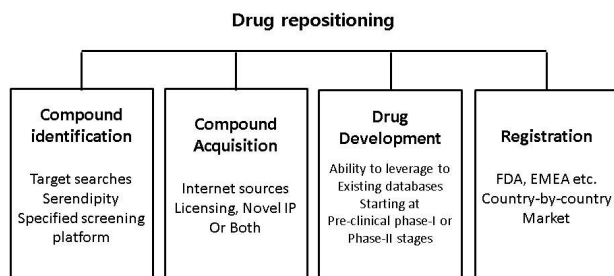
Fig. 1. Diagram showing the drug repositioning steps (Fig. modified from Sekhon, 2013).

Fig. 2. Exploitation of binding sites similarities between A and B for binding of a compound (Fig. modified from Sekhon, 2013).

the chemical and physical binding to the targets of protein of interest. This type of interaction has been reported to play an important role in the development or treatment of the disease. Systematic approaches, such as the use of chemical structures, amino acid sequences of target proteins, and chemical-protein interaction network, can be utilized to find new molecular targets for the existing drugs (Yamanishi *et al*., 2008, 2010; Mei *et al*., 2013). Three-dimensional structural libraries of both chemical compounds and target proteins are required for the physical binding stimulations between drugs and their targets (Jang *et al*., 2016).

Currently, studies are ongoing to identify novel uses of existing drugs by analyzing the patterns of both drug-associated and disease-associated gene sets. Results from these studies suggest there are some problems in computational approaches used to discover new drug indications, with respect to the experimental outcomes of molecular activity (Lamb *et al*., 2006; Iorio *et al*., 2010; Sirota *et al*., 2011). Recently, some researchers have focused on electronic clinical data, collected when medical services are provided to the patients in medical institutions, and includes information encompassing a variety of medical history such as prescriptions, diagnoses, and laboratory test results (Holmes *et al*., 2011; Roque *et al*., 2011; Jung *et al*., 2013). This clinical information can be used to investigate the hidden connections between diseases and clinical variables (Jensen *et al*., 2012). The clinical notes have explicit information about disease-drug relationships which are useful in drug repositioning (Jung *et al*., 2013, 2014).

DATA SOURCES

The drug bank maintains a drug database that includes 6,811 drug entities, 1,578 approved drugs, and their 22,143 synonyms (Wishart *et al*., 2008). National Health and Nutrition Examination survey (NHANES) is a data source for electronic clinical information (available at http://www.cdc.gov/nchs/nhanes.htm) that has data related to the demographics, dietary habits, health related questions, and results of laboratory tests.

DRUG REPOSITIONING PROCESS

Drug discovery and design are based on drug-target interaction (Jang *et al*., 2016). Important and necessary steps for reducing the burden of disease and finding new uses for drugs
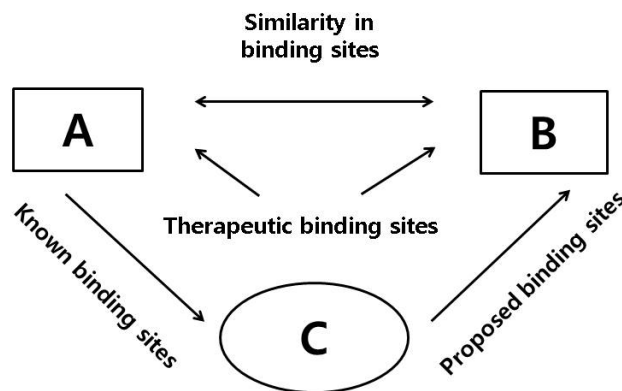
can be found by computational methods. These methods use two main strategies as follows: 1. drug/target-based (based on the chemical or pharmaceutical perspective), 2. disease-based (based on the clinical perspective of a disease or its pathology and symptomatology). The drug/target-based methods include chemical similarity, molecular activity similarity, and molecular docking, while disease-based methods include side-effect similarity, shared molecular pathology, and associative indicative transfer (Dudley *et al*., 2011a). Currently, in silico methods such as data mining, bioinformatics, and novel screening platforms are being used in drug repositioning projects for the identification and screening of potential repositioning candidates (Li *et al*., 2006; Yildirim *et al*., 2007; Campillos *et al*., 2008; Yamanishi *et al*., 2008; Kieser *et al*., 2009; Morrow *et al*., 2010; Chen and Zei, 2011; Dudley *et al*., 2011b; Ekins *et al*., 2011; Haupt *et al*., 2011; Sanseau and Koehler, 2011; Lounkine *et al*., 2012; Phatak and Zhang, 2013). Some researchers have also developed computational methods to represent and align biding sites (Fig. 2) (Haupt and Shoroeder, 2011).

According to pharmacological study, drug molecules often interact with multiple targets. Prediction of polypharmacology of known drugs and new molecules against multiple targets is more useful for drug repositioning (Liu *et al*., 2013).

ADVANTAGES OF DRUG REPOSITIONING

Adoption or integration of drug repositioning strategy offers some valuable advantages. These include easy availability of the active ingredients, increased success rates, decreased time to launch, reduced drug development costs, availability of numerous druggable compounds in the drug libraries that have the potential to be repurposed, integration of standard process of resource utilization, and de-risking and acceleration of drug development process using repurposing technology. Since the existing drugs have already undergone and cleared significant number of toxicology and safety assessments, the chances of failure of the repositioned drugs are greatly reduced. Drug repositioning candidates include known compounds with new targets or those with known mechanism for new indications (Oprea *et al*., 2011).

DRUG REPOSITIONING BASED ON PATHWAY

Few researchers have focused on pathway-based approach for drug repositioning. Several studies have reported success of drug repositioning through manual analysis of casual associations in drug-involved pathways (Sivachenko *et al.*, 2006; Kotelnikova *et al.*, 2010; Cramer *et al.*, 2012; Strittmatter, 2012). For example, bexarotene, an anti-cancer drug has been used for the treatment of Alzheimer's disease (AD) (Cramer *et al.*, 2012). The nuclear receptor PPAR (peroxisome proliferator-activated receptor) is activated by bexarotene and LXR (liver X receptor), in coordination with RXR (retinoid X receptor), and then up-regulates the expression of the *ApoE* (apolipoprotein E) gene (Li and Lu, 2013). This entire process plays a key role in the clearance of amyloid beta (Aβ) from the brain, thus resulting in the alleviation of AD. One drug and one disease chain causality was examined and took the following advantage in the bexarotene-related pathways knowledge: 1. drug-target (bexarotene is an RXR agonist); 2. target involved pathway (LXR: RXR activation pathway); 3. transcriptional responses in a given pathway (increased ApoE gene expression in the LXR: RXR activation pathway); 4. genetic mechanism of disease (ApoE is associated with AD). Pathway based on this computational method has been used to build a network of casual chains between drugs and diseases. This method was built by a multi-layer casual network, consisting of chains from drug to target, target to pathway, pathway to downstream gene, and gene to disease (Li and Lu, 2013).

THE USE OF ZEBRAFISH TO SCREEN REPOSITIONING DRUGS FOR INFLAMMATORY DISEASES

The host is usually protected from infection and injury to maintain homeostasis by an inflammatory response, which is a complex reflective process (Medzhitov, 2008). Usually, illness and death are majorly caused by inflammatory disorders such as auto-immune diseases, allergies, asthma, and sepsis. Drug repositioning is a faster and cheaper approach than traditional drug discovery (Hall *et al.*, 2014).

Zebrafish is a valuable drug discovery platform. To define and characterize drug activity in a high-content manner, whole live bioassay approach is carried out using embryos and larvae of zebrafish. Furthermore, zebrafish is a well-established model for studying leukocyte behavior. Zebrafish embryos populated with neutrophil and macrophage lineages two days post-fertilization function similar to human neutrophil and macrophage lineages (Hall *et al.*, 2014). Zebrafish is suited for *in vivo* phenotypic drug screening and larval zebrafish has revealed several new drugs that interfere with multiple complex behaviors used by high-throughput behavioral profiling (Rihel *et al.*, 2010). The suppression of neutrophil recruitment is an initial selection criterion of anti-inflammatory activity in

Table 1. Drug names, formulas, and mechanism of action of the 12 most significant hits from the zebrafish anti-inflammatory screen

Drug name	Generic names	Therapeutic group	Mechanism of action
Acetohexamide	Dymelor	Antidiabetic (type-II noninsulin dependent)	Blocks ATP-sensitive K plus channels/stimulates insulin release
Alfuzosin hydrochloride	Uroxatral, Rilif, Tevax, Unibenestan, Urion, UroXatral OD, Weiping, Xatger, Zofu	Antihypertensive	Alpha 1-adrenergic antagonist
Amodiaquine	Amadaquin, Amobin, Amochin, Basoquin, Trimalact, Camoquin, Creaquine, Larimal	Antimalarial	Heme polymerase inhibitor
Chlorophenesin carbamate	Cloricool, Kalsont, Maolate, Muslax Rinlaxer, Skenesin, Steacol	Muscle relaxant	Blocks nerve impulses
Clonidine hydrochloride	Clonidine, Mylan, Clonidural, Cloniprex, Clonistada, Clonnirit, Clophelin	Antihypertensive	Alpha 2 agonist/imidazoline agonist
Etodolac	Etodol, Etodolac, Apotex, ETOFACT, EtoGesic	Anti-inflammatory (NSAID)	Cox inhibitor
Fludrocortisone acetate	Flrinef, Astonin-H, Cortineff, Florineff Acetaat, Astonin, Merk, Lonikan	Mineralocorticoid	Causes kidneys to retain sodium
Mafenide hydrochloride	Sulfamylon, Abamide, Emilene, Homonal, Malfamin, Marfanil	Antibacterial	Inhibitor of folic acid biosynthesis
Methyldopa	Aldomet, Aldochlor, Aldopren, Aldotensin, Alfametildopa, Datleal, Dopagrand	Antihypertensive	L-aromatic amino acid decarboxylase inhibitor
Nefopam hydrochloride	Acupainlex, Acupan, Acuten, Anton, Benoton, Glosic, Ketopen, Licopam, Neforex, Paton, Sezen, Tonfupin, Xripa	Analgesic	Unknown
Niflumic acid	Donalgin, Flogovital, Forenal, Niflactol, Niflam, Landdruma	Anti-inflammatory (NSAID)	Cox inhibitor
Pinacidil	Pindac	Vasodilator	K$^+$ channel Ca^{2+} activator

NSAID, nonsteroidal anti-inflammatory drugs.

zebrafish tail fin wounds. A total of 251 drugs, with significant anti-inflammatory effect, (p<0.05) have been identified from zebrafish screening. This represents 22.4% of the drugs in the library. About 43.9% of non-steroidal anti-inflammatory drugs and 51.9% of corticosteroids, present in the library, were identified as having conserved anti-inflammatory activity in the zebrafish screen (Hall *et al*., 2014). Table 1 shows the 12 most significant hits from the zebrafish anti-inflammatory screen.

REPOSITIONING DRUGS OF SEPSIS

A systematic inflammatory response syndrome caused by infection is called sepsis. In well-developed and high-income countries, severe sepsis (sepsis accompanied by acute organ dysfunction) is the leading cause of death and a common cause of death among critically ill patients in intensive care units (Russell, 2006). Since 2001, recombinant activated protein C (APC), approved by FDA was the only drug available for the treatment of sepsis and septic shock. However, in October 2011, APC was withdrawn from the market due to side effects and lack of efficacy (Bernard *et al*., 2001). Researchers and physicians have continued to search for new therapeutic approaches and targets against sepsis. Therefore, drug repositioning can be used in these situations where the currently used drugs are not efficient (Kwak *et al*., 2015).

Methylthiouracil (MTU)

The systematic name of MTU is 6-methyl-2-thiouracil, as per International Union of Pure and Applied Chemistry (IUPAC). Molecular formula and weight of MTU are $C_5H_6N_2OS$ and 142.18 DA, respectively. It is slightly soluble in benzene, diethyl ether, ethanol, and methanol and insoluble in water. In the mid-1940s, MTU was introduced as a thionamide, an antithyroid drug for the treatment of hypothyroidism (Glock, 1946; Reddy and Kaul, 1979; Kwak *et al*., 2015). MTU has been repositioned to treat sepsis that includes multiple organ failure by cecum ligation and puncture (CLP) such as liver injury, renal injury, and overall tissue injury (Kwak *et al*., 2015). MTU has demonstrated anti-sepsis effects through inhibition of the release of high mobility group box 1 protein (HMGB1) and HMGB1-mediated inflammatory responses. MTU inhibited the expression HMGB1 receptors such as toll-like receptor 2 (TLR2) and TLR4. MTU also inhibited HMGB1 mediated hyper-permeability via suppression of the activation of p38. The translocation of NF-kB from cytosol to nucleus is also inhibited by MTU (Kwak *et al*., 2015).

Simvastatin

Simvastatin belongs to the statin class of drugs and is widely used to control hypercholesterolemia and hypertriglyceridemia. It reduces cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase and is widely used in hyperlipidemia to reduce the risk of atherosclerotic complications (Robinson, 2007). Simvastatin has been repositioned as an anti-sepsis drug and has demonstrated improved survival rates in septic patients with multiple organ dysfunction syndrome (Schmidt *et al*., 2006).

Simvastatin has shown to prevent the loss of integrity of the blood brain barrier (BBB), induced by polymicrobial sepsis (Yang *et al*., 2015). In addition, it also possesses anti-inflammatory and anti-oxidative properties and it is possible that its preservative properties may act by mitigating the detrimental effects of systemic inflammation on the BBB integrity (Yang *et al*., 2015).

Mangiferin

Mangiferin, a xanthone glucoside, is an active phytochemical present in various plants, including *Mangifera indica* L (Matkowski *et al*., 2013). Mangiferin has been reported to possess antioxidant, antitumor, antiviral, and immunomodulatory activities (Guha *et al*., 1996). In addition, the aqueous extract of *M. indica* leaves was shown to possess hypoglycemic activity (Aderibigbe *et al*., 1999). Mangiferin has been repurposed to treat sepsis-induced acute kidney injury (AKI). Sepsis-induced AKI is a multifactorial disease that involves inflammatory reactions by systemic cytokine storm or local cytokine production (Zarjou and Agarwal, 2011) and tubular dysfunction, induced by oxidative stress. The activation of NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome contributes in the pathogenesis of lipopolysaccharide-induced rat kidney proximal tubular cell (RPTC) apoptosis and CLP-induced sepsis (He *et al*., 2014). Mangiferin ameliorates CLP-induced oxidative and inflammation-mediated renal damage via enhancement of Nrf2 expression and prevention of NLRP3 activation. Sepsis-induced AKI is attenuated via NLRP3 inflammasome inhibition, reduction in the secretion of IL-1β and IL-18 secretion, and upregulation of Nrf2 expression by mangiferin (He *et al*, 2014).

REPOSITIONING DRUGS OF ASTHMA

Asthma has a complex and multifactorial pathogenesis, affecting over 300 million people worldwide (Papi *et al*., 2018). Inflammation in asthma is primarily mediated by Th2 lymphocytes and is characterized by pulmonary eosinophilia, production of Th2 cytokines and allergen-specific immunoglobulin E (IgE), mucus hypersecretion, expression of inflammatory factors such as inducible nitric oxide synthase (iNOS), and airway hyperresponsiveness (Barnes, 2015, 2017). Airway inflammation, airway hyperreactivity (AHR), goblet cell metaplasia, and increased levels of Th2 cytokines and IgE play key roles in allergic asthma (Bateman *et al*., 2008; Holgate, 2008; Hamid and Tulic, 2009). The inflammatory cell influx in asthma is triggered by the endothelial cell adhesion molecules, such as vascular cell adhesion molecule 1 (VCAM-1) and intracellular adhesion molecule (ICAM-1) (Woodside and Vanderslice, 2008; Hasegawa *et al*., 2010). Table 2 shows repositioned drugs targeting various inflammatory mediators.

Rapamycin

Rapamycin, also known as sirolimus, is used to coat coronary stents, prevent organ transplant rejection, and treat a rare lung disease called lymphangioleiomyomatosis (Vezina *et al*., 1975). This compound has immunosuppressant functions and antiproliferative properties due to mTOR inhibition (Waldner *et al*., 2016).

Glucocorticoids and bronchodilators are the first-line therapy for asthma. However, these therapies are not effective in all the patients. Rapamycin has been repositioned as a new treatment option for asthma. Rapamycin attenuates allergic asthma through inhibition of mTOR and suppression of various key mediators. Allergen-induced IL-13 and leukotriene

Table 2. Repositioned drugs for targeting inflammatory mediators

Drug	Inflammatory mediators for target	Disease
Artemisia apiacea Hance	IκBα, NF-κB p65, p38, RANTES, IL-8, IL-6, and TARC	Atopic dermatitis
Heparin	iNOS, Il-4, ARG1, and ARG2	Asthma
Mangiferin	Nrf2 expression, IL-1β & IL-18, and NLRP3	Sepsis
Methylthiouracil	TLR2, TLR4, RAGE, and p38, NF-κB	Sepsis
Rapamycin	mTOR, IL-13, and IgE	Asthma
Rifampicin	Histamine, β-HEX, PGD2, proinflammatory cytokines, TNF-α, and COX-2	Atopic dermatitis
Simvastatin	IL-1, IL-6, IL-8, IL-12, CD4 T–cell, Th2, ICAM-1, and VCAM-1	Sepsis and Asthma

TLR2, toll-like receptor 2; TLR4, toll-like receptor 4; RAGE, receptor for advanced glycation end products; p38, protein kinase 38; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid 2 (NFE2)-related factor 2; IL, interleukin; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion protein 1; mTOR, mammalian target of rapamycin; IgE, immunoglobulin E; iNOS, inducible nitric oxide synthase; ARG1, arginase 1; ARG2, arginase 2; β-HEX, β-N-acetylhexosaminidase. Hexosaminidase A; PGD2, prostaglandin D2; TNF-α, tumor necrosis factor alpha.

levels have been reported to be suppressed by rapamycin. Additionally, AHR, IL-13, and IgE were completely decreased by rapamycin (Mushaben *et al*., 2011).

Heparin

Heparin is commonly known as unfractionated heparin (UFH) and is used as an anticoagulant. It is mainly used to treat and prevent deep vein thrombosis and arterial thromboembolism. In addition, it is also used in the treatment of heart attacks and unstable angina. Various low molecular weight derivatives of heparin (LMWH) have shown to possess anti-inflammatory properties and were found to be therapeutically active against various inflammatory diseases, including asthma (Mousavi *et al*., 2015; Oduah *et al*., 2016; Alaez-verson *et al*., 2017).

LMWH and sulphate non-coagulant heparin (S-NACH) are highly effective in blocking different asthma traits in mice (Ghonim *et al*., 2018). Th2 inflammation is blocked via impeding IL-4 mediated signal transduction by S-NACH. S-NACH treatment blocked the expression of IL-4 induced expression of iNOS and reduced the basal levels of ARG1 and ARG2 (Ghonim *et al*., 2018). S-NACH has also demonstrated protective effects against lung dysfunction by reducing inflammation.

Simvastatin

Statins also have shown anti-inflammatory effects and are proposed as novel drugs for treating inflammatory diseases, including asthma (Samson *et al*., 2006; Kim *et al*., 2007; Menzies *et al*., 2007; Ostroukhova *et al*., 2009; Maneechotesuwan *et al*., 2010; Huang *et al*., 2011; Lokhandwala *et al*., 2012). Statins suppress inflammation via reduction in the levels of secretory cytokines and chemokines, such as IL-1, IL-6, IL-8, IL-12, and tumor necrosis factor-α (TNF-α) in asthma. Additionally, airway inflammation, remodeling, and AHR are attenuated by simvastatin in a dose-dependent manner through inhibition of the RhoA pathway. Simvastatin significantly reduces the CD4+ T cells numbers and the CD4/CD8 ratio along with attenuation of AHR, airway inflammation, and Th2 cytokine levels. After simvastatin treatment, the expression of ICAM-1 and VCAM-1 decreased significantly (Liu *et al*., 2014). Furthermore, treatment with simvastatin resulted in a decrease in the expression of cell adhesion molecules, inhibition of the migration of inflammatory cells from the blood into the airways and sites of inflammation, and reduction in augmentation of

IL-4 and IL-13 and eosinophils. Simvastatin attenuated airway responsiveness and allergic inflammation, via reduction of T-cell influx, thereby resulting in a decrease in the expression of cell adhesion molecules (Liu *et al*., 2014).

Repositioning drugs of atopic dermatitis

Atopic dermatitis (AD) is an inflammatory skin disorder associated with epidermal hyper-reactivity to allergens (Leung *et al*., 2004). AD is associated with elevated serum levels of IgE due to increased inflammatory infiltration (Bergmann *et al*., 1998; Chang and Shiung, 2006). Mast cells release histamine, which is a major mediator of hypersensitivity and a potent vasoactive agent observed near allergic lesions (Petersen *et al*., 1996). Mast cells induce allergic inflammation through the release of pro-inflammatory cytokines, such as TNF-α, interleukin-4 (IL-4), IL-8, and IL-13 (Kalesnikoff and Galli, 2008).

Rifampicin

Rifampicin, also known as rifampin, is an antibiotic used to treat several types of bacterial infections such as tuberculosis, leprosy, and Legionnaires disease (Eule *et al*., 1974). It is a polyketide belonging to the chemical class of compounds known as ansamycins. Bacterial RNA synthesis is inhibited by rifampicin via inhibition of bacterial DNA-dependent RNA polymerase (Wehrli *et al*., 1968). Rifampicin suppresses inflammatory effects and plays a major role in relieving neuropathic pain and in immune modulation. In addition, it also exhibits therapeutic effects against psoriasis in clinical practice (Bellahsene and Forsgren, 1980; Tsankov and Angelova, 2003). Rifampicin showed anti-AD activity and effectively decreased the elevated serum levels of IgE and IL-4, which are characteristic features of AD (Kim *et al*., 2017). Thus, rifampicin can be considered as an effective drug for the treatment of AD based on the reduction in the severity of symptoms and IgE production. Mast cells and basophils store β-hexosaminidase (β-HEX) in secretory granules. When mast cells are activated, β-HEX is released along with histamine, which in turn acts as a biomarker for allergic reactions. Rifampicin decreases both β-HEX and histamine secretion. Rifampicin is used as a new anti-allergic agent owing to its suppressive effect of degranulation of mast cell by controlling intracellular calcium concentrations (Kim *et al*., 2017).

Artemisia apiacea Hance

Artemisia apiacea Hance is a herb commonly found on the river beaches of eastern Asia. It is used as a traditional medicine in various east Asian countries including China, Korea, and Japan to treat fever, eczema, and jaundice. It is a common oriental medicine used for treating malaria, jaundice, and dyspepsia (Ryu *et al*., 2013). Artemisinin was isolated and identified in the early 1970s as an active antimalarial ingredient. Thereafter, various studies showed that it possesses anti-inflammatory, antipyretic, antibacterial, antiparasitic, and immunosuppressive effects. Recently, *A. apiacea* was repositioned as anti-inflammatory and anti-atopic dermatitis drug (Ryu *et al*., 2013). Ethanolic extracts of *A. apiacea* Hance (EAH) inhibited the production of chemokines and pro-inflammatory cytokines, such as RANTES, IL-8, IL-6, and TARC, and inhibited the activation of p38, ERK without JNK inhibition. The expression of proinflammatory cytokines and chemokines was also found to be regulated by EAH via the p38/NF-κB pathway in allergic inflammation. EAH inhibited the degradation of IκBα and the translocation of NF-κB p65 (Yang *et al*., 2018). Furthermore, skin lesions were improved and thickness of dorsal skin, ear skin thickness was reduced by EAH in 2,4-dinitrochlorobenzene-induced AD-like model. These results suggested that EAH possessed therapeutic properties to reduce AD-like symptoms in mice (Yang *et al*., 2018).

CLOSING REMARK

Drug repositioning has become a significant drug development strategy since its advent in the 1990s. Several repositioned drugs are already being marketed as drug candidates for disease that have failed drug indications. Drug repositioning offers promising success rate in drug development and safer treatments without the full cost or time required for *de novo* drug development. It allows alternative therapeutic use of approved drugs for the treatment of many diseases.

Inflammation is a protective response involving immune cells, blood vessels, and molecular mediators. The main aims of inflammation are to eliminate the initial cause of cell injury, clear out necrotic cells and tissue damaged from original insult and the inflammatory process, and initiate tissue repair. Additionally, inflammation is driven by various inflammatory mediators, such as TLR-2, TLR-4, iNOS, and interleukins.

In this review, we mainly focused on repositioned drugs used for the treatment of inflammatory diseases such as sepsis, asthma, and atopic dermatitis. First, we summarized the advances in drug repositioning methods till date. Then, we discussed three repositioned drugs used to treat sepsis, namely, methylthiouracil, mangiferin, and simvastatin. These drugs mitigate sepsis via reduction in inflammatory cytokines, inflammatory receptors, and inflammasomes. We also discussed three repositioned asthma drugs, namely, rapamycin, heparin, and simvastatin. These drugs inhibit the inflammatory cytokines and IgE to ameliorate asthma. Rifampicin, a repurposed drug used for the treatment of atopic dermatitis, decreases the levels of histamine, intracellular calcium, and pro-inflammatory cytokines and reduces COX-2 expression, thereby alleviating atopic dermatitis.

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