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Chapter

Drug Repurposing in Dermatology: Molecular Biology and Omics Approach

Farid A. Badria and Abdullah A. Elgazar

Abstract

The withdrawal of several blockbuster drugs due to severe adverse effects and the failure of several developed drugs in clinical trials raised questions about the efficacy of current approaches of drug discovery. Moreover, the limitation of resources and the long and costive process of drug discovery made a lot of pharmaceutical companies to employ drug repurposing strategies to get new insights about activities that were not considered during their initial discovery. The development of therapeutics for treatment of dermatological condition is not considered as priority although it affects the lifestyle of thousands of people around the world. Serendipity and observations have contributed significantly in this field but immerse efforts have been exerted to find systematic methods to identify new indications for drugs, especially with the unprecedented progress in molecular biology and omics. So, in this chapter, we will emphasize on different approaches used for drug repositioning and how it was applied to find new therapeutics for different dermatoses.

Keywords: drug repositioning, alopecia, psoriasis, acne, hirsutism, hyperpigmentation

1. Introduction

In the early years of this century, it was expected that revolutionary development in industry and technology will allow an unprecedented opportunities for drug discovery and development; however, the disappointing rate of drug approval in the last 20 years shed the light on the urgent need to reassess the efficiency of current strategies of drug discovery.

Despite the large amount of investment that has been put in drug development, several drug candidates fail to pass due to pharmacokinetic issues or severe side effects that mainly are not demonstrated until clinical phases, which lead to extreme economic loss to pharmaceutical companies that might spend more than billion dollars in the process.

These facts were not overlooked by pharmaceutical industries or academia; so, they started to apply a new strategy that embraces new application of approved drugs rather than starting from scratch, which is known as drug repositioning. While the term was first coined in 2004, the approach has already led to the discovery of several therapeutic agents in the last century; however, serendipity, trials, and errors were the main players in most of these cases.

This means that harnessing our highly advanced tools of molecular biology and computational techniques would guarantee the rediscovery of new indications for already approved drugs, which will not only increase our arsenal of therapeutic agents but also will drastically decrease the time and costs of the whole process.

Moreover, this approach could help for finding therapeutic solutions for orphan diseases or clinical conditions that affects low number of population which are usually neglected by pharmaceutical corps as in the case of dermatologic therapeutics due to the low prevalence of many dermatoses and the inappropriate estimation of the burden of psychological and physical impact of skin disorders on the quality of life.

Indeed, the field of dermatology covers wide range of disorders, but this means that drug repurposing strategy may be uniquely successful, hence the broad variety of pathophysiological process affecting the skin. In that aspect, the liver research laboratory (FAB-Lab, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt) has utilized several approaches for not only optimization and enhancing the therapeutic effect of commonly available natural products but also recognizing novel application for them so that one therapeutic agent could be used for treatment of several or complex conditions (**Table 1**). In this chapter, we will review different strategies for drug repositioning and their application in dermatological and cosmeceutical field.

No.	**Studies for discovery of new indications for natural products**		**Ref**
	Compounds	**Indication**	
1.	Compounds from frankincense	Anti-herpes	[1]
2.	Frankincense oil	Immunomodulatory activity	[2]
3.	Myrrh standardized extract	Schistosomicidal	[3]
4.	Free-B-ring flavonoids	Colon cancer	[4]
5.	Anti-neoplaston A-10	Immune-modulatory in breast cancer patients	[5]
6.	Ricinine alkaloids analogs	Oral squamous cell carcinoma	[6]
7.	Stemmadenine alkaloid derivative	Antiproliferative activity against different cancers	[7]
8.	Curcumin	Iron accumulation in liver	[8]
9.	Cucurbitacin B	Chemo-sensitization of cisplatin-resistant ovarian cancer	[9]
10.	Bi-aryl methyl eugenol analogs	Breast cancer invasion inhibitors	[10]
	Studies for discovery of new target for natural products		
	Compounds/extract	**Targets**	`
1.	Flavonoids containing an alpha-keto group	Tyrosinase inhibitors	[11]
2.	Cycloartane glycoside	Lactate dehydrogenase inhibitor	[12]
3.	Betulinic acid analogs	Topoisomerase inhibitors	[13]
4.	Gingerol derivatives	LTA_4H inhibitory activity	[14]
5.	Curcumin derivative	Alpha-amylase inhibitory	[15]
6.	Glycyrrhizin derivative	Acetylcholinesterase inhibitory activity	[16]

Table 1.
Studies of natural product repositioning in FAB-Lab.

2. Drug repositioning strategies

Drug repositioning is achieved by understanding of molecular mechanisms of drug action and by identification of the interacting proteins of the drug. In many cases, molecular mechanism of drug action is poorly understood or completely unknown. The drug action can be observed by identification of drug targets and their specific interactions, drug-induced change in expression of a specific gene and the associated pathways, and change in disease phenotypes.

Current approaches for drug repositioning come from the so-called "drug action spectrum" concept as shown in **Figure 1**, which is based on three paradigms, namely, target-centric, drug-centric, and disease-centric repositioning. The first and second modules are closely related and usually applied interchangeably; the target-centric module focuses on finding new indication for the already established target; for example, the discovery of the role of androgenic receptor in hair loss allowed the repurposing of finasteride for treatment of androgenic alopecia.

Drug-centric module aims in finding a new target for therapeutic agent, experimental or abandoned drugs; for example, the notorious thalidomide, which was firstly indicated for treatment of nausea and caused the phocomelia crisis, has been repurposed for treatment of myeloma and several dermatological conditions related to immune diseases.

These types of repositioning use computational ligand- and structure-based techniques [12, 13], chemical proteomics [16, 17], and off-target screening to identify potential therapeutic applications; so, we will explain the theory behind its approach and its application in drug repositioning.

In the third module, the repurposing depends on the similarity of pathophysiological nature of diseases; for example, different types of cancers or different autoimmune diseases which allow the expansion of drug to a closely related indication so that extensive analysis of the associated molecular targets may not be required. Nevertheless, this type of repositioning strategy is the most observed type

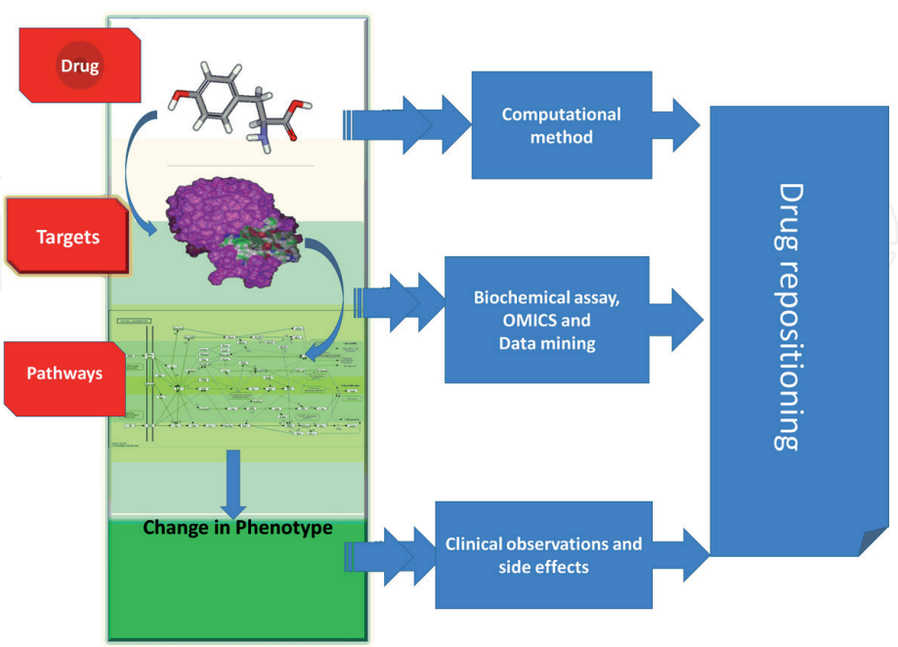


Figure 1.
The concept of drug action spectrum in drug repositioning is based on three paradigms, namely, drug-centric, target-centric, and disease-centric repositioning. In the first and second approaches, computational approaches are used extensively to identify novel targets for compounds that were used for different applications. Omics, data mining, and meta-analysis of clinical trials could also be used to analyze the relationship between diseases and novel molecular targets that was previously investigated in different diseases.

in drug repurposing field; it is worthy to note that retrospective analysis of several repurposing cases could be explained exclusively by drug-target interaction [18].

The main tools used for applying disease-centric repositioning are gene or protein expression profiling [14, 15], phenotypic screening [11], clinical observations [19], side effect analysis [20], and data mining and neural networks [21, 22]. In the following section, we will shed the light on the application of these tools in drug repositioning, especially in dermatology.

2.1 Application of drug-target interaction in drug repositioning

2.1.1 Ligand- and structure-based approaches

Ligand-based approaches are usually employed when no structural information about the target under investigation is available. They are not only used for virtual screening but also for lead optimization [17]. The key concept in ligand-based approaches is to determine common structural features or descriptors that could be found in compounds with the same pharmacological activity; therefore, pharmacophoric function groups which are necessary to maintain the activity could be elucidated (**Figure 2**) [19].

In structure-based approach, the 3D structure of biological target is used to recognize how an active compound bind to its active site; hence, molecular docking could be used for identifying other drugs that can bind to the active site in similar fashion [20]. It is worthy to note that such approach could be used also for identifying the ability of drugs to bind to diverse types of targets, which is known as target fishing or inverse docking; this could be achieved by docking drug of interest against database of targets of clinical significance (**Figure 3**) [21].

Indeed, drug repositioning cases derived from this approach are still limited, but it has been extensively used to give insights on the mode of action of natural products and the rationale behind their use in traditional medicine. For example, ricinoleic acid **(1)**, acteoside **(2)**, amentoflavone **(3)**, quercetin-3-O-rutinoside **(4)**, and hinokiflavone **(5)** were expected to be prostaglandin D2 synthase inhibitors by inverse docking, which could explain their use in herbal preparation for hair loss treatment [22]; another study revealed that the anti-inflammatory effect of *Bryophyllum pinnatum* is due to the ability of quercetin 3-O-α-L-arabinopyranosyl-(1 → 2)-O-α-L-rhamnopyranoside **(6)** to inhibit PDE4B, a prominent target in the pathogenesis of psoriatic arthritis, and atopic dermatitis [23, 24]; also, the antiaging effect of allicin was linked to its ability to act as leukocyte elastase inhibitor [25].

Bagherzadeh et al. applied pharmacophore and structure-based virtual screening to identify tyrosinase inhibitor from zinc database; among them, five compounds showed the potential to be used as potent inhibitor according to molecular

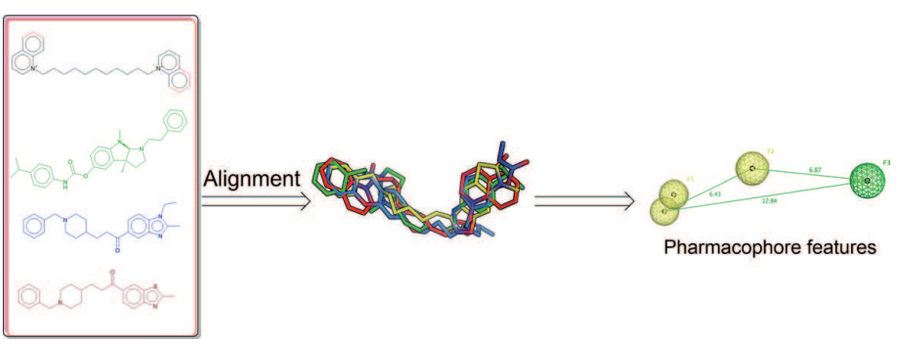


Figure 2.
Ligand-based approaches depend on the elucidation of structural features that could be found in set of active drugs (fingerprint) so that compounds possessing the same pharmacophores could be identified.

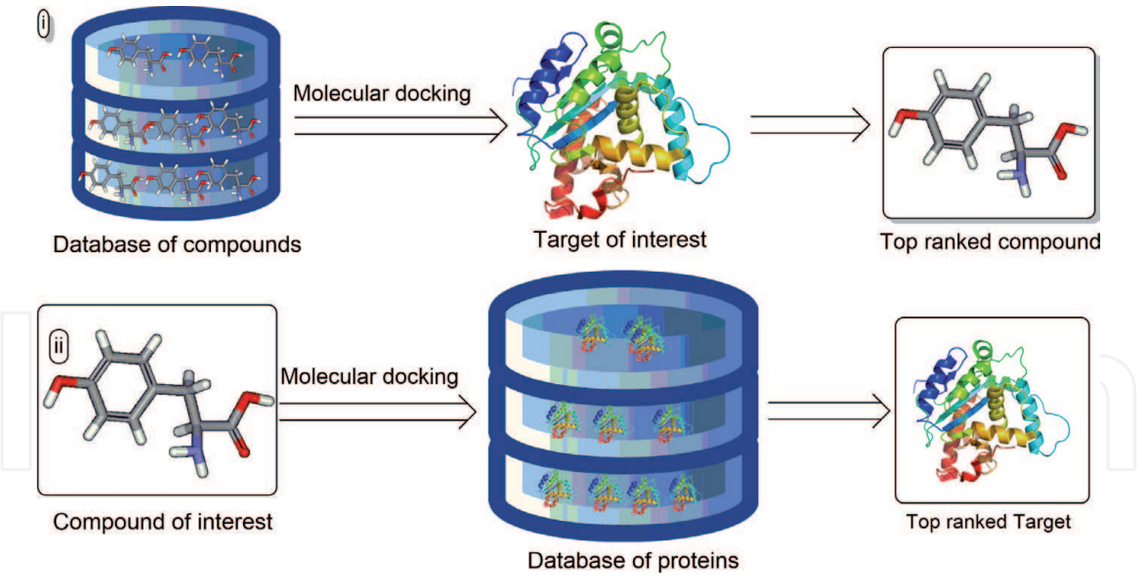


Figure 3.
Structure-based virtual screening employ two main approaches: (i) molecular docking where databases of thousands of compounds could be docked to the active site of target of interest to identify the top ranked compounds and (ii) inverse docking, as the name suggests, where compound of interest is docked against a panel of different targets to identify new potential targets.

dynamic simulation [26]. Interestingly, Choi et al. used structure-based virtual screening for repurposing thiopurine drugs such as mercaptopurine **(7)** as tyrosinase inhibitors for treatment of hyperpigmentation [27]. The chemical structure of compounds **(1–7)** is shown in **Figure 4**.

2.1.2 Off-target-based repositioning

The ability of most of drugs to induce side effects is originated from their binding with other targets that might share certain homology with the original targets,

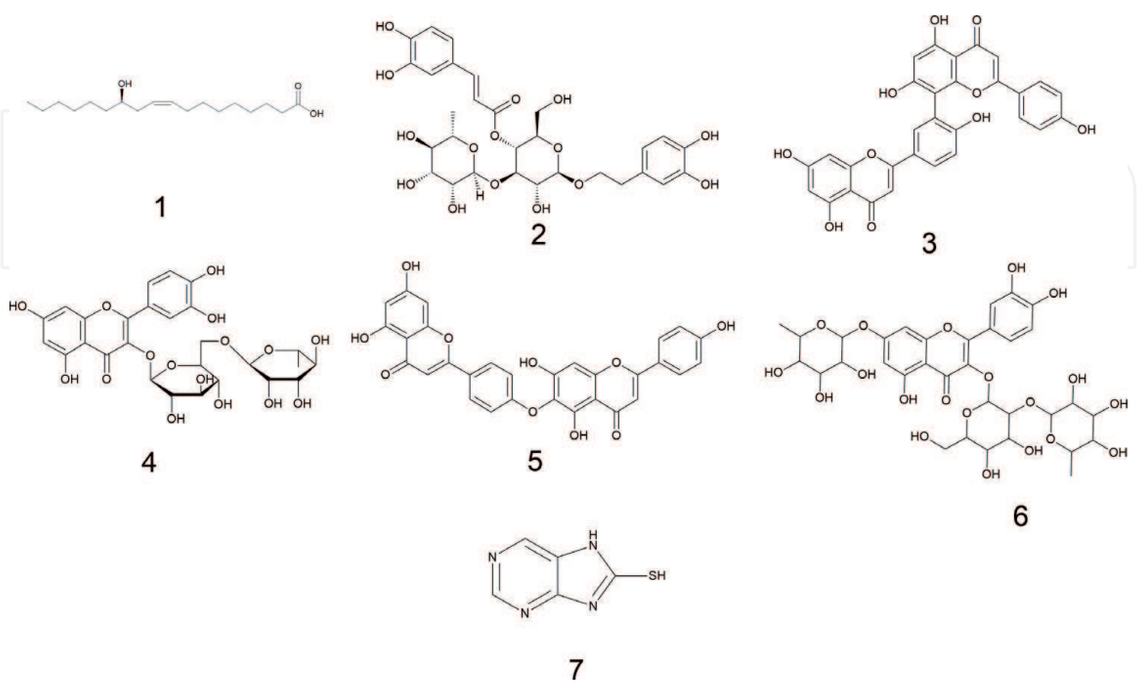


Figure 4.
Chemical structure of ricinoleic acid **(1)**, *acteoside* **(2)**, *amentoflavone* **(3)**, *quercetin-3-O-rutinoside* **(4)**, *hinokiflavone* **(5)**, *quercetin 3-O-α-L-arabinopyranosyl-(1 → 2)-O-α-L-rhamnopyranoside* **(6)**, *and mercaptopurine* **(7)**.

so it could be quite handful to use this drugs in treatment of diseases where these targets are dysregulated.

Spironolactone **(8)** is an antagonist to aldosterone; so, it is used for treatment of hypertension due to its diuretic effect; however, its steroidal nature allows it to act as a competitive antagonist at androgenic receptor; so, it was suggested to be used in treatment of androgenic alopecia; however, its effects on hair growth patterns in males might be not clinically preferable. On the other hand, it proved to be significantly effective in treatment of polycystic ovary syndrome and hirsutism in females, due to its ability to inhibit hair regrowth in androgen-dependent regions of the body, which was proven by several clinical trials.

Another intriguing example for off-targets drug repositioning is doxepin **(9)** which is a tricyclic antidepressant; it prevents reuptake of serotonin and norepinephrine, leading to an increase in the synaptic concentrations of those neurotransmitters. Nevertheless, there are several off-target effects that are associated with the use of this class of drugs, which are mainly mediated by muscarinic and histamine receptors. This could be explained by its high affinity to H_1 receptor which is much higher than hydroxyzine by 56 times and diphenhydramine 800 times; such observation opened the gate to the FDA approval for treatment of dermatological conditions such as pruritus, psychodermatosis, and chronic urticaria as topical and systemic agents.

Off-target effects are also influenced by the route of administration; sodium valproate **(10)**, an anti-epileptic drug, inhibits the cellular sodium influx by blocking voltage-dependent sodium channels and induces chloride influx by gamma hydroxyl butyric acid (GABA)-mimetic effect. It also reduces the release of GABA, thereby attenuating neuronal excitation induced by glutamate receptors. It was reported by several clinical trials that oral administration of valproate could induce hair loss in dose-dependent manner by decreasing biotinidase activity leading to alopecia induced by biotin deficiency.

However, sodium valproate topical treatment induced hair growth in male C3H mice model, which could be explained by its ability to inhibit glycogen synthase kinase 3β and activation of Wnt/β-catenin pathway, which in turn, is associated with hair regeneration and anagen induction. This result was supported by randomized interventional study, where 7.2% spray of sodium valproate applied twice daily on scalp up to 24 weeks showed the efficacy of valproate spray on androgenic alopecia.

Dapsone **(11)**, which is known to be one of the few agents used to fight leprosy, was developed as an antistreptococcal agent by targeting dihydropteroate synthetase in bacteria; it was only matter of time until its anti-inflammatory effect was noticed due to its effect on numerous neutrophil-mediated and autoimmune processes; so, it is now used for recurring neutrophilic dermatosis, cicatricial pemphigoid, linear IgA dermatosis, IgA pemphigus, erythema elevatum diutinum, acropustulosis infantilis, and prurigo pigmentosa [28].

Finally, thalidomide **(12)** is a distinguishable case in drug repositioning; it was used for treatment of morning sickness in pregnant women after its withdrawal due its teratogenic effect; such side effect was studied thoroughly and explained by the ability of the drug to inhibit vascular endothelial growth factor (VEGF) which has a significant role in angiogenesis and embryo development; so, this drug was repositioned for treatment of multiple myeloma; also, it was found that thalidomide is a strong inhibitor for tumor necrosis factor alpha (TNF-α) and was approved by FDA for management of erythema nodosum leprosum [29, 30]. The chemical structure of compounds **(8–13)** is presented in **Figure 5**.

2.1.3 New target indication-based repositioning

In this approach, data analysis based on omics is used to identify new function instead of finding new targets for certain chemical entity; hence, it might be the

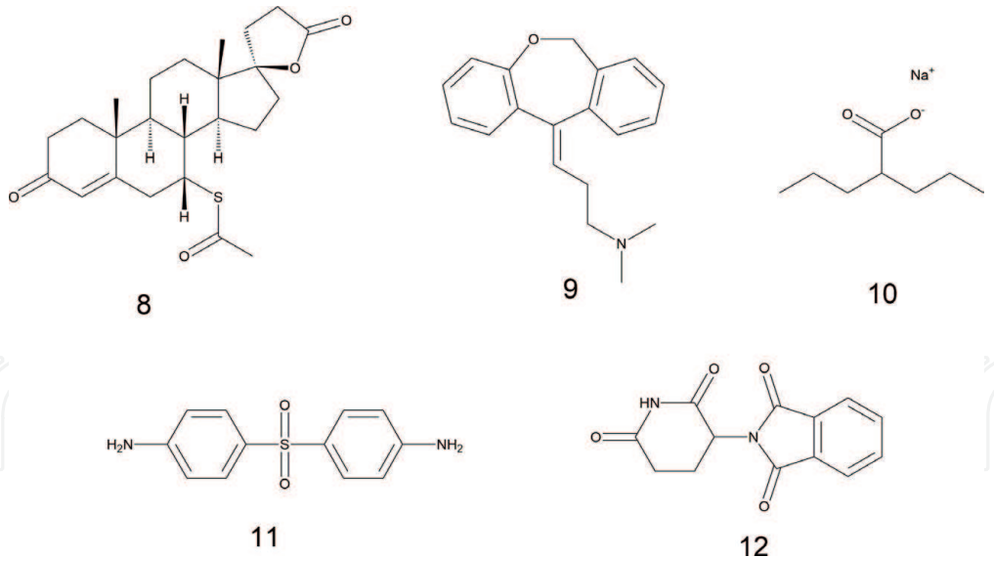


Figure 5.
Chemical structure of spironolactone **(8)**, *doxepin* **(9)**, *sodium valproate* **(10)**, *dapsone* **(11)**, *and thalidomide* **(12)**.

most challenging approach as it depends on the advances of molecular biology tools which can reveal the role of already known target in completely different diseases.

Finasteride **(13)** is a drug that was developed for treatment of benign prostatic hyperplasia, by acting as 5α-reductase enzyme inhibitor; this enzyme was found later to be contributing in the development of androgenic alopecia; hence, finasteride at low doses was repositioned to treatment of baldness in men.

Another example is the repositioning of eflornithine **(14)**, which was used for treatment of African trypanosomiasis by inhibiting ornithine decarboxylase; several years later, the homolog enzyme in humans was found to be responsible for hair growth and eflornithine was suggested as potential treatment of hirsutism in woman due to its ability to reduce hair growth. This observation was supported by several clinical trials and is currently marketed as topical preparation.

Zileuton **(15)** is a 5-lipoxygenase inhibitor which is used for treatment of asthma, by blocking the biosynthesis of leukotriene B4, which contributes significantly in tissue inflammation in acne; so, several studies on the experimental and clinical levels have been performed to understand its mode of action, as well as safety of this compound in the management of acne vulgaris. Zileuton demonstrated a significant efficiency in patients with moderate acne, whereas a decrease in inflammatory lesions was noticed in comparison to the placebo group. Also, the tolerability and safety of zileuton were satisfactory in all conducted clinical studies [31]. The chemical structure of compounds **(13–15)** is shown in **Figure 6**.

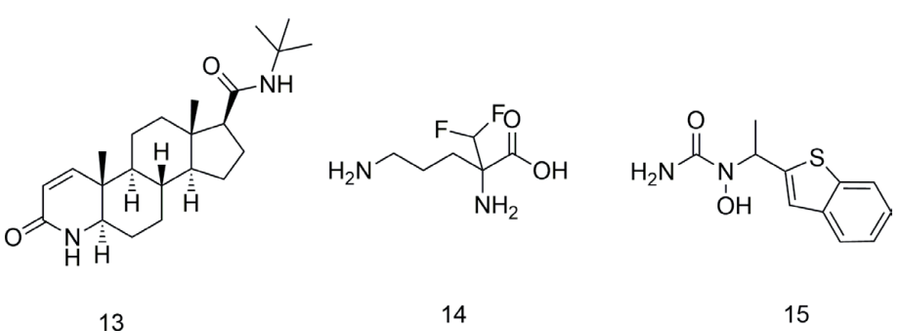


Figure 6.
Chemical structure of finasteride **(13)**, *eflornithine* **(14)**, *and zileuton* **(15)**.

2.2 Disease-centered drug repositioning

2.2.1 Application of data mining and omics in drug repositioning

In disease-centered paradigm, the observation and analysis of data from phenotypic assays, clinical trials, and literature could be an important resource for drug repositioning, as previously mentioned, this type of repositioning is oriented toward the clinical outcomes rather than the exact molecular mechanism behind the drug switch; from other angle, the researcher aims to find certain fingerprint on the genetic or proteomic level to support the repositioning hypothesis; for example, the transcriptomic analysis of different types of autoimmune diseases could reveal similar pattern of gene expression, which means that the same drug could be used for different types of immunity-related condition.

Qu et al. applied integrative clinical transcriptomic analyses for finding new drugs for treatment of psoriasis. First, gene expression analysis of samples collected from psoriasis patient and normal volunteers were used to identify molecular targets associated with the disease, and then, connectivity map analysis revealed potential drugs for the identified targets, which were resveratrol **(16)**, tiabendazole **(17)**, monobenzone **(18)**, parthenolide **(18)**, doxycycline **(19)**, and methotrexate **(20)** [32].

Also, Patrick et al. gathered drug-related information from more than 20 million articles using machine learning based on word embedding to build a model that highlights drug-disease relationship in order to repurpose drugs for treatment of immune-mediated dermatological conditions, where prednisone **(21)**, triamcinolone **(22)**, budesonide **(23)**, hydroxychloroquine **(24)**, and leflunomide **(25)** were among the top five predicted drugs for treatment of psoriasis [33]. The chemical structure of compounds **(15–25)** is demonstrated in **Figure 7**.

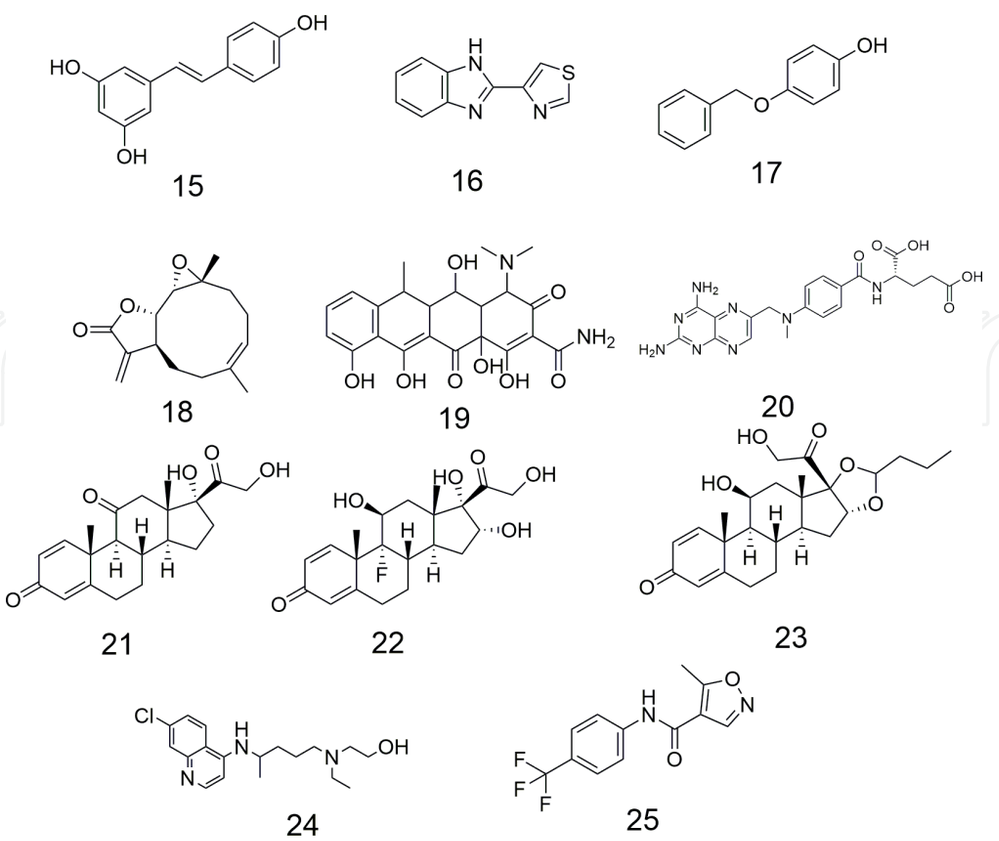


Figure 7.
Chemical structure of resveratrol **(16)**, *tiabendazole* **(17)**, *monobenzone* **(18)**, *parthenolide* **(18)**, *doxycycline* **(19)**, *methotrexate* **(20)** *prednisone* **(21)**, *triamcinolone* **(22)**, *budesonide* **(23)**, *hydroxychloroquine* **(24)**, *and leflunomide* **(25)**.

2.2.2 Clinical observation-based drug repurposing

Bimatoprost **(26)**, a prostaglandin analog, was used for treatment of glaucoma patient, but several clinical observations reported the occurrence of eyelash hypertrichosis; so, it was used for induction of eyelash regrowth in alopecia areata and for cosmeceutical purposes [34, 35].

Phenytoin **(27)** is one of the first discovered antiepileptic drugs; after its introduction to the market, gingival hyperplasia was reported as a side effect for the treatment, which triggered dermatologist to evaluate its ability to heal wounds; so, phenytoin has been evaluated by several clinical studies, where it proved to be useful in treatment of wounds in topical and oral forms; however, the exact mechanism of action is still ambiguous [36].

Bevacizumab, a monoclonal antibody that is used for treatment of several types of cancer, was observed to achieve complete remission of psoriasis in metastatic colon cancer without any other treatment for psoriasis [37]; a case which was reported again in another study that described the same effect in metastatic renal cell cancer, psoriasis, and psoriatic arthritis patient, which means the bevacizumab could be repurposed for treatment of these dermatoses; also, it sheds the light on the importance of (VEGF) as a target for treatment of inflammatory skin conditions [38].

The Janus kinase (JAK) inhibitor, tofacitinib **(28)**, was developed originally for management of rheumatoid arthritis, ulcerative colitis and other autoimmune diseases, but it was repurposed for psoriasis and atopic dermatitis since JAK was found to be contributing in the pathogenesis of these diseases, and currently, several clinical trials were performed to assess its clinical significance and concluded that response rates in tofacitinib-treated group were significantly higher compared to that in placebo [39–41].

Metformin **(29)**, a type-2 diabetes medication, reduces insulin resistance; however, its mechanism is not completely understood; so, it was suggested as a treatment of several dermatological conditions associated with insulin resistance such as acanthosis nigricans and acne; this was supported by several clinical trials where the patients showed complete resolution. It also was employed in treatment of hyperpigmentation due to its inhibitory effect on tyrosinases, the key enzymes in melanin biosynthesis. The anti-melanogenic effect of metformin was demonstrated experimentally on human skin biopsies and reconstituted human epidermis; also, clinical trials showed that metformin efficacy is comparable to TCC in treating melasma [42–44].

Finally, minoxidil **(30)**, which is a well-known case in drug repositioning, was initially used for treatment of hypertension since its strong vasodilator effect but during clinical trials, hair regrowth was noticed in patients with androgenic alopecia such effect is contributed by stimulating the vascular bed nearby the hair follicles which lead to better environment for hair growth. It was suggested that the ability of minoxidil to activate cytoprotective prostaglandin synthase-1 and stimulate adipose-derived stem cells (ASCs) [45, 46].

2.2.3 Phenotypic screening for drug repositioning

Niclosamide (NCL) **(31)** is an anti-helminthic drug that has been utilized for long time with considerable safety profile; several studies reported its anti-inflammatory and anticancer activities, highlighting the potential of repurposing for different indications; Thatikonda et al. used imiquimod (IMQ)-induced BALB/c mouse model to evaluate the efficacy of NCL for treatment of psoriasis, where it alleviated epidermal hyperplasia and inflammation induced by IMQ via down-regulating p65, STAT3, NFATc-1, and NF-κB transcription factors along with Ki-67, ICAM-1, and Akt protein expression [47].

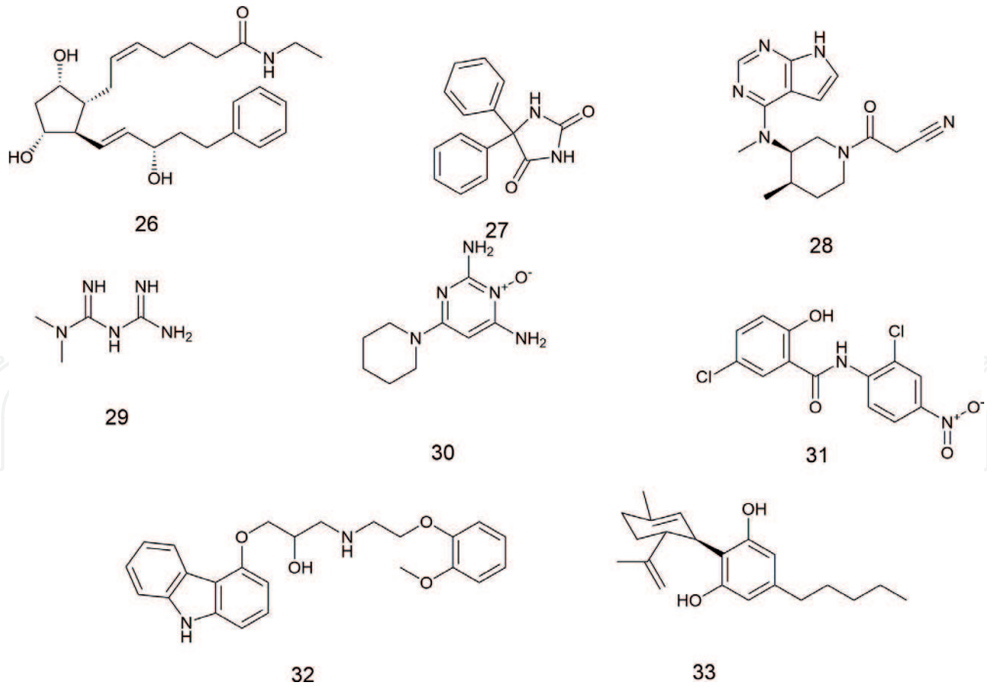


Figure 8.
Chemical structure of bimatoprost **(26)**, *phenytoin* **(27)**, *tofacitinib* **(28)**, *metformin* **(29)**, *minoxidil* **(30)**, *niclosamide* **(31)**, *carvedilol* **(32)**, *and cannabidiol (CBD)* **(33)**.

Hall et al. used zebrafish neutrophil migration assay, for evaluation of the suppressive effect of 1280 approved drugs on recruitment of neutrophils; where drugs showing prominent anti-inflammatory activity were further tested in atopic dermatitis animal model, among them 11 drugs which was not reported previously as anti-inflammatory agent [48].

Chang et al. used in vivo model of chemically induced murine skin tumorigenesis to confirm the hypothesis of repositioning of beta blocker for treatment of skin cancer, since several studies showed that stress-related catecholamine hormone expression can affect tumor progression [49].

Carvedilol **(32)**, when administrated orally and topically, prevented DMBA-induced epidermal hyperplasia, suggesting that it may serve as a new agent for protecting against skin cancer [50], which was supported by another study that demonstrated the preventive effect of carvedilol applied topically after UV exposure; so, it can be repositioned as prophylactic agent against skin inflammation and cancer [51].

Cannabidiol (CBD) **(33)** is a nonpsychoactive phytocannabinoid found in *Cannabis sativa*. It is approved recently for the treatment of seizures associated with two uncommon and serious forms of epilepsy, Dravet syndrome, and Lennox-Gastaut syndrome. Oláh et al. reported that CBD-treated human sebocytes and human skin organ in vitro showed strong antiproliferative, lipostatic, and anti-inflammatory effects mediated by a plethora of receptors, ion channels, and other components of the endocannabinoid system [52]. These findings were confirmed later by clinical trial showing that CBD administrated as an ointment is an effective and noninvasive option for enhancing the quality of life in patients with some skin disorders, especially those with inflammatory background [53]. The chemical structure of compounds **(26–33)** is depicted in **Figure 8**.

3. Concluding remarks and future perspective

Drug repositioning is an important strategy to maximize the benefits from already approved drugs; it will not only contribute to reduction of time and cost

for drug discovery but also could help to develop new therapeutics for orphan and ignored diseases. While historic cases of drug repositioning were inspired by serendipity and observations, more systematic approaches became well established by time. In silico and data mining tools could help to analyze the large amount of data available from omics, phenotypic assay, and clinical investigations by revealing novel relationship between drugs, targets, and different pathways of diseases as described in this chapter; the integration of different tools of drug repurposing will allow the identification of safe and effective therapeutics for treatment of dermatological condition and enhance the quality of life of patients.

Conflict of interest

The authors declare no conflict of interest.

Author details

Farid A. Badria[1*] and Abdullah A. Elgazar[2]

1 Department of Pharmacognosy, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt

2 Department of Pharmacognosy, Faculty of Pharmacy, Kafrelsheikh University, Kafrelsheikh, Egypt

*Address all correspondence to: faridbadria@gmail.com

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