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Review Article

An overview of polypharmacology: A multifaceted approach to drug development

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Abstract

The idea of polypharmacology describes the ability of a molecule to interact with two or more targets at once. When compared to traditional single-targeting compounds, it has numerous advantages. Several proteins and pathways are involved in the initiation and progression of complex and multifactorial diseases such as cancer. A chemical must be promiscuous, or able to interact with various targets, to be considered polypharmacologic. It must also be able to avoid attaching to anti-targets, which would cause off-target negative effect. Researchers anticipate whether or not a developed molecule will be promiscuous by looking for specific structural traits and physicochemical qualities. Promiscuity is determined using cutting-edge, modern computational techniques. The "one drug, multiple targets" polypharmacology paradigm has many uses, particularly in drug repurposing which is the process of developing an already-approved medication for novel use. Details on how one might purposefully introduce promiscuity into compounds to make them polypharmacologic are also provided in this review.

Keywords: *Polypharmacology, Anti-targets, Recognizing promiscuity, Pharmacophore modeling*

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INTRODUCTION

The idea behind polypharmacology is that a chemical may connect to two or more targets at once, and by doing so, it achieves a broader therapeutic effect than if it only binds to one target. Polypharmacology is based on the concept of "one drug-multiple targets," in contrast to the traditional drug discovery paradigm of "one drug-one target," where a single drug is intended to operate on numerous targets in a single disease pathway or multiple targets involved in different diseases [1,2]. The ability of a molecule to inhibit targets that yield a response opposite to the primary therapeutic target of the molecule, ultimately leading to a more pronounced therapeutic impact, is often referred to as polypharmacology [3].

Traditionally, research has focused on creating extremely targeted compounds with minimal to no off-target interactions to reduce the negative consequences of the chemical. This method has demonstrated broad success, particularly in the case of basic disorders with a known mechanism of action [4-6]. A single-target approach, however, is less successful when treating diseases that are more complicated and multifactorial, such as cancer, disorders of the central nervous system (CNS), and infections

[4,5,7]. Since polypharmacologic medication targets several proteins and processes involved in the initiation and progression of the disease, it may be far more helpful for these conditions [7]. Studies has made significant strides in revealing the causes of numerous illnesses, including schizophrenia, asthma, and heart disease, as well as identifying several etiological factors for these conditions [8,9]. All of these aspects emphasize how important polypharmacologic medications are, and their growth has recently accelerated sharply [10].

Need for polypharmacology

Finding drugs with a single target has long been the main goal of pharmaceutical research. Numerous single-target medications have been found while side effects from "off-target" interactions are avoided. The rate of medication attrition has increased over the past few decades despite these advancements, mostly as a result of compounds proving ineffective. Furthermore, it was discovered through retrospective investigations that few medications were effective on several targets, suggesting that their multi-targeting mechanism is probably responsible for their therapeutic efficacy [11].
This implies that single-targeting approach to drug research is connected to sub-efficacy attritions. Because of these benefits over traditional single-target drug design, a growing number of research groups are choosing to build medications with multiple targets. The constraints of single-target molecules have generally been shown. In yeast, there was no noticeable change when 85 – 90 % of the identified individual targets were inhibited. Furthermore, only 10 % of all targetable genes were efficient as single therapeutic targets, according to mouse knockout studies [12,13].

The development of drugs for complex and multifactorial disorders requires the use of multi-targeting compounds. To achieve a larger therapeutic effect, treating such diseases involves simultaneous therapy on several targets. This is accomplished by employing a single polypharmacologic medication or by including many medications in the treatment plan, each of which targets a distinct single pathway (polypharmacy). While polypharmacy help manage many chronic conditions by increasing therapeutic efficacy and enhancing a patient's quality of life, a polypharmacologic approach has many advantages over a polypharmacy approach [13]. In particular, polypharmacology improves patient compliance while lowering treatment complexity, pharmacokinetic complexity, and drug-drug interactions. Through a drug-drug interaction known as synergism, simultaneous activity on numerous targets boosts therapeutic efficacy.

Multi-kinase inhibitors (MKIs), which operate on several pathways controlling proliferation, angiogenesis, and migration, are one specific example of polypharmacology-induced synergism in cancer treatment [12,14]. Because all kinases have a highly conserved adenosine triphosphate (ATP) binding site, kinase inhibitors have a significant potential for multi-targeting. Epidermal growth factor receptor (EGFR) and ErbB2 were the targets of lapatinib, an early MKI that was promoted to avoid side effects from earlier MKI designs, such as imatinib [15]. Fallahi *et al*, also reported on the application of MKI cabozatinib in several cancer types [16]. Network pharmacology is this synergistic multi-targeting of proteins. Network pharmacology maps out the signaling pathways associated with disease and targets specific nodes (proteins) on the mapped network that may be associated with the same or different signaling pathway with a single chemical [13,17].

Drug resistance is a major factor in the failure of traditional medicines, including anticancer and antibacterial medications. Over time, microbial and tumor cells undergo mutations and gain resistance to drugs due to a variety of reasons, including drug efflux and target overexpression [12,18,19]. He *et al*, for example, showed that the compound AEE788 targeted EGFR/HER2 and vascular endothelial growth factor receptor (VEGFR) at the same time, causing triple-negative breast cancer cells to overcome the resistance usually seen with mTOR-targeted therapy [20]. On the other hand, unlike polypharmacy, when a single polypharmacologic drug modulates several sites, only the therapeutic impact is synergized, not the side effects. When several targets are unique to sick cells rather than healthy cells, this "selective synergism" is apparent [21,22]. One such example is the powerful analgesic tapentadol, which works by inhibiting norepinephrine reuptake in addition to agonizing the μ opioid receptor. Because of this dual action and its precise targeting of the μ-opioid receptor, it is safer and has fewer side effects than traditional opioids like morphine. Tapentadol has a greater equianalgesic dose than morphine, and because of its dual-targeting selective synergism, tapentadol has far fewer harmful side effects than morphine [23,24].

Complex and multifaceted CNS illnesses like schizophrenia and Alzheimer's are often treated with a variety of unfavorable side effects [25,26].

Modulating the target protein and blocking the pathways causing the side effects at the same time is one method of improving the therapy's overall effectiveness. Drugs that are extremely specific to a particular target typically cannot accomplish this, and their severe side effects frequently force the therapy to be stopped. For instance, because of its cardiotoxicity, the anti-obesity serotonin reuptake inhibitor chlorphentermine was taken off the market [27]. Compared to aripiprazole, it demonstrated stronger antagonistic activity at 5-HT2A, which may account for the decreased dopamine 2 (D2) receptor inhibition-mediated akathisia [28]. Additionally, brexpiprazole showed a higher affinity for the adrenergic α1 and serotonin 5-HT1A receptors, which alleviated the 5-HT1A depressed symptoms and the α1 extrapyramidal motor side effects [29,30]. Brexpiprazole's well-balanced action reduces the likelihood of weight gain and extrapyramidal motor adverse effects, while also lessening the symptoms of schizophrenia [31]. Brexipiprazole's increased effectiveness leads to a reduced daily dosage, which lessens the medication's adverse effects [32]. Finally, given the several clinical trials required for each unique medicine and its specific target, creating a therapy with multiple targets is more cost-effective.

Drug design based on polypharmacology

Anti-targets: the minefields to avoid

To be considered polypharmacologic, a molecule must have every structural characteristic needed to act on more than one target. "Promiscuity" refers to a molecule's capacity to interact with several proteins within a disease pathway. The characteristic that renders a molecule polypharmacologic is its intrinsic quality. Even while promiscuity and polypharmacology go hand in hand, the word is frequently used negatively, suggesting that promiscuity binds to off-targets and has unfavorable effects. Consequently, a molecule must be selectively promiscuous to attach to several therapeutic targets while preventing off-target effects to qualify as polypharmacologic.

A polypharmacologic drug must have low binding to an "anti-target" to be effective and free of off-target effects. A preliminary screen of a library of compounds for anti-target binding is one way to find possible binders of an anti-target. This would lessen the possibility of future attrition or medication withdrawals in addition to safeguarding clinical trial volunteers. Early screening would also lessen the need to alter a well-optimized molecule later on, which is a significant setback for any group involved in drug development research [12,33].

Research groups have selected a narrower set of anti-targets to screen their compounds against in order to prevent duplication. This will aid in the identification of promiscuous molecules and the prediction of unfavorable effects associated with anti-target binding. In a combined effort, researchers from AstraZeneca, GSK, Pfizer, and Novartis identified 44 targets, which they then suggested as a "minimal panel" for early safety assessment [12,34]. For instance, human cardiovascular side effects are not reliably predicted by rodent models. This is mainly because human ion channels contribute differently than those of rats [12,35]. Because of this, it is advised by the International Council for Harmonization (ICH) S7A guidelines for safety screening that ligand binding or enzyme tests be utilized to identify adverse effects associated with anti-target binding [12,35]. However, because these in vivo and in vitro techniques are time-consuming and expensive, in silico computer-aided drug design techniques are being used more frequently to anticipate interactions. In addition to anti-target interactions, assessing a molecule's pharmacological profile helps forecast the molecule's possible side effects. A novel chemical is also likely to have similar side effects if its pharmacological objectives are the same as those of a well-known medication [36,37]. When combined, pharmacological profile screening and anti-target screening aid in the prediction of a molecule's probable side effects as well as promiscuity. Furthermore, the presence of specific chemical characteristics like lipophilicity and ionization state may be able to predict promiscuity, which in turn may predict polypharmacology.

Recognizing promiscuity

As was previously mentioned, promiscuous medicines were frequently found during the period of single-targeting drug research. Many of these medications were recently shown to be accidentally polypharmacologic, despite the fact that they were intended to be single-targeting medications. As polypharmacology has gained popularity in drug development, the promiscuity of a molecule is frequently found during the latter phases of biological screening. Following the identification of promiscuity, the molecule is logically enhanced for greater therapeutic efficacy by multitargeting. Later-stage molecular optimization is frequently more expensive and time-consuming. Certain chemical characteristics of molecules likely to make them promiscuous (described in detail below), have been identified

by medical chemist [38]. These molecular features coupled with various drug design techniques aid in early promiscuity identification and in developing a multi-target lead.

Promiscuity detection using physiochemical characteristics

Numerous studies conducted since 2006 have connected certain physicochemical characteristics, like lipophilicity, ionization state, and molecular weight, to promiscuity. Since the majority of protein binding sites are hydrophobic and lipophilic interactions play a significant role in ligand affinity, lipophilicity is often regarded as a strong predictor of pharmacological promiscuity. As a result, molecules with high lipophilicity tend to be more promiscuous. Pharmacological promiscuity rose dramatically with CLogP greater than 2, as shown by a library of compounds from different pharmaceutical companies [12,38]. It is interesting to note that compounds with comparable lipophilicities frequently differ significantly in terms of promiscuity. Furthermore, when lipophilicity was similar, pKa seemed to have a secondary effect on promiscuity. Basic compounds, for instance, showed a sigmoidal relationship between ClogP and promiscuity, with an inflection point at ClogP ~ 2. The sigmoidal relationship, however, was less evident for neutral molecules, since they only showed a modest increase in promiscuity relative to ClogP. Furthermore, neutral compounds were typically found to exhibit strong promiscuity at ClogP > 1 [38]. This indicates that while lipophilicity is a significant predictor of promiscuity, other molecular features must also be taken into account [12,38]. Apart from lipophilicity, a molecule's ionic state also significantly affects promiscuity. It's possible that compounds that ionize at physiological pH don't normally display promiscuity. The reason for this seems to be the particular angle and distance constraints needed for hydrogen bonding and other polar interactions to occur [38,39]. An ionized molecule cannot engage with a target through hydrogen bonding or other polar interactions if it is improperly orientated or is not near enough to the oppositely charged amino acid residue on the target. The molecule would become less promiscuous as a result. Nevertheless, promiscuity is often seen in safety screens for basic compounds (pKa > 6), which are normally protonated at physiological pH and particularly if they have two or more aromatic rings near the basic core (acridines, for example). Furthermore, the BioPrint database showed that bases showed greater promiscuity than acids, neutral chemicals, zwitterions, and uncharged bases [40]. However, a sizable portion of these targets between 15 and 25 % are anti-targets, thus the positive charge might be viewed as a promiscuity risk. Aminergic anti-targets, like the serotonergic 5-HT2B, also exhibit a high hit rate for molecules that have a basic core. Aminergic anti-targets have been shown to bind with sub-micromolar affinity to over one-third of basic chemicals in the BioPrint database [38,40]. A positive charge was also discovered to be the primary predictor of off-target interactions in a safety screening of Roche drugs [38,41]. Studies have also been conducted on the impact of molecular weight on promiscuity. Higher molecular weight molecules tend to be more complex, hence molecular weight generally indicates a molecule's level of complexity. Consequently, a low molecular weight compound's simplicity may make it more likely that its surface will complement the binding site, increasing its promiscuousness. Conversely, a molecule with a higher molecular weight may be more likely to contain the protein binding site's pharmacophoric characteristics. Peptide hormones are one instance of this, where the pharmacological interaction of the molecule is attributed to only a small region of the molecule [38]. Studies have also shown these contradicting features. Higher molecular weight compounds were shown to be more promiscuous in Novartis' safety screening data, although an inverse association between molecular weight and promiscuity was seen in Pfizer's high throughput screening (HTS) data [42]. Molecular weight does not appear to be a reliable indicator of promiscuity as a result.

While other chemical characteristics are less reliable indicators of promiscuity, lipophilicity and ionization state are strong indicators. These less useful molecular characteristics include the number of ring assemblies, rotatable bonds, and rings (all of which frequently have a positive link with promiscuity). These molecular characteristics have an indirect impact on promiscuity, which is correlated with their lipophilicity, which may be the main underlying factor [38, 42]. In a similar vein, molecules that have less polar surface area and fewer donors/acceptors of hydrogen bonds are more promiscuous and have higher lipophilicity [43]. Moreover, because they need strong shape complementarity to attach to the intended protein binding site, molecules with a lot of side chains and minimal flexibility are frequently less promiscuous [12,43].

Characteristics of structures that indicate promiscuity

Pharmacophoric similarity between unrelated proteins and within a target protein family may be

used to explain a molecule's promiscuous behavior [12,44]. Aminergic G protein-coupled receptor (GPCRs) and kinases are two examples of such protein families that are linked to promiscuity and share pharmacophoric characteristics. The standard aminergic GPCR and ion channel pharmacophore is made up of basic amines (secondary or tertiary) linked to an aromatic ring by a linker consisting of two to five atoms. As a result, molecules with these characteristics are probably promiscuous 8 [3]. Comparably, the "2 – 0" rule aids in identifying compounds that are probably kinase active. According to the rule, some structural fragments must be counted, such as more than two heteroaromatic nitrogen (such as N or NH) or more than zero aromatic NH substituents and nitriles. In contrast, kinase activity is considerably more predicted when a "heteroaryl-NH-aryl" motif is present [12]. Only promiscuity may be predicted by the existence of these molecular and structural characteristics. One must examine current chemical and biological databases to ascertain which targets the compound interacts with. Nevertheless, because they contain all available data on chemical scaffolds and biological proteins, these databases are incredibly big. It is therefore very difficult to relate the chemical and biological domains. Efficient computer-based strategies have emerged to better forecast the link between two spaces and resolve this complexity.

Utilizing computation to detect promiscuity

The interaction of a molecule with a panel of targets is predictable through cutting-edge computational techniques, which also enable scientists to forecast molecule's pharmacokinetic characteristics and promiscuity. Presynthetic iterative design and optimization is the time to accomplish this. Computational methods encompass many different techniques, but they are broadly categorized into three groups: ligand-based approaches, structure-based approaches, and statistical data analysis and bioinformatics. Each group has advantages and disadvantages of its own [6].

Drug design based on structure (DDBS)

The underlying idea of DDBS methods, also referred to as target-centric methods, is that a collection of proteins with similar structures would have similar selectivity properties and would therefore bind to similar compounds. These methods examine the 3-D structure of the macromolecular target, which is usually a protein or ribonucleic acid (RNA). It highlights important locations and exchanges that would ultimately lead to their pharmacological action. The target's three-dimensional structure must be determined before using DDBS [45]. Molecular modeling tools are utilized to examine the physical and chemical characteristics of drug binding site after it has been identified. Drug properties analyzed include hydrophobicity, polarity, hydrogen bonding ability, electrostatic field, and essential amino acid residues for binding. The next step is to search the chemical database for compounds with a high binding affinity and a complementary shape to the binding site. This help to forecast promiscuity and polypharmacology by essentially finding many biological targets for the same chemical structure.

Pharmacophore modeling

Pharmacophore modeling is another way to achieve DDBS. The word "pharmacophore" refers to chemical characteristics required for ligand to engage with a biological macromolecule and trigger an action. Various functional groups satisfy this crucial criterion of molecular properties (hydrogen bond donors, hydrogen bond acceptors, aromatic moieties, etc.), and many different molecules that exhibit these necessary qualities will properly interact with the protein. The ability of a single molecule to have the pharmacophoric characteristics required to activate various proteins is ascertained by pharmacophore modeling. Using a technique known as reverse pharmacophore matching, the PharmMapper online database determines a test molecule's possible protein targets. This leads to identification of all proteins whose pharmacophoric requirements are fulfilled by the molecule and to which the molecule is expected to bind promiscuously [46].

Binding site

Comparison and analysis of DDBS is used to determine molecule's promiscuity through binding site analysis and comparison. This method, as its name implies, compares a set of proteins' binding sites in a methodical manner. Eventually, this comparison aids in finding a set of proteins that might have a common ligand, indicating the potential promiscuity of those ligands. This is accomplished by applying the quick and semi-automated BioGPS method, which uses molecular interaction fields to characterize binding cavities [47]. Using BioGPS, Duran-Frigola *et al*, found 87,300 binding holes in 31,900 protein chains derived from 3700 distinct proteins. The binding pockets were then compared, and those with a score of 0.6 or higher were categorized as "similar" pockets. Analyzing the co-crystallized ligands allowed for

the confirmation that binding pockets were similar. Pairs of binding pockets with scores over the cutoff were found to accommodate the same ligands, indicating that the method may be applied to determine promiscuity [49].

Generally, DDBS is an effective computational method that may quickly and affordably discover promiscuity in addition to finding new therapeutic lead compounds. Drug design based on structure aids in precise prediction of promiscuity by employing the target's three-dimensional structure and examining the ligand's steric and electrostatic complementarity with the binding site. By predicting a molecule's ability to bind to a target based on structural similarity to a known ligand, a chemical similarity approach lead to false positives and negatives. This technique is overcome by this method. Furthermore, DDBS facilitates the evaluation of the structural resemblances between binding sites on different targets and the identification of putative protein-ligand interactions at pivotal points in a disease process. Drug design based on structure is not without restrictions, though. It works only with proteins whose crystal structures are known, and its efficacy is limited by the unpredictable conformations of the binding site residues [48].

Ligand based drug designing

The target protein crystal structure is not a need for ligand-based computational approaches, in contrast to the previously discussed techniques. These techniques, often referred to as compound-centric approaches, are predicated on the idea that compounds that resemble the known ligand structurally or chemically are likely to bind to protein targets that are important to biology [46]. A pharmacophoric model is developed using the structure of the known ligand, highlighting the essential structural elements required for target interaction. It is assumed that a molecule with these essential structural characteristics binds to the known ligand's biological target. While the chemical library is examined to determine which known pharmacophoric properties the new molecule exhibits, the process is similar to the pharmacophore modeling method used in DDBS. Because a molecule may concurrently possess the essential pharmacophoric characteristics of two or more targets, making it polypharmacologic, this method is also helpful in predicting promiscuity [46].

Similarity ensemble approach

When determining if a molecule has the required pharmacophoric properties, ligand-based techniques frequently employ a technique called the similarity ensemble approach (SEA), in which the 3-D structure of the molecule is compared to that of known ligand of various targets. Rapid overlay of chemical structures (ROCS), a 3-D shape similarity analysis program, is used in this method to anticipate which protein targets a molecule might bind to base on how similar its shape is to the known ligand. This results in the molecule's pharmacological profile [12,46]. The SEA has become popular and has been successfully used in predicting possible targets of several compounds. For instance, the inhibition of cyclooxygenase-1 (COX-1) by the synthetic estrogen chemical chlorotriazine was effectively predicted. This provided an explanation for the abdominal pain side-effect observed from chlorotriazine treatment [12].

Machine learning approach

Recently, ligand-based techniques for target prediction have been developed using machine learning (ML). Regression algorithms including support vector machines (SVM), decision trees (DT), k-nearest neighbor, naïve Bayesian models, and artificial neural networks are used to rank substances according to their likely activity and classify them into active or inactive groups [49]. When particular chemical characteristics from the target and the compound that are involved in the drug-molecule interaction are added, the accuracy of the predictions produced by these algorithms employing machine learning techniques may be further enhanced. In polypharmacology, effective target deconvolution techniques are necessary for multi-target activity evaluation. This is crucial for protein families like kinases, which are highly targeted and share similar structures and sequence domains.

The knowledge gathered from comparable kinases and compounds are used to predict the activity of as-yet-undiscovered compound-kinase interactions through the use of machine learning techniques [50]. Then, quantitative outcomes are enhanced when machine learning techniques are combined with the Illuminating the Druggable Genome (IDG) consortium (https://druggable genome.net/), a Common Fund program of National Institutes of Health (NIH) that aims to enhance knowledge of understudied proteins within three drug-targeted protein families: protein kinases, ion channels, and G-protein coupled receptors. Through kinome-wide profiling small-molecule agents, the program specifically intends to improve targeting of understudied kinases in order to further explore the activity profile for the understudied human kinome [50]. When specific disease models are

available for a study, analyzing drug response profiles with molecular and genomic profiling of the disease models (e.g., copy number variation, proteomic, transcriptomic, methylation, and exome and RNA-Seq datasets) improves the results obtained by applying machine learning algorithms [51]. When it comes to a variety of purposes, including identifying compounds as strong inhibitors and non-inhibitors of cytochrome P450 and forecasting the anti-target interactions of tivozanib, an experimental VEGFR inhibitor, machine learning techniques are more advanced and more accurately applied than other computational methods [52]. A thorough guide explaining ML techniques and their applications is provided by recent publications by Cicho´nska *et al* [50]. As was previously said, the primary benefit of a ligand-based strategy is that protein's structural structure is not necessary.

Consequently, it cannot be applied to protein targets for which a ligand is unknown. Furthermore, it may be expected that novel compounds that have too different a structure from the ligands now in use may not bind with a protein target. This might lead to a false negative since it's possible that not all of a protein target's active chemical structures have been found. It would be very challenging to predict the polypharmacological characteristics of such compounds. On the other hand, if novel molecules differ at crucial locations involved in the target interaction and their structure is strikingly similar to that of known ligand, this could result in a false positive.

In these circumstances, assessing the molecule's steric and electrostatic complementarity to the target binding site using DDBS would be more helpful and accurate. Generally speaking, combining ligand-based and DDBS approaches would yield more reliable and accurate findings for identifying polypharmacologic compounds because each has pros and cons of its own. Apart from facilitating the discovery of appropriate target combinations and forecasting ligand promiscuity, in silico quantitative flux modeling calculates the extent of modification necessary to yield the intended therapeutic outcome with the least amount of side effects. Maximum treatment efficacy would be attained by partial regulation of target combinations as opposed to full modulation of a single target, according to this hypothesis of targeting numerous pathways with low drug dosages [7]. Yang *et al* investigated cyclooxygenase and lipoxygenase, the distinct branches of the arachidonic acid metabolic network, in human polymorphous leukocytes and predicted the ideal target combinations required for synergistic effects using time resolved flow analysis. Time-resolved LC-MS/MS profiling of arachidonic acid's pro- and anti-inflammatory metabolites was subsequently used to validate these [7].

Applications of polypharmacology

Drug repurposing

Drug repurposing, or the use of an already-marketed medication for a new indication [12, 53], is one of the most beneficial uses of polypharmacology. The topic has garnered increased attention lately due to the evaluation of numerous authorized medications in clinical trials for novel purposes [54]. This is beneficial since, in most cases, developing a proven medicine for a new indication is less expensive, although it is time-consuming, and dangerous when compared to developing a novel one. Studies that have already been conducted, such as pharmacokinetic, toxicology, and formulation studies in humans, aid in the redevelopment of an approved medication for a new indication [12].

It is possible to "rescue" molecules that have not been approved or that have been taken off the market because of unfavorable reactions if the advantages of their repurposed indication outweigh the risks of using them [55]. The resurgence of thalidomide following its 1961 withdrawal owing to its severe teratogenic effects is a prime example. Thalidomide was repurposed in 1964 as a treatment for erythema nodosum leprosum (ENL), an excruciating inflammatory consequence of leprosy, following a fortuitous finding. Thalidomide's polypharmacologic action on tumor necrosis factor α (TNF-α), which is erroneously generated in inflammatory tissue, is the reason for this repurposed indication. Thalidomide is being utilized to treat multiple myeloma; this is because of its multi-target effect on VEGF and interleukin-6 (IL-6) [12].

Repurposing a marketed medication with a medically beneficial side effect is also referred to as drug repurposing. For instance, it is well known that codeine have a sedative effect. In fact, this adverse effect may be helpful for those who have trouble falling asleep. A promiscuous compound's affinity profile is changed from one therapeutic target to another via such repurposing. Sulfacarbamide, for instance, was a well-known sulfonamide antibiotic with a brief half-life that was transformed into the more potent derivative 1. On the other hand, hypoglycemia was a noticeable adverse effect of derivative 1. Later, the medication was changed to carbutamide and sold as an oral antidiabetic in

Europe. Carbutamide did, however, show lingering antibiotic activity, raising the possibility that it would become resistant to microbes. Although carbutamide's unacceptable side effects prevented it from being approved for use in the United States, it was further developed into tolbutamide, which lacked antibiotic activity and instead acted on adenosine-5'-triphosphate-sensitive potassium channels (KATP channel), making it a significant treatment for noninsulin-dependent diabetes [12, 56].

Polypharmacology in epigenetics

The study of heritable and reversible variations in gene expression caused by modifications other than those in the deoxyribonucleic acid (DNA) sequence itself is known as epigenetics [57]. Azacytidine and decitabine were the first epigenetic modulators to receive FDA approval in 2004 and 2006, respectively. These medications, which were approved for the treatment of hematological malignancies, inhibit the enzymes known as DNA methyltransferase (DNMT).

Clinical candidates have also recently been discovered for other epigenetic targets, including arginine methyltransferases (PRMTs), lysine demethylases (KDM), bromodomains (BRDs), and lysine methyltransferases (KMTs). Pharmacological resistance is one of the reasons why a single epigenetic targeting strategy may not work, even if many of these drug candidates have a number of epigenetic targets. The primary cause of phenotypic aberrations in cancer is the evolution of signaling pathways over time in response to drug-induced effects such as growth inhibition, cell death, DNA repair, and metabolic changes. In actuality, creating a multi-targeted medication that operates on several signaling pathway nodes would be the secret to creating an effective epigenetic targeting treatment [57]. A multi-targeting medication may simultaneously modify two epigenetic targets or one epigenetic target and one non-epigenetic target in such epigenetic polypharmacology. When multiple routes are targeted simultaneously, the likelihood of acquired resistance resulting from one target compensating for the other is reduced significantly. A histone deacetylase inhibitor (HDACi) coupled to another pharmacophore (usually a tyrosine kinase inhibitor) has been the main component of most multi-targeting epigenetic medicines discovered to date. In general, treating complicated illnesses including cancer, CNS disorders, and infections will benefit tremendously from polypharmacologic molecule's multi-targeting properties. It is frequently considerably more successful to target several nodes in these disease pathways, which leads to lower effective doses and less harmful side effects [7,58].

CONCLUSION

Polypharmacological medication development is more challenging than single-targeting medication. But with today's knowledge of many illnesses and chemical functional groups, the possibility of purposefully developing polypharmacological medication has increased. This review has presented a case for the necessity of polypharmacology in order to address the inadequacies of available treatments. The challenges that could arise in the pursuit of polypharmacological drug design have been discussed. It is hoped that this review will serve as a guide, outlining the sophisticated instruments, databases, techniques, and cautionary tales that one would require when pursuing a polypharmacologic lead.

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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