Review Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

MULTI-TARGETS DRUGS: A NEW THERAPEUTIC APPROACH

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ABSTRACT

Multi-targets drugs, have occupied significant attention in the former decade, as possible therapeutic keys to diseases of complex disorders as diabetes and drug resistant tumors due to their significant advantages. The old lock and key paradigm, it is no longer appreciated due to the idea of highly specific drug targeting only one target is no longer valid. The concept of Multi-targets Drugs has been proven in significant in the treatment of many disorders including but not limited to; Caner, Alzheimer's disease, Parkinson's disease, inflammation, depression and more exceeding the advantages of single-target drug with lower drug interactions and side effects and more expected pharmacokinetics. Of course, this technique is fairly young and much more research and development are needed. In a complex disorder X, two targets are needed to be modulated so the patient have to receive two drugs C1 and C2. By using one drug (C3, Multi-targets agent) that can interact with both targets, side effects can be minimized with better patient compliance.

KEYWORDS

Multi-targets drugs, Complex disorders, Drug resistance and Drug repositioning.

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INTRODUCTION

Multi-targets drugs, multi-functional drugs or network therapeutics have engrossed significant attention in the former decade, as possible therapeutic keys to diseases of complex disorders[1-3] and health conditions linked to drugresistance[1,2]. According to the "one drug, one target" model, highly effective and specific (single-target) drugs would be endured due to reduction of side effects off the target. Yet, unfortunate correlation between *in vitro* actions and in vivo efficacy of a drug is usually found with target-driven approximations[1,2].

While the first plan might be effective to treat single gene disorders, disease is often a multifactorial complaint including a grouping of constitutive and/or environmental aspects. Biological systems are flexible to single-point disorder due to compensatory mechanisms[1]. Under such view, disorders usually result from the collapse of strong biological systems due to several genetic and/or environmental issues, leading to the creation of strong disease manifestations[1]. Thus, complex disorders are more likely to be treated or eased though concurrent modifications of various targets. However, this approach has only been introduced in the earlier decade, numerous of the already known drugs are Multi-targetsagents[9], which is particularly factual for those agents that were discovered by phenotypic screening, traditional medicine or even by chance. Within all these cases, the pharmacological effect of the drug was known before the accurate determination of the mode of action. Therefore, Multi-targets therapeutics have always been identified and efficiently utilized in the medical practice but have ultimately been found by coincidence or by phenotypic screening[1].

Definitions

Enzyme promiscuity is defined as the ability of enzyme to catalyze multiple reactions. The most common examples of promiscuous proteins are Lipases which known to hydrolyze triglycerides, but it was found that these enzymes can catalyze the hydrolysis of aryl esterase of carboxylic acids (which is substrate promiscuity), and catalyze amide bond hydrolysis (which is catalytic promiscuity). Another example is Serum albumin which is a non-enzymatic protein; it was found that albumin can catalyze carbamate hydrolysis (example of catalytic promiscuity).

Compound promiscuity is rationalized as the ability of small molecules to specifically interact with multiple targets; some therapeutic categories, e.g., mood disorder medications, are particularly abundant on classical examples of Multi-targets drugs. Aspirin has been known to act by a variety of molecular mechanisms in addition to cyclooxygenase inhibition[1]. In the context of polypharmacology, Polypharmacology which refers to the property of many bioactive compounds or drugs to act on multiple physiological targets, modulate different signaling pathways, and elicit multi-target-dependent pharmacological effects.

LOCK AND KEY PARADIGM OF MULTI-TARGETS DRUGS

The most common way used to describe the interaction between a ligand and a target is the classical lock and key model or the update concept that speculates the ligand and the target flexibility. The generic idea that the key (represents the ligand) should be compatible with the lock (represents the target) to get the lock open (cause biological response). Ligand with different structures but similar or common arrangements can elicit same actions on the same target activity Figure No.1, paradigm No.1 and 2. Contrarily, a single ligand can interact with different targets simultaneously Figure No.1, paradigm 3. This can be achieved by different approaches; the ligand can act on different isoforms of the same protein family e.g. xilocaine (lidocaine) can block sodium channels in the heart and peripheral and central nervous system which produce anticonvulsant, antiarrhythmic and anesthetic effects, different members of a given pathway can share ligand specificity, or a given ligand can could interact with different unrelated targets[2]. This can be selective non-selectivity but non-selective non-selectivity (ligand promiscuity) might be very unfavorable. Figure No.1, paradigm No.4 and 5 represent that a ligand can hinder the interaction of another ligand with the same target.

APPLICATIONS OF MULTI-TARGETS DRUGS

Complex Disorders

Complex disorders are typically caused by several inherent and/or environmental factors. They include but not limited to; cancer, diabetes, chronic inflammation and neuro degenerative diseases. In such complicated diseases, many targets need to be modulated by different medications but using Multi-targets drug/s in these conditions would be an

advantage with reduced risk of drug complications and interactions, better patient compliance and more predictive pharmacokinetics. Detailed examples are to be discussed later in this article.

Drug Resistance

Multi-targets drugs could be an advantage in patients expressing intrinsic or induced variability in drug response due to modifications in key disease-relevant biological pathways and activation of compensatory mechanisms[2,3]. The clearest application is epilepsy. One third of the epileptic patients suffer from refractory epilepsy[6,2]. One of the predominant propositions to clarify refractory epilepsy cases suggests that at least som of the non-responsive patients might show differences in the targets of antiepileptic agents[Error! Bookmark not defined.]. Isobolo graphic studies in animal models and medical practice propose that combination of drugs with diverse mechanisms might to be helpful[2-5]. On contrary, while there exists harmony concerning the use of single-target drugs for the treatment of some specific epilepsy manifestations, broad spectrum antiepileptic drugs as valproic acid are of the most utilized antiepileptic agents and might be valuable in Patients where, at the onset of epilepsy, diagnosis of the exact condition is indefinable[6,2,3].

Drug Repositioning

Repositioning of drugs, including approved, discontinued, shelved, and experimental drugs, is screening of already known therapeutics to find a second or further medicinal use[2,3]. Most of the successful drug repositioning cases have been found by chance or through use of the main mechanism of action of a drug for new drugs. Computational methods to target repositioning have always been fixated on retrospective drug repositioning. Retrospective drug repositioning is screening known drugs to find novel uses for already known drugs. In contrast, prospective drug repositioning is discovering drug repositioning potentials earlier in the process of drug discovery. This can be further used by designing drug that majorly target co-existing more frequent disorders e.g. diabetes and cardiac disease; anxiety and peptic ulcer disease, epilepsy, and depression.

DESIGNING AND SCREENING OF MULTI-TARGETS AGENTS

The most common approaches to develop a Multi-targets disease is; selective combination of pharmacophores from single-target ligands which is known as fragment-based approach, and screening of collections of compounds by simultaneous application of multiple computational models or by optimized assays to screen as many compounds as possible at once with high efficiency and accuracy[2,3].

In the former approach, the different pharmacophores are joined together by a cleavable or stable linker or, otherwise, they are overlapped by taking advantage of structural similarities. The use of linkers is usually leading to compounds with unfavorable biopharmaceutic or pharmacokinetic profile[25]. On the other hand, the use of cleavable linkers is beneficial but it also limits some of the qualities of the Multi-targets approach in comparison with combination therapies[2]. Moreover, the fragment-based approach could lead to poor ligand efficiency metrics, which refer to the binding efficiency per atom. It might be speculated that, since only a part of the molecule can interact with each of the proposed targets, the other part can become an obstacle for the binding event, reducing the binding efficiency because of enthalpic and/or entropic reasons.

TARGETS SELECTION

The main criteria of the target are that target must have the potential to be disease modifying. In case of infections or deregulated cells, the target must exclusively or preferentially be expressed in the infectious antigen or in the cancer cell, target proteins should not have homologous proteins in the same patient or the homologous proteins should be different enough to maintain selectivity. Moreover, the target should be assessed for its drug ability by general considerations (at least one member of the protein family to which the target belongs is targeted by a drug) which is based of ligand-binding site prediction. But this approach is generic for both single- and Multi-targets approximations[2,3]. Several

other factors should be considered; the nature of the disease (infectious disease or complex disorder) and/or the possible mechanisms of drug resistance (adaptive mechanisms, target amplification or mutation). Other routes for target selection are; targeting different targets in a single pathway through weak partial inhibitions (vertical targeting) which might be useful against resistance due to target mutation[2], or targeting parallel signaling pathways which may be valuable to block escape routes, adaptive resistance mechanism and compensatory homeostatic responses. A relevant issue is the choosing whether to completely block or to modulate the selected target.

Strategies of attacking targets include; attacking a highly connected key nodes in the cell biochemical network, or modulate multiple non-crucial nodes adjoining the key nodes with low affinity Multi-targets ligands which might be better to avoid severe side effects that might manifest when attacking the main nodes[2]. To evaluate the significance and contribution of metabolic pathway, metabolic control analysis could be utilized to ultimately determine the optimal target[2].

Docking studies

Docking and computer-assisted drug design are utilized to explore and expect how a drug (ligand) interacts at the molecular level with its target, evaluating the energies and interactions exist between them. Thus, docking approaches rank these interactions according to energy values, exploring several drugs while offering structural interaction theories[2]. A score-weighted docking prediction paradigm shows evidence regarding the bindings between a drug and a target[2]. Docking methodologies were applied in many different conditions with different targets and ligands such as Alzheimer's disease, cancer, Kinases, antibiotics, anti-inflammatory, and even with traditional medicines[33].

POTENTIAL APPLICATIONS OF MULTI-TARGETS APPROACH

Cancer

Clinical trials have proved many Multi-targets drugs activities in a wide range of tumor types including ones that is drug resistant. The most prevalent example is sunitinib which was effective against kidney cancer, gastrointestinal stromal tumor and retinal cell carcinoma. Sunitinib was found to target platelet-derived growth factor receptor, vascular endothelial growth factor receptor, receptor rearranged during transfection, tyrosine kinase receptor c-Kit, Receptor-type tyrosine-protein kinase and colony stimulating factor 1 receptor in addition to targeting different genes including RET oncogene. Despite the side effects of this drug, this agent and more are evidence of the applicability of selective Multi-targets for the management of drug resistant and less complicated tumors.

Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disorder that affects up to 80% of those aged 65years; dementia only occurs in a small percentage of individuals at this age yet the frequency of dementia in Alzheimer rises to 25% in individuals 80 years or more[3-5]. The most common used treatment of Alzheimer's disease is acetyl cholinesterase inhibitors but recently acetyl cholinesterase/butyryl cholinesterase inhibitors were gained more attention.

Numerous promising important ligands have been discovered, enabling further development of new drugs for the treatment of Alzheimer's disease. A novel class of compounds consist of multifunctional prochelators or chelators with added characteristics which are inhibitors of β-secretase, β-site amyloid precursor protein-cleaving enzyme 1, in addition to modulation of γ-secretase with peroxisome proliferator-activated receptor γ[1].

Parkinson 's disease

Brain-selective monoamine oxidase-AB and iron increase with age and in Parkinson's disease patients, these increases can lead to oxidative stress-dependent neurode generation. In the light of these datum, ladostigil, TV-3326 (N-propargyl-3R-

aminoindan-5yl)-ethyl methylcarbamate, Figure No.2) was found to have neuroprotective activity through Multi-targets actions which are cholinesterase butyryl esterase and brain-selective monoamine oxidase-AB inhibitory activities. Iron chelator-radical scavenging drug (M30, Figure No.3), in addition to its iron chelation activity, was found to have brain-selective monoamine oxidase-AB inhibitory activity and the neuroprotective-neuro rescue activities[4].

Inflammation

Non-steroidal anti-inflammatory drugs and cyclooxygenase-2 selective inhibitors are being usually used for the treatment of inflammation and pain these agents work through inhibiting single arachidonic acid oxidative cascade metabolic pathway which lead to disruption in the levels of oxylipin with cardiovascular and gastrointestinal side effect. These findings have led to finding Multi-targets agents that simultaneously inhibit multiple pathways for arachidonic acid metabolism which was proven to be a new valued possibility to minimize the side effects of the drugs[4].

Phytotherapeutic Applications

For millennia, medicinal plants have been aappreciated source of therapeutic agents, and still many of today's drugs are plant-derived natural products or their derivatives. However, since natural product-based drug discovery is associated with some intrinsic difficulties, pharmaceutical industry has shifted its main focus toward synthetic compound libraries and high throughput screening for discovery of new drug leads. The obtained results, however, did not meet the expectations as evident in a declining number of new drugs reaching the market. This circumstance revitalized the interest in natural product-based drug discovery, despite its high complexity, which in turn requires broad interdisciplinary research approaches[4]. In the area of malaria management, phyto extracts were proven to be more effective that isolated phytochemicals. This is due to the Multi-targets effects of the many metabolites present in the extracts[1].

FUTURE PERSPECTIVE

It cannot be denied that Multi-targets drug concept is still novel and not really stablished. This section will bear the thoughts of the authors to take idea of Multi-targets agents to the next step. Multi-targets agents and compounds are already known in nature with being strictly pinpointed e.g. quercetin, a natural flavonoid isolated from different medicinal plants and foods such as *capparis spinosa, rumex, ceratonia siliqua, coriander, nasturtium officinal*, radish, red onion, kale, wax peper and many more[5]. Quercetin was found to have the following effects and activities; anti-allergic immune response[5], blood pressure reduction activity[6], inhibiting adipogenesis and lipogenesis in obesity[6], antidiabetic[6], counteracting oxidative stress[6], anti-cancer[6], anti-inflammatory[50] and more. It is obvious that quercetin is a Multi-targets agent but it has never been studied from this view.

In the research for or the design of Multi-targets agents, the following should be considered; the agents should not have very wide spectrum of activity (highly promiscuous) to avoid unwanted interactions and side effects, the drugs should target only target related to one specific disease (cancer, diabetes) or targets that should be modulated for the treatment of different co-existing disorders, and the Multi-targets compounds should be specific to abnormal or mutated targets without any or great interactions with normal similar targets.

GRAPHICAL ABSTRACT

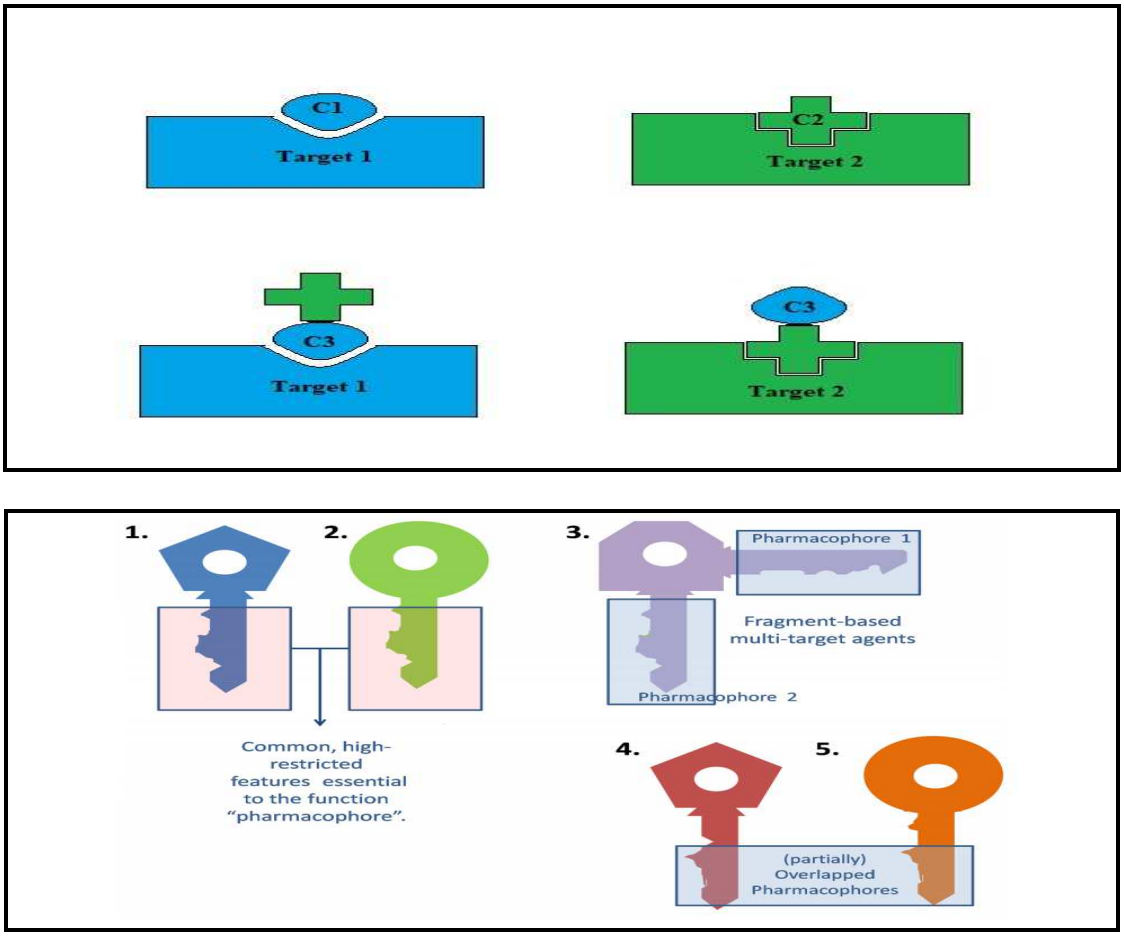

Figure No.1: Representation of classical key and lock paradigm of Multi-targets drugs[10]

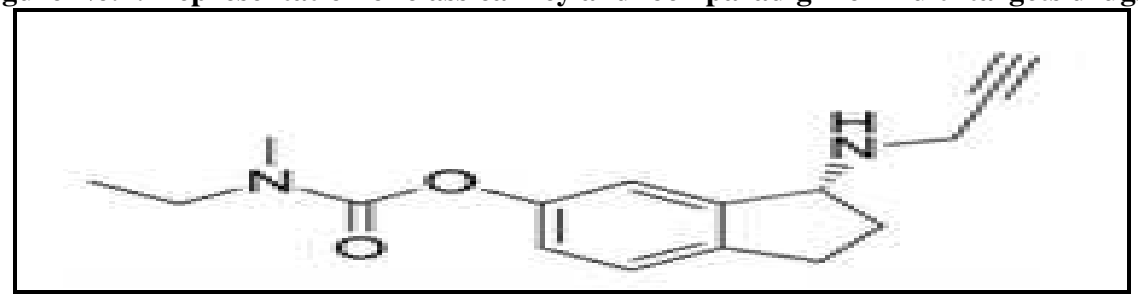

Figure No.2: Ladostigil structure

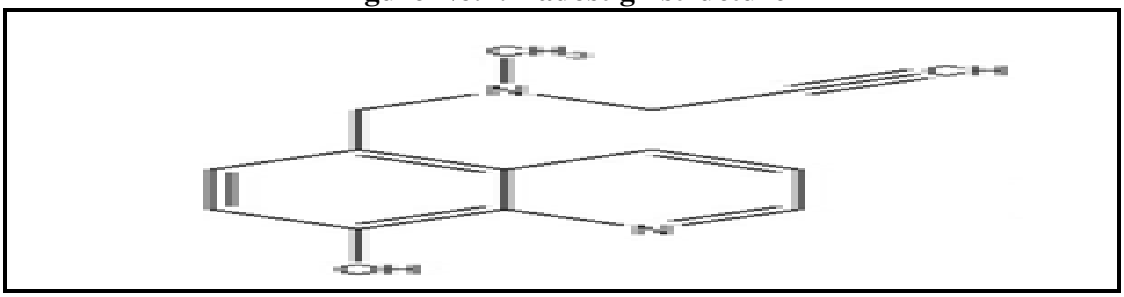

Figure No.3: M30 structure

CONCLUSION

Multi-targets drugs are a promising approach to face intricate, multifactorial diseases and drug resistance problems. Moreover, they can be valued in prospective drug repositioning for the treatment of complicated conditions or both the original pathology and its symptoms, which is a disregarded application to the moment. Compared to combination treatments, Multi-targets agents have numerous advantages, including expected pharmacokinetics and less likelihoods of drug interactions.

ACKNOWLEDGEMENT

The authors would like to thank Liver Research Lab, Fab-Lab and those who maintain it.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Farid A. Badria and Mohamed H. Ahmed. Multi-targets drugs: a new therapeutic approach, *International Journal of Research in Pharmaceutical and Nano Sciences,* 7(5), 2018, 205-213.