Recent Medicinal Chemistry Studies for Multitarget Agents—Part II

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Many diseases classified as complex and of multifactorial origin, such as cancer, diabetes, and hypertension respond better to treatments consisting of several drugs. But multiple dosing of medicines and the increasing risk of drug interactions and side effects lead to the development of patient non-compliance to composite therapy. Polypharmacology emerged through research in multifunctional compounds and has helped resolve these problems. Such new chemical entities (linked to more effectively fighting disease) must interact with various receptors, triggering multiple biological effects, that when united fight the disease more effectively, these are the Multi-target drugs in drug discovery (MTDD). Selective modulators of certain targets or closely related groups of targets, in fact, act via modulation of multiple proteins with diverse functions. Multi-target drugs against selected multiple targets improve therapeutic efficacy, safety, and resistance profiles by collective regulation of the primary therapeutic target, together with related compensatory elements and resistance activities. New multifunctional compounds have emerged as a modern trend in drug research that are reinforced by studies based on big data, where global view investigations of multiple causes and effects are a growing trend. This issue, Recent Medicinal Chemistry Studies for Multitarget Agents—Part II, brings manuscripts from different countries reporting recent research studies in multi-target drugs.

Pain is an unpleasant sensation that have complex and various causative etiology. Modern drug discovery focuses on identifying potential molecules that target multiple pathways with safer profile compared to those with a single target. Current treatment of pain and inflammation with the available therapeutics has a number of major side effects. Pain is one of the major clinical problems that needs functional therapeutics which act on multiple targets and with low toxicity. Curcumin, a naturally occurring polyphenolic compound from Curcuma longa, has been used for years in Ayurvedic, Chinese, and in many other systems of traditional medicine. Pre-clinical data published thus far, demonstrated that curcumin possesses multi-target biological functions, suggesting its potential use to cure different diseases. However, there is no or little systematic review on its potential use in pain and inflammation with underlying mechanisms for such activities. Accordingly, the aim of the review of Dr Mubarak and co-workers, Curcumin and its Multi-target Function Against Pain and Inflammation: An Update of Pre-clinical Data, was to update the pre-clinical data of curcumin and its multiple targeting pathways for analgesic and anti-inflammatory action, and to further propose a molecular mechanism. Literature study was conducted using different known databases including Pubmed, Sci-finder, Google scholar, and Science Direct. Available pre-clinical data suggest the ameliorating effect of curcumin in pain and inflammation is rendered through the modulation of a of pain pathways including inhibition of a number of pro-inflammatory mediators, inhibition of oxidative stress and Cox-2, down-regulation of Ca²⁺/calmodulin-depend protein kinase II (CaMKIIα) and calcium channels like transient receptor potential (TRP), modulation of metabotropic glutamate receptor-2 (mGlu2), modulation of monoamine system, inhibition of JAK2/STAT3 signaling pathway, remodeling of extracellular matrix proteins, inhibition of apoptosis, inhibition of JNK/MAPK and ERK/CREB signaling pathway, and activation of opioid system. Taken all together, it is evident that curcumin is one of the promising safe natural polyphenolic molecules that target multiple molecular pathways in pain, and can be beneficial in the treatment and management of pain and inflammation.

Parkinson's disease is one of the most common adult-onset, a chronic disorder involving neurodegeneration, progressively leading to deprivation of dopaminergic neurons in substantia nigra, causing a subsequent reduction of dopamine levels in the striatum resulting in tremor, myotonia, and dyskinesia. Genetics and environmental factors are believed to be responsible for the onset of Parkinson’s disease. The exact pathogenesis of Parkinson's disease is quite complicated and the present anti-Parkinson's disease treatments appear to be clinically insufficient. Comprehensive researches have demonstrated the use of natural products such as ginseng, curcumin, ashwagandha, baicalein, etc. for the symptomatic treatment of this disease. The neuroprotective effects exhibited by these natural products are mainly due to their ability to increase dopamine levels in the striatum, manage oxidative stress, mitochondrial dysfunction, glutathione levels, clear the aggregation of α-synuclein, induce the autophagy and decrease the pro-inflammatory cytokines and lipid peroxidation. The paper entitled Herbal Resources to

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Alzheimer’s disease is a common and most chronic neurological disorder (NDs) associated with cognitive dysfunction. Pathologically, Alzheimer’s disease (AD) is characterized by the presence of β-amyloid (Ab) plaques, hyper-phosphorylated tau proteins, and neurofibrillary tangles, however, persistence oxidative-nitrative stress, endoplasmic reticulum stress, mitochondrial dysfunction, inflammatory cytokines, pro-apoptotic proteins along with altered neurotransmitters level are common etiological attributes in its pathogenesis. Rivastigmine, memantine, galantamine, and donepezil are FDA approved drugs for symptomatic management of AD, whereas tacrine has been withdrawn because of hepatotoxic profile. These approved drugs only exert symptomatic relief and exhibit poor patient compliance. In the current scenario, the number of published evidence shows the neuroprotective potential of naturally occurring bioactive molecules via their antioxidant, anti-inflammatory, anti-apoptotic and neurotransmitter modulatory properties. Despite their potent therapeutic implications, concerns have arisen in context to their efficacy and probable clinical outcome. Thus, to overcome these glitches, many heterocyclic and cyclic hydrocarbon compounds inspired by natural sources have been synthesized and showed improved therapeutic activity. Computational studies (molecular docking) have been used to predict the binding affinity of these natural bioactive as well as synthetic compounds derived from natural sources for the acetylcholine esterase, α/β secretase Nuclear Factor kappa-light-chain-enhancer of activated B cells(NF-kB), Nuclear factor erythroid 2-related factor 2(Nrf2) and other neurological targets. The review of Dr Iqbal et al, Current Quest in Natural Bioactive Compounds for Alzheimer’s Disease: Multi-Targeted-Designed-Ligand Based Approach with Preclinical and Clinical Based Evidence, discussed the molecular etiology of AD, focused on the pharmacotherapeutics of natural products, chemical and pharmacological aspects and multi-targeted designed ligands (MTDLs) of synthetic and semisynthetic molecules derived from the natural sources along with some important on-going clinical trials.

Lack of adequate sleep is a major source of many harmful diseases related to heart, brain, psychological changes, high blood pressure, diabetes, weight gain etc. The 40 to 50 % of the world’s population is suffering from poor or inadequate sleep. Insomnia is a sleep disorder in which individual complaint of difficulties in starting/continuing sleep at least four weeks regularly. It is estimated that 70% of the heart diseases are generated during insomnia sleep disorder. The main objective of this study to determine the all work conducted on insomnia detection and to make a database. We used two procedures including network visualization techniques on two databases including PubMed and Web of Science to complete this study. Dr Khan and co-workers found 169 and 36 previous publications of insomnia detection in the PubMed and the Web of Science data-bases, respectively. They analyzed 10 datasets, 2 databases, 21 genes, and 23 publications with 30105 subjects of insomnia detection. The work, Progress in Detection of Insomnia Sleep Disorder: A Comprehensive Review, has revealed the future way and gap so far directed on insomnia detection and has also tried to provide objectives for the future work to be proficient in a scientific and significant manner.

Artificial Intelligence revolutionizes the drug development process that can quickly identify potential biologically active compounds from millions of candidate within a short period. The review of Dr Nayarisseri and co-workers, Artificial Intelligence, Big data and Machine Learning approaches in Precision Medicine & Drug Discovery, is an overview based on some applications of Machine Learning based tools such as GOLD, Deep PVP, LIB SVM, etc. and the algorithms involved such as support vector machine (SVM), random forest (RF), decision trees and Artificial Neural Networks (ANN), etc in the various stages of drug designing and development. These techniques can be employed in SNP discoveries, drug repurposing, ligand-based drug design (LBDD), Ligand-based Virtual Screening (LBVS) and Structure-based Virtual Screening (SBVS), Lead identification, quantitative structure-activity relationship (QSAR) modeling, and ADMET analysis. It is demonstrated that SVM exhibited better performance in indicating that the classification model will have great applications on human intestinal absorption (HIA) predictions. Successful cases have been reported which demonstrate the efficiency of SVM and RF model in identifying JFD00950 as a novel compound targeting against a colon cancer cell line, DLD-1 by inhibition of FEN1 cytotoxic and cleavage activity. Furthermore, a QSAR model was also used to predict flavonoid inhibitory effects on AR activity as a potent treatment for diabetes mellitus (DM), using ANN. Hence, in the era of big data, ML approaches evolved as a powerful and efficient way to deal with the huge amounts of generated data from modern drug discovery to model small-molecule drugs, Gene Biomarkers, and identifying the novel drug targets for various diseases.

We, the Guest-Editors, would like to express our gratitude to the many authors who contributed to this special issue, reporting investigations in various aspects of RECENT MEDICINAL CHEMISTRY STUDIES FOR MULTITARGET AGENTS-PART II.

REFERENCES


Scotti, L.; Mendonca, F. J. B.; Scotti, M. T., Hybrid Compounds as Multitarget Agents in Medicinal Chemistry - Part I. *Current Topics in Medicinal Chemistry* 2017, 17 (8), 843-844.

Scotti, L.; Mendonca, F. J. B.; Scotti, M. T., Hybrid Compounds as Multitarget Agents in Medicinal Chemistry - Part II. *Current Topics in Medicinal Chemistry* 2017, 17 (9), 957-958.
