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A Data and Informatics Driven Drug Discovery Framework to Bridge Traditional and Modern Medicine

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Abstract

Systems biological models of complex diseases provide a rational way to target their molecular control mechanisms. On the other hand, traditional medicinal systems offer empirical evidence for efficacy of plant extracts against diseases. Informed with our recent research explorations, we propose a data and informatics driven integrative framework that bridges traditional and modern medicine for prospection of therapeutic phytochemicals. This framework has the potential to transform the drug discovery process by intelligently juxtaposing knowledge derived from complementary domains and enables hypothesis driven search for therapeutic molecules.

Introduction

Diseases are manifestations of irregularities in cellular and molecular mechanisms. A large number of diseases have been scrutinized at the level of pathways and molecular causative agents, in addition to understanding contributing environmental factors. However, contrary to expectations, reductionist investigations of complex diseases have led to increase in noise making it difficult to ascertain specific causative molecular mechanisms that could be used to control the disease [1]. Hence prompted by increasing need of integrating disparate molecular elements, systems biological strategies have been developed to create a holistic picture of molecular mechanisms underlying complex diseases [2-7]. These integrative models allow one to wade through the noise and to pin down specific targets and regulatory mechanisms, thus providing a rational strategy towards disease control.

Historically, through trial and error, plant extracts have been identified as effective means of mitigating diseases without necessarily understanding their mode of action. Traditional medicinal systems are rich source of such information which is often complemented by modern medicinal studies. How could we possibly bridge traditional knowledge and modern medicine to facilitate accelerated drug discovery? In this article, informed with our research explorations, we provide a data and informatics driven framework that juxtaposes systems biological models of complex diseases, reported efficacy of medicinal plant extracts, and compilations of structured libraries of small molecules, aimed at an effective and rational drug discovery process (Figure 1) [5-15].

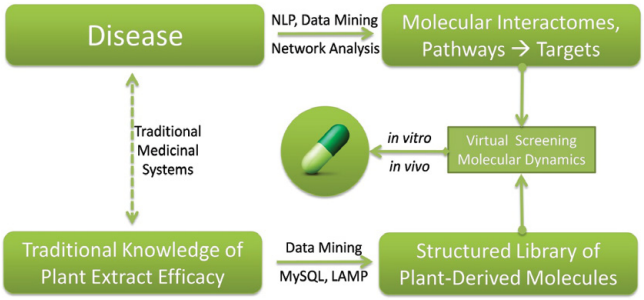

Figure 1: An integrative framework driven by data and informatics approaches for bridging traditional and modern medicine, and for prospection of therapeutic phytochemicals. The proposed strategy brings together jigsaw pieces of data and knowledge pertaining to diseases, their interactome models, traditional knowledge of efficacy of plant extracts, phytochemicals characterization, and computational tools for screening molecules. This framework represents a rational strategy for discovery of novel drugs.

Control Mechanisms of Complex Diseases using Systems Biological Models

Over the decades, studies investigating genetic correlates of complex diseases, such as cancer and diabetes, have created a large repertoire of data. These studies have often aimed at finding 'the target' disregarding the subtle interconnected nature of molecular mechanisms. Findings from such studies have added to the information as well as to the noise. Lately, the focus has been towards creating systems biological molecular interactome models of complex diseases using these data [2–7]. This endeavour has been supported by methodologies such as data mining, Natural Language Processing (NLP), crowd sourcing and graph theory [2,3,16]. These explorations aim to filter noise from large scale data and to identify potential therapeutic targets of diseases. Network analysis, graph theoretical approach for study of interconnected systems, has been extensively used for analysis of disease interactomes. Diseases have been modelled and analysed to represent their protein–protein interactions, metabolic pathways and gene regulatory networks. These studies have paved way for 'network medicine' in deciphering causal relationship of diseases and molecular agents using various means such as linkage based method, disease module based method, and diffusion based method [2,17].

Traditional Medicinal Knowledge of Plant Products

Plants contain vast array of natural compounds with important pharmacological properties and their extracts have been used for

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treating various diseases from ancient times [18,19]. These organic compounds play a central role in health management systems and have become an important part of drug discovery process. Identification of biologically active components of therapeutic value against various diseases is a crucial step towards discovery of drugs. Synthetic molecules tend to have serious adverse drug reactions as compared to organic molecules. Whereas molecules derived from plant extracts have been reported to be effective against various diseases and are devoid of serious adverse drug reactions [20,21]. Knowing the advantages of plant-derived molecules, there has been an increasing emphasis on development of novel phytochemicals-based drugs inspired from traditional medicinal system.

In addition to deriving medicinal benefits from plants, Indian subcontinent has had a long history of culinary practices in which food has nutritional as well as medicinal value. Ayurveda, the classic medicinal system of India, proposes that food plays as much therapeutic role as drugs. Taking a lead from our recent data-driven discovery of 'contrasting (negative) food pairing' in Indian cuisine, we aim to identify chemical constituents of the food to exploit their potential therapeutic value [11,13,14]. Interestingly, our studies have revealed central role of spices in rendering characteristic molecular composition of Indian cuisine, which we propose is not coincidental but is a feature emerging out of use of spices by choice for preparing food that has health benefits. Spices are known to serve as antioxidant, anti-inflammatory, chemopreventive, antimutagenic, and detoxifying agents [22,23]. Our recent experimental studies have shown the beneficial role of capsaicin, an active ingredient of cayenne (12). Similarly, various other compounds from dietary ingredients, such as turmeric, garlic, ginger are reported to have benevolent properties [21–24].

Structured Databases of Plant Derived Molecules

Plants emerge as abundant source of natural molecules of therapeutic value. This is reflected in the fact that medicinal preparations (extracts) derived from plants have been in widespread use against an array of diseases for centuries as part of traditional medicinal systems [21]. Knowing the efficacy and potential of such Plant Derived Molecules (PDMs) the diverse phytochemical space can be explored for systematic extraction of therapeutic molecules. With the knowledge of importance of PDMs, researchers have been isolating and characterizing PDMs from various medicinal plants. Yet, these efforts are too scattered and unorganized to be effectively used for testing a hypothesis and informatics driven discovery of potential therapeutic molecules. We propose that natural language processing and data mining could be used for compilation of data of PDMs from published literature to create structured libraries. These data include the details of source plant, part of the plant it is extracted from, chemical structure, physicochemical properties, IUPAC and SMILES. Such a molecular repository facilitates proposing a hypothesis on probable mode of action of PDMs, which can be tested with the help of in silico studies, and could further be validated with in vitro and in vivo assays. Availability of computer recognizable chemical representations (such as SMILES), and open source tools like OpenBabel, LAMP (Linux-Apache-MySQL-PHP) and Autodock is an important contributor for such an endeavour.

We have demonstrated the proposed strategy by prospecting for therapeutic molecules from *R. serpentina* through inhibition of aldose reductase, a potential drug target for diabetes and its complications (8). This study sought for novel PDMs from *R. serpentina* that could inhibit aldose reductase which is a key bottleneck enzyme of polyol pathway. The strategy used in this study bridges traditional knowledge of efficacy of extracts of *R. serpentina* and modern knowledge of molecular mechanisms central to complications of diabetes. Towards implementation of this strategy we have created a structured database of *R. serpentina* PDMs (9). Further, this work has been extended to include more medicinal plants endemic to Himalayas that are reported to be of important medicinal value in Ayurveda (10). We believe that construction of such structured libraries will propel the drug discovery process and will serve as a catalyst by leveraging the power of computational tools.

Computational Screening for Potential Therapeutic Molecules

Computational screening has gained increasing significance in pharmaceutical research in recent times as an economic means of accelerating the drug discovery process [25]. As depicted in Figure 1, availability of structured information of phytochemicals of medicinal plants and rationally derived molecular control mechanisms (targets) facilitate implementation of high throughput virtual screening studies.

Starting from a target protein and computational repertoire of phytochemicals, one could implement a virtual screening strategy with the help of molecular docking and molecular dynamics to identify potential leads. This step is expected to bring down the number of molecules by screening molecules based on their steric and electrostatic complementarity with the binding pocket of target protein and stability of binding. Further these PDM leads can be used to systematically extract unique molecular scaffolds, which could be chemically elaborated to generate novel leads and to screen molecules from drug-like libraries [26]. PDM leads can also be used to search the neighbourhood of chemical space to obtain their analogs from small molecules database such as ZINC [27]. The PDM leads and analogs thus obtained could further be verified through in vitro and in vivo assays hastening the discovery of novel drugs.

Conclusion

The suggested data and informatics driven framework provides an effective and rational drug discovery strategy by juxtaposing knowledge derived from various sources rooted in traditional as well as modern medicine.

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