CHAPTER 1 INTRODUCTION

1.1 Background and Rationale

Drugs are the chemical substances that are made from botanical specimens for early medicines and are currently derived or purified from chemical compounds (Burger, 1995). The mechanisms of drugs are normally the interactions with macromolecular components within the cells. Because of their strong affinities, drugs can alter the function of the relevant components and initiate the biochemical and physiological changes. These actions elicit characteristic of the response to drugs (Ionescu and Caira, 2010). Drugs are administered to achieve favorable therapeutic results on some mechanism within the diseased person or toxic on regulatory processes in foreign organisms infecting patient. But no effects are completely profitable (Hammann, et al., 2010). Any substance that is capable of producing a therapeutic effect can also produce unwanted or unintended outcomes. The undesirable events are named adverse drug reactions (ADRs), significantly harmful or unpleasant reactions which are the results from an intervention related to the use of a medicinal product (Edwards and Aronson, 2000). Additionally, variations in DNA sequences lead to phenotypic differences. These influence the risk of disease and the response to environment as well as individual efficacy and toxicity of drugs (Meyer, 2000; Sachidanandam, et al., 2001; Shah, 2005; Kingsmore, et al., 2008). Even though the modern medicines have brought the ability to manage untreatable diseases, ADRs have deducted the usefulness by reducing treatment efficacy. This increases costs of care, affects quality of life, and aggravates the confidences in medication (Wu, et al., 2010).

At the moment, studies in pharmacology have been changed to pharmacogenomics (PGx) and pharmacogenetics (PGt). Moreover, systems pharmacology has also became known as the effects of perturbation in the complex network landscape. These three concepts shifted the perception of pharmaceutical pipeline from “one drug fits all” to the rather more individual, “personalized medicine”. They explain interindividual variability and complexity in drug response or ADRs affecting the pharmacokinetics (PK) and pharmacodynamics (PD) (Allorge and Loriot, 2004; Zanger, et al., 2004; Ekins, et al., 2005; Berger and Iyengar, 2009; Mitri, et al., 2010). The rapid growth of these studies has reflected in the blooming number of related publications in various knowledge databases. Unfortunately, PubMed/Medline, the largest published literature repositories that contain an overwhelming amount of biomedical information available as text (Yu, et al., 2007), is difficult to explore and typical to ask if it be read automatically (de Bruijin and Martin, 2002; León and Markel, 2006). The abilities to systematically compare large data sets with all the knowledge that was derived from the public resources are required. They allow the biological relevance of the data to be comfortably interpreted. According to these advantages, literature-mining tools and data mining are now becoming essential to researchers (Jensen, et al., 2006; Ivanciuc, 2008).

Considering that cell comprises of various types of harmonious interactions between cellular components, analysis of specific components and their interacting partners or substrates can be used to assemble biochemical interactions networks (Joyce and Palsson, 2006; Zhu, et al., 2007; Buchanan, et al., 2010). Integration of different resources is used to improve the accuracy of interactions and make functional predictions. However, much of the existing information is hidden and spatially dispersed (Kuhn, et al., 2008). The database, a collection of interrelated stored data that is a valuable resource for multiple users, is therefore applied (Teorey, et al., 2008). The derived knowledge from computer sciences is also helpful in biology as well as pharmaceutical sciences. Structured database entries are designed to enable efficient data retrieval, exchange, and analysis. A number of pharmacological databases have been created from several purposes. Most of them are attended to the relationships of drugs and targets (Chen, et al., 2002; Wishart, et al., 2006; Gao, et al., 2008; Kuhn, et al., 2008; Wishart, et al., 2008; Kanehisa, et al., 2010; Kuhn, et al., 2010b; Zhu, et al., 2010;). Nevertheless, no database has ever been constructed from ADR-drug-protein relationships. The opportunities to build this database may reveal the universal understanding of underlying molecular mechanism of drug-induced ADRs, as well as, advantage for drug discovery process and avoidance of possible ADRs.

1.2 Objective of Study

The Ultimate objective of this study is to exhibit the general hidden information of the associations between ADRs, drugs, and proteins. The advantageous prototype database is designed to deposit ADR-drug-protein relationships which ADRs are connected to proteins using literature mining approach and predictive scores have been given to drugs for ADR class. These efforts can improve the understanding of ADRs.

1.3 Scope of Study

In order to achieve the objectives, the first scope of this study is to extract published information of ADRs and relevant proteins in PubMed using an appropriate literature mining tool. In addition, drugs were scored for causing ADR class by utilizing the classification method. The elicited information then was linked with ADR-drug and drug-protein relation data to construct ADR-drug-protein association database. This prototype database was checked for consistency and can be experienced its advantages on web browser.

1.4 Expected Results

The prototype database of ADR-drug-protein associations was built from putative relations of ADR-protein, relevant drugs and their targets data, and comprehensive ADR-drug reports. The ADR-protein relations are elicited from literatures' abstract that stored in PubMed using an appropriate literature mining tool. Drugs were also scored for potential ADR group using the prediction model. The database can be queried by several manners and has the abilities to increase the knowledge of ADRs and their relevant biological entities.

1.5 Benefit of Study

Accumulation of dispersed ADR-related proteins and integration with associated information will facilitate the research of ADRs. This specific database reveals implicit proteins and drugs involved in ADRs from their connections. Moreover, the scoring of hypothetical ADR class for drugs can easily guide preventing the undesirable effects. The exploration of the database information improves the understanding of ADRs mechanism, facilitates drug discovery process, and reduces the unpleasant reactions.