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MINI REVIEW

In-silico approach in risk assessment of nutraceutical properties

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Abstract

Dietary supplements, including those containing botanical ingredients and botanical-derived compounds, have been marketed to consumers globally for many decades. However, the legislative framework for such products remains inconsistent across jurisdictions internationally. A common problem, concerning these nutraceutical products, is deficient information and lack of data for assessing the hazards posed to human health. The main objective is to explore the use of in silico tools in a risk assessment context of nutraceutical product, to relate properties of the molecular structure to the toxic effect of the chemical substance, by using principles and methods of computational chemistry. Further consideration of the actual impact of adverse events arising from nutraceutical food supplement usage will be helpful in guiding such issue as a potential for misidentification, and adulteration of botanical supplements by pharmacologically active substances.

1. Introduction

A nutraceutical can be defined as a food or food product that is reported to provide medical benefits, such as prevention and treatment of diseases. It is produced under Good Manufacturing Practice (GMP) conditions and may range from isolated nutrients, dietary supplements and specific diets to genetically engineered foods, herbal products and process food (Mohammad *et al.,* 2015). Example of nutraceutical products includes vitamins, mineral, herbal supplements, a semi-purified substance from natural sources, plant extract, functional food and beverages, probiotics and topical application for skincare (Labadi, 2017). The illness that is normally administered by nutraceutical products is anti-arthritic, cold and cough, prevention of certain cancer, diabetes, sleep disorders, hypertension and osteoporosis (Pandey *et al.,* 2010). Nutraceutical can be divided into three main segments, which are natural products, dietary supplements and functional foods. A nutraceutical products segment with rapid growth due to the high level of interest and demand by the consumer (Nutrition Business Journal, 2006). They are often seen as more flattering as compared to pharmaceutical drugs as they are being seen as more natural and likely to incur minimum side effects (Teschke *et al.,* 2013). Besides, the availability of the nutraceutical products over the counter of the supermarket, health food shop and pharmacies make it easier to be reached by consumers (Posadzki *et al.,* 2013).

High cost incurs by modern disease treatment make the consumer look for alternative or complementary beneficial product such as the appealing nutraceutical product. Recently, nutraceutical product has been scientifically supported with nutritional and medical evidence and become a potentially effective alternative (Dillard and German, 2000). A sturdy regulation and assessment need to be developed and implemented to give impact on consumer and to standardise the nutraceutical compound. Besides, the requirement of the execution of clinical studies, provide a basis for health claims, commercial positioning and functional claims of nutraceutical products should be evidence-based that supported by convincing scientific data from well design studies. Moreover, nutraceutical products are often taken as "self-medication" without concern from the medical doctor regarding any diseases that may lead to uncertainty in the observed effects. Therefore, there should be special aspects that need to be considered instead of a basic design study that is similar to that of pharmaceutical studies (Gao *et al.,* 2014).

A considerably high number of cases that have been reported on the adverse effects of nutraceutical products that pose a real risk to the public (Rocha *et al.,* 2016). The arising issue recently was the adulteration of

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nutraceutical products with pharmaceutical substance and accidental replacement of botanicals with some other toxic plant or substance (Stegelmeier *et al.,* 2015). Besides, compounds such as alkylbenzenes, estragole and methyl eugenol that are naturally contained in some botanicals are found to be genotoxic and hepatocarcinogenic based on the animal study done by Scientific Committee on Food European Commission (SCF EC., 2001). Reports on human studies associated with the severity of the effect of the consumption of botanicals range that caused an elevation in blood pressure, acute liver failure requiring liver transplantation, tumours of the urinary tract and even death (Fujita *et al.,* 2007; Nortier *et al.,* 2009).

Unravelling the kinetic profiles and rectifying the bioavailability of nutraceutical properties and nutritional compounds posture some challenge especially in dealing with complex mixture derived from herbal plants. The main problem is to characterise the exact bioactive compound that regulates the bioactive intake. The difficulty is due to the variation in the plant. The variation further complicates the interpretation of different bioactive within the botanical compound in nutraceutical that may exert either antagonistic or synergistic interaction (Schmitt and Farro, 2013).

Animal testing has been used to provide toxicological information, but in addition to the ethical consideration, it is both expensive and time consuming. Alternatives to animal data, i.e., non-testing data is therefore desirable and is highlighted to promote alternative methods for the assessment of hazards substances. Non-testing data (as known as non-animal-testing data) includes *in vitro* data but can also be generated using *in silico* tools. In silico means within computer, and the term 'in silico tools' is collectively used to refer to methods as structure reactivity relationships (SARs), quantitative structure-activity relationships (QSARs) (Puzyn *et al.,* 2010) and network pharmacology.

With the continuous maturation of computer technology, increase use of in silico tools for non-testing data as structure-activity relationships (SARs), quantitative structure-activity relationships (QSARs), and pathway and network analysis. This led to the rapid elucidation of the complex relationships between compounds and their various target activity (Rubio-Perez *et al.,* 2015). The main objective of this review is to explore the use of in silico tools in a risk assessment context of nutraceutical products. In particular, this review attempted to relate properties of the molecular structure to the toxic effect of the chemical substance, by using principles and methods of computational chemistry and determine the impact of adverse events arising from nutraceutical food supplement.

2. Risk assessment and regulation

The assessment criteria for the nutraceutical products are generally similar between some country such as Australia, USA and Europe (EU). Particularly, information related to the requirement of basic information of the botanical substance and description of the botanical substance and description of the manufacturing process (Low *et al.,* 2017). However, jurisdiction regarding the specific toxicology data requirement, clinical trial data and adverse reaction report of nutraceutical product are mostly diversified. An example can be seen in term of requirement on specific toxicological studies. Food and Drug Administration (FDA) and Therapeutic Goods Administration (TGA) describe the necessary toxicity studies in detail as compared to the European Food Safety Authority (EFSA) which is comparatively brief. FDA even take an initiative to come out with a "Safety Testing Recommendation Matrix" that has been a good reference for business operations as it recommends a different combination of toxicology data based on the historical used of the ingredients to determine the possible toxicity of their products. This matrix helps the business operator in a way of reducing the cost and the hassle of conducting the toxicity study (Center for Drug Evaluation and Research (CDER) FDA, 2008).

Data on clinical trials are required by TGA guideline for risk assessment as TGA regulates the nutraceutical product as complementary medicine rather than food supplement (TGA, 2016). EFSA, on the other hand, does not acquire such data. This is not also obligatory for FDA to provide the clinical trials data; however, they require to at least have a tolerability study on adsorption, distribution, metabolism and excretion (ADME) studies to determine the safety margin for one product (Center for Drug Evaluation and Research (CDER) FDA, 2008).

The development of extraction technologies poses a new risk related to botanical through the dynamic of economically motivated fraud. Moreover, there are some aspects that have not been considered in the guideline for risk and safety assessment of nutraceutical products. Despite the uncertainty of the authentication and differences in regulation, the global nutraceutical market has been valued at USD 109.8 billion and expected to grow to an expected value of USD 180 billion by 2020 (Persistence Market Research, 2015). Therefore, the current issues should set the direction in the nutraceutical field that highlight the evidence-based nutraceutical approach can make an important contribution to public

health.

3. SAR and QSAR

SAR analysis is the identification of chemical properties or specific fragments of the molecular structure involved in an observed or measured effect. A QSAR model approximates the relationship between the molecular structure and biological activity in a quantitative manner (Eriksson *et al.,* 2003). The QSAR model can be used to determine SAR. The quantitative correlation was established, the biological or toxicology activity, as well as the chemical and structural properties, were defined with numerical values. The outcome of biochemical and toxic effects of substances was measured in vitro assays. QSAR modelling involves a set of chemical structures that are assumed to act through the same mechanism of action. The development of QSAR model then follows a stepwise process illustrated in Figure 1.

The organisation for economic cooperation and development (OECD) had outlined the principle for QSAR validation (OECD, 2007) for regulatory acceptability. According to these principles, a QSAR model should be associated with 1) a defined endpoint, 2) an unambiguous algorithm, 3) a defined domain of applicability, 4) appropriate measures of goodness-of-fit, robustness and predictivity, and if possible, 5) a mechanistic interpretation. The principle aims to ensure that selection of the chemical descriptors is well-considered concerning the endpoint of the investigation, and that any association found between the chemical descriptors and the endpoint is documented (OECD, 2007).

Toxicity of a substance is ruled by their chemical structure where it has a direct relationship with the properties and thus toxicity of a substance. The relationship may be statistically calculated to describe the molecular properties of a substance base on the descriptor of a compound structure (Deeb and Goodarzi, 2012). The first work on QSAR was published by Hansch *et al.* (1962) that developed the relationship between biological activity with the descriptor of compound structure.

The study on the in silico quantitative structure toxicity relationship has been conducted by Pasha et al. (2009) on aromatic nitro compounds. A total of 148

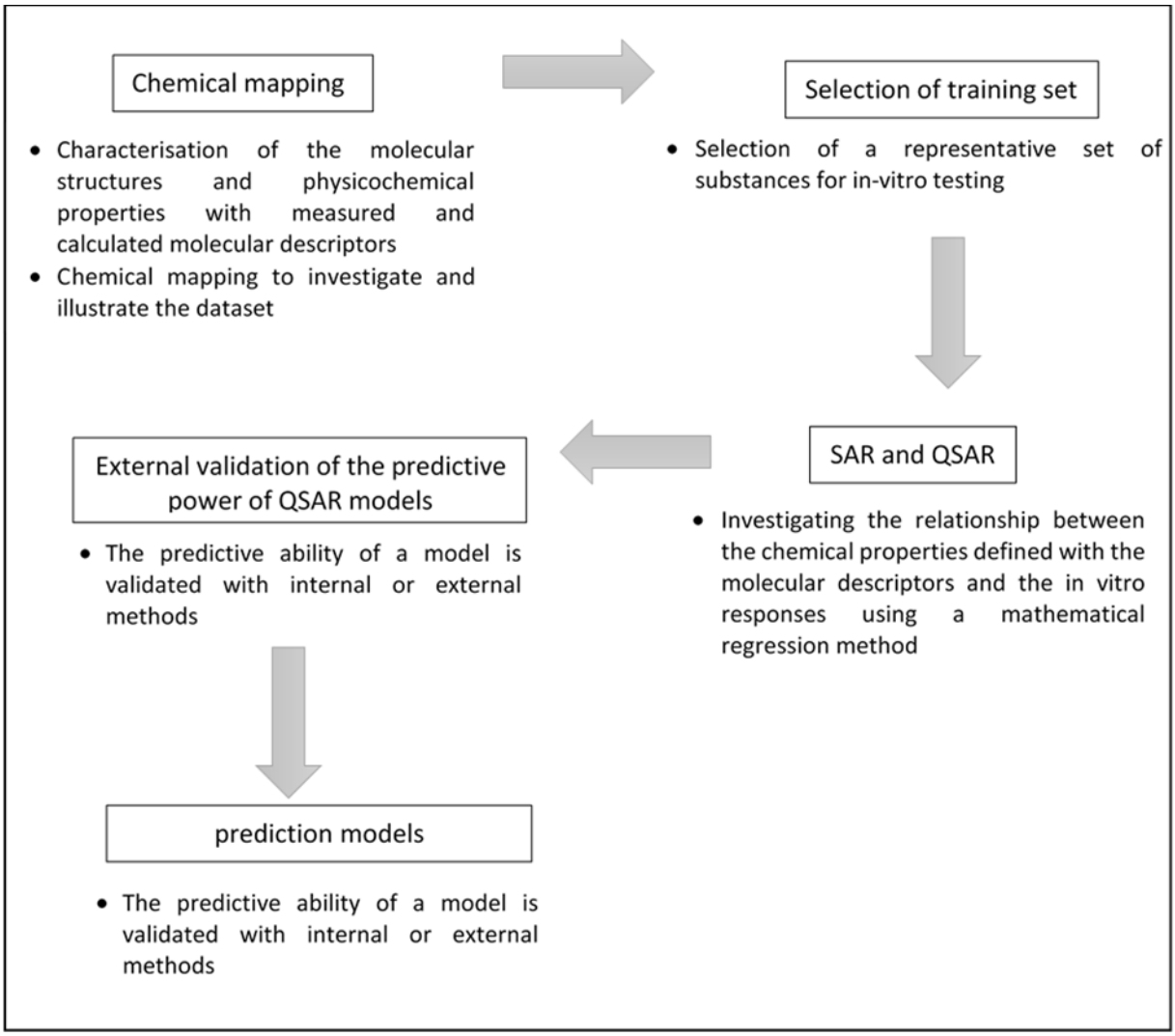

Figure 1. Stepwise QSAR/ in silico approach

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aromatic nitro compounds with similar structures were assayed with different targets. Based on the activities determined by the assays, two dimensional (2D) quantitative structure-toxicity relationship models were developed using twenty chosen topological descriptors. Then, the author applied the multiple linear regression analysis to associate the variation of molecular properties with toxicity. From the study, a strong framework for understanding the link between molecular toxicity with the aromatic nitro compounds structure has been proposed by the authors. In conclusion, the molecular size, branching and molecular flexibility strongly associated with the toxicity of the nitro compound based on the best correlation between topological descriptor and molecular toxicity in the model.

4. Pathway and network analysis

In recent years, with an increasingly in-depth understanding of the structure and function of compounds, a series of new technologies and methods have been applied to the development of medicinal plants (Yi *et al.,* 2016). The verification of the in vivo and in vitro pharmacological experiments can be established by accurately predict a large number of chemical compounds. Based on the prediction, a significant improvement in the efficiency of evaluating the chemical activities of nutraceutical product can develop a quick and convenient pathway.

The continuous maturation of computer technology nowadays, enable the utilization of the computer platform to calculate the combinations of simulated compound and target to be more efficient and accurate. In addition, the development of network pharmacology technologies has enabled the rapid elucidation of the complex relationships between compounds and their various activity targets (Rubio-Perez *et al.,* 2015).

The complexity of network pharmacology technology is reflected not only in the composition of the chemical constituents but also embodied in the network of relationships between the prescription and the human body and the exertion of pharmacological effects through multiple channels, multiple targets and the overall regulatory mechanism (Zhang *et al.,* 2016).

Yi *et al.* (2018), have developed a set of effective and accurate methods to unravel the pharmacological effect of plant materials and predict the bioactive compound. The first crucial part is to verify the research significant of the plants. There are three categories of plants the first category is the plant that is a common herbs with complex mechanism followed by the herbs with long history traditional usage and the last category is the herbs with known traditional usage but now with new utilization. Next is to construct and organize the natural product database. Then, proceed with the pre-treatment of the compounds (ADME/T, prediction and exclusion of false-positive compounds followed by the important technique which is the in silico virtual screening. Next step is the analysis of the group of targets identified. Lastly, the construction of network relationship between medicinal plants, natural compound, biological targets, signaling pathways and disease. Abiding to this method enables the authors to predict the potential pharmacological activities of the bioactive compounds in medicinal plant.

5. Conclusion

The alternative strategies for the assessment of hazards to complement in vitro and in vivo studies for nutraceutical products have been explored. The potential of using different in silico methods for this purpose has been investigated and QSAR models have been studied. Information contained into diverse datasets of nutraceutical product was searched with SAR and QSAR methods. A wide-ranging complete technical route that utilizes a series of in silico approaches to reveal the pharmacological basis of the effects of medicinal plants were proposed. This in silico methodology can resolve the status of medicinal plants that are difficult to study on a practical level and can predict and clarify the mechanisms of the active ingredients in nutraceutical product. Through more practical researches and development examples to upgrade the entire process of in silico methodology, we believe that in the future, this methodological process will enable the discovery of new active compound more efficiently, accurately and quickly. This methodology will be more widely used in future work on revealing and predicting the basis of nutraceutical materials.

Conflict of Interest

The authors declare no conflict of interest.

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