Food and Chemical Toxicology 128 (2019) 163–170

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Development of quantitative structure-activity relationship models to predict potential nephrotoxic ingredients in traditional Chinese medicines

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ARTICLE INFO

Keywords:
QSAR
Nephrotoxicity
Traditional Chinese medicines

ABSTRACT

The broad use of traditional Chinese medicines (TCMs) and the accompanied incidences of kidney injury have attracted considerable interest in investigating the responsible toxic ingredients. It is challenging to evaluate toxicity of TCMs since they contain complex mixtures of phytochemicals. Quantitative structure-activity relationship (QSAR) is an efficient tool to predict toxicity and QSAR study on TCMs-induced nephrotoxicity remains lacked. We developed QSAR models using three datasets of 609 compounds: natural products, drugs, and mixed (contained both kinds of data) datasets. Each dataset was used for modelling by utilizing artificial neural networks (ANN) and support vector machines (SVM) algorithms separately. Both internal and external validations were performed on each model. Six QSAR models were developed and yielded reliable performance in the internal validation. For external validation, 30 ingredients in the TCMs were predicted well by the natural product models (accuracy: ANN 96.7%, SVM 93.3%). The mixed models (accuracy: ANN 76.7%, SVM 66.7%) showed a better performance than the drug models (accuracy: ANN 50%, SVM 53.3%). Particularly, natural product models produced the most reliable results. It has the application not only on screening the nephrotoxic ingredients in TCMs, but it is also helpful at prioritizing the subsequent toxicity testing of natural products.

1. Introduction

Traditional medicine has gained popularity for various uses including prevention and treatment of diseases, weight loss, and relief of anxiety (Fan et al., 2015). The World Health Organization (WHO) reported that traditional medicine serves as a medical treatment for up to 75%–80% of the world population (WHO, 2013). Due to their natural properties, traditional Chinese medicines (TCMs) have spread beyond China and Asia, with increasing worldwide acceptance (Stickel et al., 2005; Teng et al., 2016). However, there are some cases reported that TCMs or herbal medicines caused severe side effects (Xu et al., 2012, 2015) or interacted harmfully with prescription medications (Gouws et al., 2012). Specifically, nephrotoxicity accounts for a large proportion of TCM-induced toxicities (Yang et al., 2018). According to a review of adverse drug reactions (ADRs) reports (Zeng and Jiang, 2010), over 10% of ADR cases were renal adverse effects. For example, the aristolochic acid nephropathy (AAN), a rapidly progressive interstitial nephritis that leads to end-stage renal disease and urothelial malignancy (Debelle et al., 2008; Nortier and Vanherweghem, 2002; Vanherweghem et al., 1993), was caused by aristolochic acids, one major ingredient of many TCMs, such as *Aristolochia fangchi*, *Aristolochia manshuriensis Kom* and *Aristolochia Manshuriensis* (Krumme et al., 2001; Poon et al., 2007; Yang et al., 2007). Nephrotoxicity issue in TCMs needs for greater awareness. However, some other potential nephrotoxic ingredients of TCMs remain to be identified.

TCMs contain a wide variety of ingredients, the safety evaluation of each ingredient using conventional experimental testing is time-consuming and labour-intensive (Barlow et al., 2012; Shaw, 2010). The increasing public interest in reducing the number of animals used for experimental testing are driving the need to finding alternatives such as *in vitro* and computational methods (Ekins, 2014). However, it is difficult to screen potential toxic ingredients from TCMs using *in vitro* methods, since many of them are not easily to get sufficient amounts of pure compounds by isolation and purification. *In silico* toxicology is one type of toxicity assessment that utilizes computational methods to analyse, simulate, visualize, or predict the toxicity of chemicals using only “virtual” structures of compounds (Raies and Bajic, 2016; Roncaglioni et al., 2013; Toropov et al., 2014; Valerio, 2009). Among in

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https://doi.org/10.1016/j.fct.2019.03.056
Received 19 January 2019; Received in revised form 26 March 2019; Accepted 31 March 2019
Available online 04 April 2019
0278-6915/

Abbreviations

2D	two-dimensional
AAN	aristolochic acid nephropathy
Acc	accuracy
ADRs	adverse drug reactions
ANN	artificial neural network
EPA	Environmental Protection Agency
MCC	Matthew's correlation coefficient
OECD	Organization for Economic Cooperation and Development
QSAR	quantitative structure-activity relationship
SE	sensitivity
SP	specificity
SVM	support vector machine
TCMs	traditional Chinese medicines
WHO	World Health Organization

silico approaches, quantitative structure-activity relationship (QSAR) modelling is a low cost, high-throughput alternative method for mapping molecular structural features to biological properties (Roy et al., 2015), especially by filling data gaps in TCM safety analysis and prioritizing additional experimental studies (Benfenati, 2016). The Organization for Economic Cooperation and Development (OECD) has published guidelines for QSAR model development and validation (OECD, 2014). With the recommended procedures, several studies have been reported to predict organ toxicity induced by synthetic compounds based on the combination of chemical structure and bioactivity (Liu et al., 2015, 2017; Zhu et al., 2014). However, there are few QSAR models to predict various toxicity of specific ingredients of TCMs, except the hepatotoxicity, which has been benefited from the growing number of database regarding the liver toxicity of TCMs (Huang et al., 2015; Zhao et al., 2017), and these models showed good performance to predict the hepatotoxicity of pyrrolizidine alkaloids, the well-known hepatotoxins (Wiedenfeld and Edgar, 2011). However, QSAR modelling for evaluating nephrotoxicity induced by TCMs is still in its infancy due to the limited TCMs-related renal toxicity experimental data.

In this study, we developed and validated QSAR models for predicting the nephrotoxicity of ingredients in TCMs, according to OECD recommended procedures. The total modelling workflow is depicted in Fig. 1. In order to have a wide applicability, we collected nephrotoxicity data in human and animal studies (*in vivo*) from multi-source for both natural products and drugs, and developed separately QSAR models. The QSAR models were internally and externally validated to evaluate the predictive performance, and to find the model with the best performance.

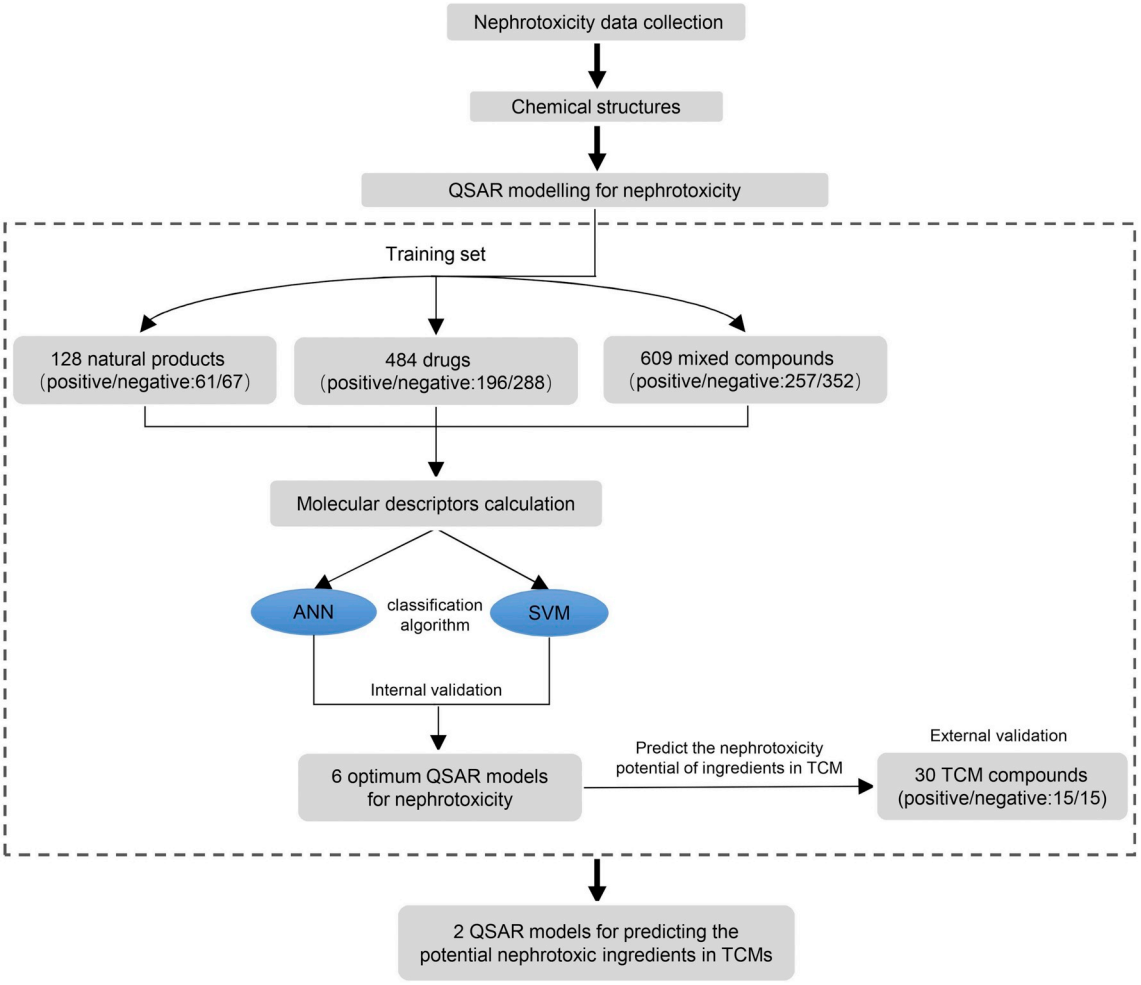

Fig. 1. Overview of QSAR modelling process.

2. Materials and methods

2.1. Data set

2.1.1. Natural product dataset

To obtain the required amount of data for QSAR modelling, we combined the nephrotoxicity data of both natural products and compounds in TCMs. First, data on herbs and dietary supplements associated with clinical kidney injury were collected from peer-reviewed literature (Brown, 2017; Yang et al., 2018) and the Natural Medicines Comprehensive Database (Therapeutic Research Centre LLC, Stockton, CA, USA). Then, the major ingredients in these herbs and dietary supplements were identified in published literature using online search engines (PubMed, National Library of Medicine) and the TCM Database@Taiwan (Chen, 2011). Finally, 76 compounds were selected as the positive set of natural products.

For the selection of negative set of natural products, nine TCM herbs, *Salvia miltiorrhiza*, *Liuwei Dihuang teapills*, *Astragalus*, *Cinnamomum cassia*, *celery root*, *Schisandra chinensis*, *Scutellaria baicalensis*, *Ganoderma lucidum*, and *Phyllanthus emblica* (Guan et al., 2013; Lai et al., 2015; Lin et al., 2016; Nasri and Rafieian-Kopaei, 2014; Sayed et al., 2015; Zhang et al., 2014; Zhong et al., 2015), have proven renoprotective benefits in human studies. Then, the main active ingredients in the above TCMs were similarly identified. In addition, natural dietary supplements without nephrotoxicity reports were also included. As a result, a total of 82 compounds were selected as the negative set of natural products. The overall natural product data are presented in Supplementary Table 1.

2.1.2. Drug dataset

Drug nephrotoxicity data were collected by searching two databases: Side Effect Resource (SIDER, http://sideeffects.embl.de) database (Kuhn et al., 2016) and Toxicity Reference Database (ToxRefDB) (MARTIN, 2010). SIDER was developed by the European Bioinformatics Institute and contains information on drugs and their ADRs in humans. ToxRefDB, Environmental Protection Agency (EPA)'s toxicity reference database, is a dynamic resource that lists hundreds of *in vivo* endpoints observed in different tissues in animal studies and is publicly available (http://www2.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data). In this study, we searched the SIDER database and chose drugs with renal ADRs with “very common” and “common” frequency. Furthermore, we used kidney histopathology endpoints observed in rat or mouse after oral administration of the chemicals from the ToxRefDB database. As a result, we selected 196 nephrotoxic compounds from two databases as positive drug dataset, and 288 compounds without nephrotoxicity from SIDER as negative drug dataset (see Supplementary Table 2).

For the external validation, 15 compounds in TCMs with nephrotoxicity and 15 without nephrotoxicity were chosen to establish an external validation set. The remaining 128 natural products constituted Training set I for modelling. The composition of the datasets is shown in Table 1. Training sets I and II included three duplicated compounds and, therefore, training set III was not the sum of training sets I and II. The corresponding two-dimensional (2D) structures of chemicals were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), and compounds not found in the database were sketched using the Chemdraw® software. Fig. 2 shows the typical 2D structures of nephrotoxic compounds in TCMs.

2.2. Chemical descriptor

ADMET Predictor™ version 9.0 (Simulations Plus, Inc, Lancaster, CA, USA) was used to calculate hundreds of molecular descriptors from the 2D chemical structures. The descriptors included simple constitutional, topological indices, electrotopological state indices, charge-based, and hydrogen-bonding descriptors as well as those with other properties. For all compounds, 341 molecular descriptors from 2D structures were calculated using ADMET Predictor™.

2.3. Model development

We developed QSAR models using the ADMET Modeler™ module, a model-building tool in the ADMET Predictor™ software. ADMET Modeler™ supports two machine learning algorithms for model-building, the artificial neural networks (ANN) and support vector machines (SVM), which are both flexible high-performance methods that are well suited for complex data (Byvatov and Schneider, 2003; Yang, 2004). These two algorithms were used to develop the QSAR models in this study. The models based on natural products, drugs, and a mixture of both were denoted as models N, D, and M, respectively.

2.4. Model validation and performance evaluation

In this study, two validation procedures were performed. First, for the internal validation, the training datasets were randomly split into a training pool and a test set, and compounds in the training pool were used to develop the QSAR model, which was then assessed by predicting the compounds in the test set. Then, for the external validation, we applied the optimum models to a totally external validation set (15 compounds in TCM with nephrotoxicity and 15 compounds without nephrotoxicity) to evaluate the model's predictive performance.

Model performance was evaluated using internal and external validation. The commonly used parameters for evaluating the performance of QSAR models are sensitivity (SE), specificity (SP), accuracy (Acc), and Matthew's correlation coefficient (MCC). SE is the true positive rate or the percentage of positive compounds correctly predicted, while SP is the true negative rate or the percentage of negative compounds correctly predicted. MCC is a correlation coefficient between the observed and predicted binary classifications. The four parameters of measurement are defined as follows:

$$SE = \frac{TP}{TP + FN}$$

$$SP = \frac{TN}{TN + FP}$$

$$Acc = \frac{TP + TN}{TP+TN + FP+FN}$$

$$MCC = \frac{TP \times TN - FP \times FN}{\sqrt{(TP + FP)(TP + FN)(TN + FN)(TN + FP)}}$$

TP, TN, FP, and FN are the number of true positives, true negatives, false positives, and false negatives, respectively.

Table 1
Data sets used for QSAR analysis.

Data sets	Sources of compounds	Number of compounds	Number of positive compounds	Number of negative compounds
Training set I	Natural products	128	61	67
Training set II	Drugs	484	196	288
Training set III	Natural products and drugs	609	257	352
External validation set	Ingredients in TCMs	30	15	15

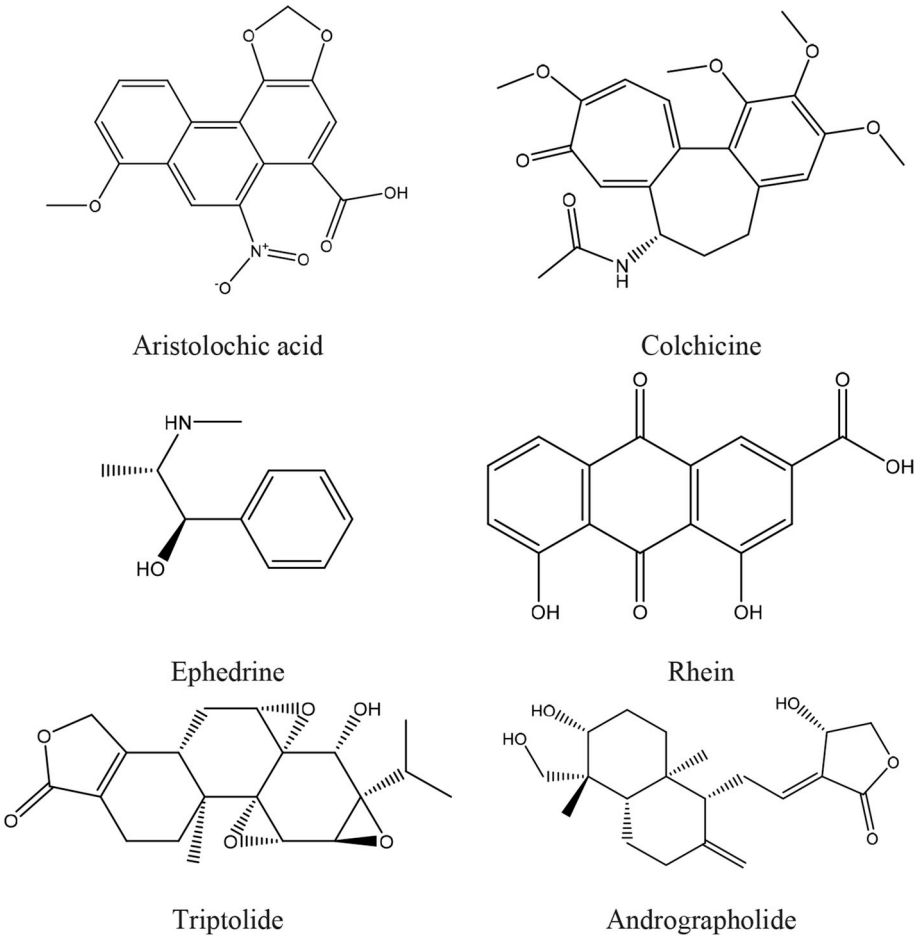

Fig. 2. The typical 2D structures of nephrotoxic compounds in TCMs included in the dataset.

3. Results

3.1. QSAR models for nephrotoxicity prediction

In this study, data on 484 drugs and 128 natural products were collected and subsequently used to form three training sets to develop predictive models for nephrotoxicity. For each training set, we conducted the internal validation using descriptor selection to evaluate the performance of the ANN and SVM machine learning algorithms. The optimum models of each algorithm and training set were chosen using the internal validation. The performance plot for models generated based on different algorithms are shown in Fig. 3. As listed in Table 2, all models for nephrotoxicity prediction yielded a reliable performance with Acc > 75%, indicating that all models can be used for further validation. For the two algorithms, both the SEs and SPs of all ANN-models were > 75%, while the SVM-models showed better SPs than SEs. Among the six models, five exhibited a better performance, with Acc > 85%, than the M_S model did.

3.2. Predictive performance of QSAR models

External validation is the most realistic setting for the practical application of models. In this study, the prediction Acc of the QSAR models in the external validation are shown in Table 3. Among these six models, the performance of model N_A and N_S derived from the natural products dataset were promising with Acc all > 90%. These two high-quality models could be used to predict the potential nephrotoxicity of compounds in TCMs. The prediction outcomes of the 30 ingredients in TCMs are listed in Table 4. TCM ingredients in the external validation set were predicted reasonably well. Only one compound was not discriminated by the model N_A and two compounds were predicted with error by the model N_S. Of these ingredients, some well-known nephrotoxins were accurately identified including aristolochic acid (Debelle et al., 2008), ephedrine (Powell et al., 1998), colchicine (Huang et al., 2007), Triptolide (Li et al., 2014), and so on (detailed prediction results of the remaining four models are available in the Supplementary Table 3).

Moreover, the mixed models performed better than the models D (based on drug dataset), indicating that including the natural product data in the training set improved the predictive power of the models for toxicity screening of ingredients in TCMs. In contrast, the performance of models D_A and D_S, which were completely based on drugs, were poor with Acc values of 50.0% and 53.3% and low MCC values at 0 and 0.089, respectively, which indicated a very low predictive ability.

Among all the models, only N_A and N_S, based on natural products, had a balanced performance (SE and SP > 90%), whereas the other models had a high SP but a relatively low SE.

4. Discussion

The widespread use of TCMs that are usually considered as harmless by the general population, has been associated with the increased number of TCM-induced adverse renal effects (Xu et al., 2015). Identifying TCMs that may cause renal injury is challenging because they contain complex mixtures of compounds. Most of them have unknown toxicological properties, which increases the difficulty in the rational use of TCMs. Therefore, it is crucial to predict and determine the potential nephrotoxicity of individual ingredient. Since the animal

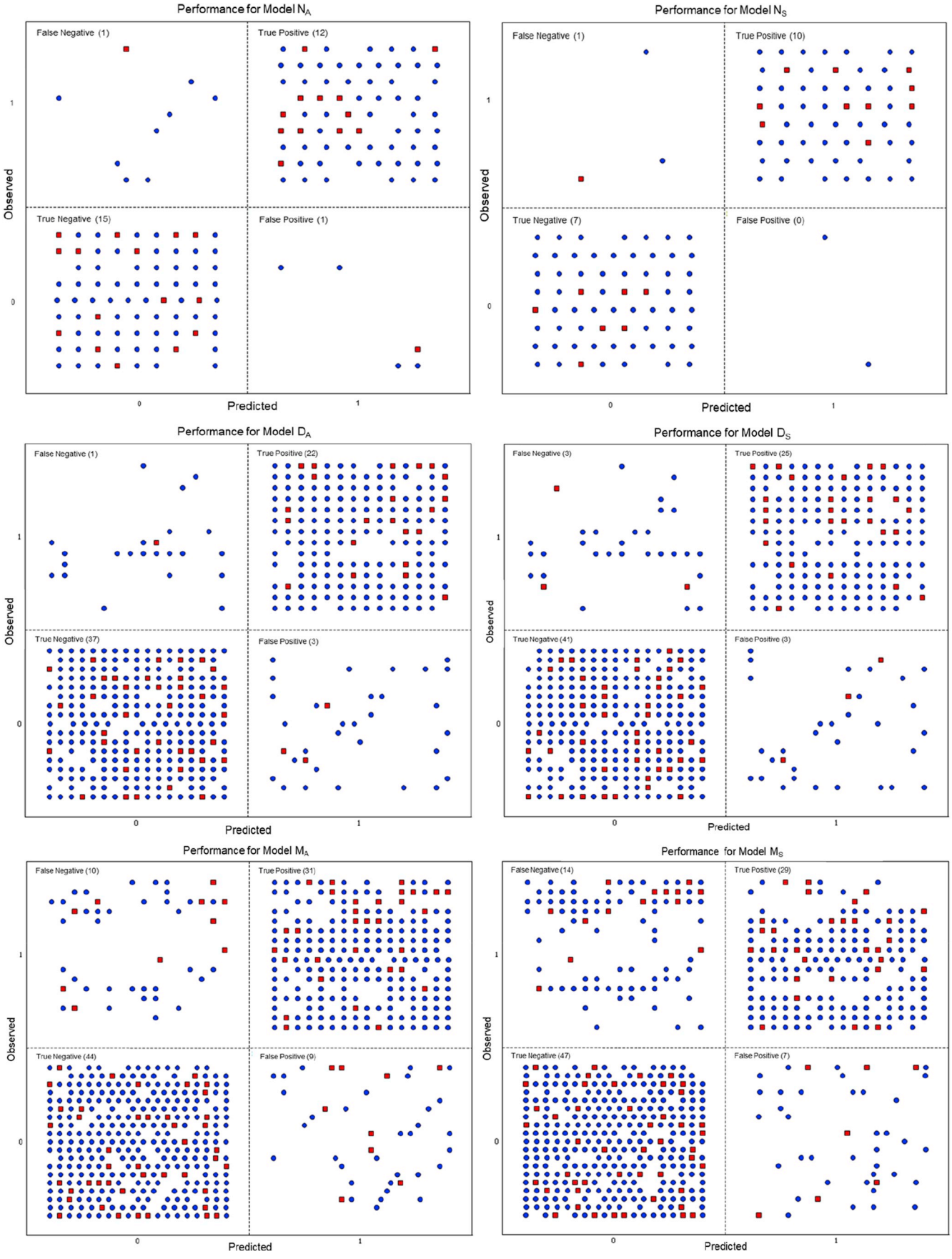

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Fig. 3. The scatter plot for six optimum models in internal validation. Training pool points are colored blue, whereas the internal test set points are highlighted in red. The plot includes a graphical two-way truth table with the number of each class - false negatives (FN), true positives (TP), true negatives (TN) and false positives (FP) indicated in the top left corner of the respective quadrants. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

experiment method is time-consuming and labourextensive, and the chemical structure of ingredients in TCMs is often the only data available, the computational approaches based on QSAR are directed towards their toxicity evaluation (Raies and Bajic, 2016).

To date, QSAR studies assessing the nephrotoxicity of compounds are extremely limited. We conducted a PubMed search using the keywords "QSAR" and "nephrotoxicity" which produced five hits (by January 2019) with no QSAR modelling for TCMs. In fact, several nephrotoxicity models were developed based on synthetic drugs and environmental chemicals (Lee et al., 2013; Myshkin et al., 2012). However, applying QSAR models completely built using synthetic compounds to predict TCM toxicity may lead to bias (Zhao et al., 2017). Furthermore, the nephrotoxicity data of TCMs needed for QSAR modelling are insufficient. In this study, we adopted a strategy that incorporated natural product data into the model dataset. We collected and sorted the nephrotoxicity related data of both natural products and drugs, and subsequently developed QSAR models based on three types of datasets to compare the predictive performance of models. To reduce the bias caused by different machine learning algorithms, we used both ANN and SVM, to construct our QSAR models.

QSAR model performance is largely dependent on three factors, the data set size, the positive/negative distribution, and how the positive/negative are determined (Wu et al., 2017). Thus, to expand the size of the data set, we selected natural products instead of only ingredients in TCMs. In addition, the ratio of positive to negative compounds in this study was basically balanced at 1:1.47 (196:288) for drugs, 1:1.10 (61:67) for natural products, and 1:1.37 (257:352) for the mixed group. It is worth mentioning that the criteria applied to annotate compounds that induce nephrotoxicity are a significant consideration in data collection. The reliable of our models can be explained by this point. In this study, we searched the clinical adverse reaction SIDER database and selected drugs with adverse effects on the kidney and with 'very common' and 'common' frequency. Moreover, to make our models have broader applicability, we chose *in vivo* animal experimental data excluding data from only *in vitro* toxicity studies. The internal validation outcomes of all the QSAR models in our study were adequate with predictive Acc > 85% except for model M_S (78.8%).

In published studies on TCM hepatotoxicity evaluation, the prediction accuracy of externally validated model is 87% (Huang et al., 2015) and 90% (Zhao et al., 2017). Our models based on natural product dataset, performed reasonably well with a predictive Acc > 90%. Whereas the accuracy of Models D (based on drug dataset) was only approximately 50%, indicating models N had a better practical value than the other models did and could play an active role in predicting the nephrotoxicity of ingredients in TCMs. Furthermore, the mixed models showed improved performance compared to models D. These results revealed that incorporating natural products data into model datasets could enhance the predictive power of models.

Table 3
Performance of QSAR models in external validation.

Model	Data source	SE (%)	SP (%)	Acc (%)	MCC
Model N_A	Natural products	93.3	100	96.7	0.935
Model D_A	Drugs	26.7	73.3	50.0	0.000
Model M_A	Mixed data	53.3	100	76.7	0.603
Model N_S	Natural products	93.3	93.3	93.3	0.867
Model D_S	Drugs	20.0	86.7	53.3	0.089
Model M_S	Mixed data	33.3	100	66.7	0.447

Sensitivity (SE), specificity (SP), accuracy (Acc), Matthew's correlation coefficient (MCC).

Moreover, we found that irrespective of the machine learning algorithm used, the results of the external validation of the drug and mixed models showed they had greater SP than SE. It is noteworthy that the chemical space (Wetzel et al., 2007), structure, and atoms of natural products differ from those of synthetic compounds. It is universally acknowledged that misclassifying a toxic chemical is more severe than categorizing a non-toxic chemical falsely. Hence, although the SP of model M_A was 100%, considering that its SE was just 53.3%, it is not advisable to apply this model practically. It was demonstrated that the models constructed using synthetic drugs were not applicable to toxicity predictions of ingredients in TCMs.

To the best of our knowledge, this is the first QSAR study on predicting nephrotoxicity of ingredients in TCMs. The developed QSAR models could predict the potential nephrotoxic ingredients in TCMs, which would be helpful in reducing animal tests and saving money and time. The accurate predictions in our study justify the suitability of utilizing QSAR model for screening nephrotoxicity of ingredients in TCMs. The limitation is that natural product dataset was small due to the lack of known nephrotoxic phytochemicals. Furthermore, the absorption and metabolism of a specific ingredient should be considered when applying QSAR model (Liu, 2018), since most herbal medicines are orally administered.

In conclusion, the developed models in this study based on natural product or mixed dataset improved the predictive power of models for screening nephrotoxicity of the ingredients in TCMs. Importantly, the models completely based on natural product dataset generated more rational results and were more workable for TCM-induced nephrotoxicity assessment than the other models. It is applicable to predicting the potential nephrotoxic ingredients in TCMs, and could prioritize phytochemicals for future toxicity testing.

Table 2
Overall Performance of QSAR Models in internal validation.

Model	Data sets	Algorithm	Number of descriptors	Number of neurons	SE (%)	SP (%)	Acc (%)	MCC
Model N_A	Training set I	ANN	80	1	92.3	93.8	91.1	0.861
Model D_A	Training set II	ANN	48	3	95.7	92.5	88.4	0.867
Model M_A	Training set III	ANN	48	6	75.6	83.0	86.1	0.588
Model N_S	Training set I	SVM	93	–	90.9	100	96.9	0.892
Model D_S	Training set II	SVM	72	–	89.3	93.2	86.8	0.825
Model M_S	Training set III	SVM	72	–	67.4	87.0	78.8	0.560

Sensitivity (SE), specificity (SP), accuracy (Acc), Matthew's correlation coefficient (MCC).

Table 4
Prediction results of known nephrotoxic and non-nephrotoxic TCM ingredients in external validation using QSAR models based on natural products data (P = positive, N = negative).

Ingredients	Pubchem CID	Source (Scientific names)[a]	Actual	Model N_A	Model N_S
Esculeoside A	10887728	*Phytolacca acinosa Roxb*	P	P	P
Ephedrine	9294	*Ephedra sinica Stapf*	P	P	P
Norephedrine	26934	*Ephedra sinica Stapf*	P	P	P
DL-Sphinganine	6603822	*Semen Pharbitidis*	P	P	P
Fangchinoline	5458555	*Stephania tetrandra*	P	P	P
Sciadopitysin	5281696	*Taxus cuspidata*	P	P	P
Paclitaxel	36314	*Taxus cuspidata*	P	P	P
Aconitine	245005	*Aconitum carmichaeli Debx.*	P	P	P
Glycyrrhizic Acid	14982	*Glycyrrhiza uralensis Fisch*	P	N	N
Parviflorin	10326164	*Annona muricata*	P	P	P
Dauricine	73400	*Rhizoma Menispermi*	P	P	P
Triptonide	65411	*Tripterygium wilfordii*	P	P	P
Colchicine	6167	*Colchicum autumnale*	P	P	P
Strychnine	441071	*Strychnos nuxvomica*	P	P	P
Aristolochic Acid	2236	*Aristolochiae Fructus*	P	P	P
Astragaloside-II	71306915	*Astragalus*	N	N	N
Astragalin	5282102	*Astragalus*	N	N	P
Astragaloside IV	158694	*Astragalus*	N	N	N
Skullcapflavone II	124211	*Astragalus*	N	N	N
Schisanhenol	73057	*Schisandra chinensis*	N	N	N
Gomisin A	68781	*Schisandra chinensis*	N	N	N
Schisandrol B	634470	*Schisandra chinensis*	N	N	N
Cinnzeylanine	85379763	*Cinnamomum cassia*	N	N	N
Cinnzeylanol	3085241	*Cinnamomum cassia*	N	N	N
Ganoderic Acid B	471003	*Ganoderma lucidum*	N	N	N
Ganoderic Acid A	471002	*Ganoderma lucidum*	N	N	N
Lucidenic Acid B	102410351	*Ganoderma lucidum*	N	N	N
Martynoside	5319292	*Rehmannia glutinosa*	N	N	N
Pedunculagin	442688	*Phyllanthus emblica*	N	N	N
Phyllanemblinin A	11135859	*Phyllanthus emblica*	N	N	N

[a] Indicates that there could be several TCMs containing this ingredient and here we selected the typical one.

Acknowledgment

This work was supported by the Special Research Project of Traditional Chinese Medicine (201507004-1).

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2019.03.056.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.03.056.

Conflicts of interest

The authors declare no conflict of interest.

References

Barlow, D.J., Buriani, A., Ehrman, T., Bosisio, E., Eberini, I., Hylands, P.J., 2012. In-silico studies in Chinese herbal medicines' research: evaluation of in-silico methodologies and phytochemical data sources, and a review of research to date. J. Ethnopharmacol. 140, 526–534. https://doi.org/10.1016/j.jep.2012.01.041.

Benfenati, E., 2016. In: Silico Methods for Predicting Drug Toxicity. Springer, New York.

Brown, A.C., 2017. Kidney toxicity related to herbs and dietary supplements: online table of case reports. Part 3 of 5 series. Food Chem. Toxicol. 107, 502–519. https://doi.org/10.1016/j.fct.2016.07.024.

Byvatov, E., Schneider, G., 2003. Support vector machine applications in bioinformatics. Appl. Bioinf. 2, 67–77.

Chen, C.Y., 2011. TCM Database@Taiwan: the world's largest traditional Chinese medicine database for drug screening in silico. PLoS One 6, e15939. https://doi.org/10.1371/journal.pone.0015939.

Debelle, F.D., Vanherweghem, J.L., Nortier, J.L., 2008. Aristolochic acid nephropathy: a worldwide problem. Kidney Int. 74, 158–169. https://doi.org/10.1038/ki.2008.129.

Ekins, S., 2014. Progress in computational toxicology. J. Pharmacol. Toxicol. Methods 69, 115–140. https://doi.org/10.1016/j.vascn.2013.12.003.

Fan, T.-P., Briggs, J., Liu, L., Lu, A., 2015. The art and science of traditional medicine Part 2: multidisciplinary approaches for studying traditional medicine. Science 347 337-337. https://doi.org/10.1126/science.347.6219.337-c.

Gouws, C., Steyn, D., Du Plessis, L., Steenekamp, J., Hamman, J.H., 2012. Combination therapy of Western drugs and herbal medicines: recent advances in understanding interactions involving metabolism and efflux. Expert Opin. Drug Metabol. Toxicol. 8, 973–984. https://doi.org/10.1517/17425255.2012.691966.

Guan, S., Ma, J., Zhang, Y., Gao, Y., Zhang, Y., Zhang, X., Wang, N., Xie, Y., Wang, J., Zhang, J., Chu, L., 2013. Danshen (Salvia miltiorrhiza) injection suppresses kidney injury induced by iron overload in mice. PLoS One 8, e74318. https://doi.org/10.1371/journal.pone.0074318.

Huang, S.H., Tung, C.W., Fulop, F., Li, J.H., 2015. Developing a QSAR model for hepatotoxicity screening of the active compounds in traditional Chinese medicines. Food Chem. Toxicol. 78, 71–77. https://doi.org/10.1016/j.fct.2015.01.020.

Huang, W.H., Hsu, C.W., Yu, C.C., 2007. Colchicine overdose-induced acute renal failure and electrolyte imbalance. Ren. Fail. 29, 367–370. https://doi.org/10.1080/08860220601166644.

Krumme, B., Endmeir, R., Vanhaelen, M., Walb, D., 2001. Reversible Fanconi syndrome after ingestion of a Chinese herbal 'remedy' containing aristolochic acid. Nephrol. Dial. Transplant. 16, 400–402. https://doi.org/10.1093/ndt/16.2.400.

Kuhn, M., Letunic, I., Jensen, L.J., Bork, P., 2016. The SIDER database of drugs and side effects. Nucleic Acids Res. 44, D1075–D1079. https://doi.org/10.1093/nar/gkv1075.

Lai, Q., Wei, J., Mahmoodurrahman, M., Zhang, C., Quan, S., Li, T., Yu, Y., 2015. Pharmacokinetic and nephroprotective benefits of using Schisandra chinensis extracts in a cyclosporine A-based immune-suppressive regime. Drug Des. Dev. Ther. 9, 4997–5018. https://doi.org/10.2147/DDDT.S89876.

Lee, S., Kang, Y.M., Park, H., Dong, M.S., Shin, J.M., No, K.T., 2013. Human nephrotoxicity prediction models for three types of kidney injury based on data sets of pharmacological compounds and their metabolites. Chem. Res. Toxicol. 26, 1652–1659. https://doi.org/10.1021/tx400249t.

Li, X.J., Jiang, Z.Z., Zhang, L.Y., 2014. Triptolide: progress on research in pharmacodynamics and toxicology. J. Ethnopharmacol. 155, 67–79. https://doi.org/10.1016/j.jep.2014.06.006.

Lin, L., Wang, Q., Yi, Y., Wang, S., Qiu, Z., 2016. Liuwei Dihuang pills enhance the effect of western medicine in treating diabetic nephropathy: a meta-analysis of randomized controlled trials. Evid. Based Complement Altern. Med. 12, 1–9. https://doi.org/10.1155/2016/1509063.

Liu, J., Mansouri, K., Judson, R.S., Martin, M.T., Hong, H., Chen, M., Xu, X., Thomas, R.S., Shah, I., 2015. Predicting hepatotoxicity using ToxCast in vitro bioactivity and chemical structure. Chem. Res. Toxicol. 28, 738–751. https://doi.org/10.1021/tx500501h.

Liu, J., Patlewicz, G., Williams, A.J., Thomas, R.S., Shah, I., 2017. Predicting organ toxicity using in vitro bioactivity data and chemical structure. Chem. Res. Toxicol.

30, 2046–2059. https://doi.org/10.1021/acs.chemrestox.7b00084.
Liu, Y., 2018. Incorporation of absorption and metabolism into liver toxicity prediction for phytochemicals: a tiered in silico QSAR approach. Food Chem. Toxicol. 118, 409–415. https://doi.org/10.1016/j.fct.2018.05.039.
MARTIN, M.T.A.R.J., 2010. ToxRefDB - Release User-Friendly Web-Based Tool for Mining ToxRefDB. U.S. Environmental Protection Agency, Washington, DC.
Myshkin, E., Brennan, R., Khasanova, T., Sitnik, T., Serebriyskaya, T., Litvinova, E., Guryanov, A., Nikolsky, Y., Nikolskaya, T., Bureeva, S., 2012. Prediction of organ toxicity endpoints by QSAR modeling based on precise chemical-histopathology annotations. Chem. Biol. Drug Des. 80, 406–416. https://doi.org/10.1111/j.1747-0285.2012.01411.x.
Nasri, H., Rafieian-Kopaei, M., 2014. Protective effects of herbal antioxidants on diabetic kidney disease. J. Res. Med. Sci. 19, 82–83.
Nortier, J.L., Vanherweghem, J.L., 2002. Renal interstitial fibrosis and urothelial carcinoma associated with the use of a Chinese herb (Aristolochia fangchi). Toxicology 181–182, 577–580. https://doi.org/10.1016/S0300-483X(02)00486-9.
OECD, 2014. Guidance Document on the Validation of (Quantitative) Structure-Activity Relationship [(Q)SAR] Models, OECD Series on Testing and Assessment. OECD Publishing, Paris.
Poon, W.-T., Lai, C.-K., Chan, A.Y.-W., 2007. Aristolochic acid nephropathy: the Hong Kong perspective. Hong Kong J. Nephrol. 9, 7–14. https://doi.org/10.1016/S1561-5413(07)60003-9.
Powell, T., Hsu, F.F., Turk, J., Hruska, K., 1998. Ma-huang strikes again: ephedrine nephrolithiasis. Am. J. Kidney Dis. 32, 153–159. https://doi.org/10.1053/ajkd.1998.v32.pm9669437.
Raies, A.B., Bajic, V.B., 2016. In Silico Toxicology: Computational Methods for the Prediction of Chemical Toxicity, vol. 6. Wiley Interdisciplinary Reviews Computational Molecular Science, pp. 147–172. https://doi.org/10.1002/wcms.1240.
Roncaglioni, A., Toropov, A.A., Toropova, A.P., Benfenati, E., 2013. In silico methods to predict drug toxicity. Curr. Opin. Pharmacol. 13, 802–806. https://doi.org/10.1016/j.coph.2013.06.001.
Roy, K., Kar, S., Das, R.N., 2015. Understanding the Basics of QSAR for Applications in Pharmaceutical Sciences and Risk Assessment. Academic Press, Boston.
Sayed, S., Ahsan, N., Kato, M., Ohgami, N., Rashid, A., Akhand, A.A., 2015. Protective effects of phyllanthus emblica leaf extract on sodium arsenite-mediated adverse effects in mice. Nagoya J. Med. Sci. 77, 145–153. https://doi.org/10.18999/nagjms.77.1-2.145.
Shaw, D., 2010. Toxicological risks of Chinese herbs. Planta Med. 76, 2012–2018. https://doi.org/10.1055/s-0030-1250533.
Stickel, F., Patsenker, E., Schuppan, D., 2005. Herbal hepatotoxicity. J. Hepatol. 43, 901–910. https://doi.org/10.1016/j.jhep.2005.08.002.
Teng, L., Zu, Q., Li, G., Yu, T., Job, K.M., Yang, X., Di, L., Sherwin, C.M., Enioutina, E.Y., 2016. Herbal medicines: challenges in the modern world. Part 3. China and Japan. Expert Rev. Clin. Pharmacol. 9, 1–9. https://doi.org/10.1080/17512433.2016.1195263.
Toropov, A.A., Toropova, A.P., Raska Jr., I., Leszczynska, D., Leszczynski, J., 2014. Comprehension of drug toxicity: software and databases. Comput. Biol. Med. 45, 20–25. https://doi.org/10.1016/j.compbiomed.2013.11.013.
Valerio Jr., L.G., 2009. In silico toxicology for the pharmaceutical sciences. Toxicol. Appl. Pharmacol. 241, 356–370. https://doi.org/10.1016/j.taap.2009.08.022.
Vanherweghem, J.L., Depierreux, M., Tielemans, C., Abramowicz, D., Dratwa, M., Jadoul, M., Richard, C., Vandervelde, D., Verbeelen, D., Vanhaelen-Fastre, R., et al., 1993. Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. Lancet 341, 387–391. https://doi.org/10.1016/0140-6736(93)92984-2.
Wetzel, S., Schuffenhauer, A., Roggo, S., Ertl, P., Waldmann, H., 2007. Cheminformatic analysis of natural products and their chemical space. Chimia International Journal for Chemistry 61, 355–360. https://doi.org/10.2533/chimia.2007.355.
WHO, 2013. WHO Traditional Medicine Strategy: 2014-2023. World Health Organization. https://www.who.int/medicines/publications/traditional/trm_strategy14_23/en/.
Wiedenfeld, H., Edgar, J., 2011. Toxicity of pyrrolizidine alkaloids to humans and ruminants. Phytochemistry Rev. 10, 137–151. https://doi.org/10.1007/s11101-010-9174-0.
Wu, L., Liu, Z., Auerbach, S., Huang, R., Chen, M., McEuen, K., Xu, J., Fang, H., Tong, W., 2017. Integrating drug's mode of action into quantitative structure-activity relationships for improved prediction of drug-induced liver injury. J. Chem. Inf. Model. 57, 1000–1006. https://doi.org/10.1021/acs.jcim.6b00719.
Xu, L.-W., Jia, M., Salchow, R., Kentsch, M., Cui, X.-J., Deng, H.-Y., Sun, Z.-J., Kluwe, L., 2012. Efficacy and side effects of Chinese herbal medicine for menopausal symptoms: a critical review. Evid. Based Complement Altern. Med. 2012, 1–19. https://doi.org/10.1155/2012/568106.
Xu, X., Nie, S., Liu, Z., Chen, C., Xu, G., Zha, Y., Qian, J., Liu, B., Han, S., Xu, A., 2015. Epidemiology and clinical correlates of AKI in Chinese hospitalized adults. Clinical Journal of the American Society of Nephrology Cjasn 10, 1510–1518. https://doi.org/10.2215/CJN.02140215.
Yang, B., Xie, Y., Guo, M., Rosner, M.H., Yang, H., Ronco, C., 2018. Nephrotoxicity and Chinese herbal medicine. Clin. J. Am. Soc. Nephrol. 13, 1605–1611. https://doi.org/10.2215/cjn.11571017.
Yang, L., Li, X., Wang, H., 2007. Possible mechanisms explaining the tendency towards interstitial fibrosis in aristolochic acid-induced acute tubular necrosis. Nephrol. Dial. Transplant. 22, 445–456. https://doi.org/10.1093/ndt/gfl556.
Yang, Z.R., 2004. Biological applications of support vector machines. Briefings Bioinf. 5, 328–338. https://doi.org/10.1093/bib/5.4.328.
Zeng, Z.P., Jiang, J.G., 2010. Analysis of the adverse reactions induced by natural product-derived drugs. Br. J. Pharmacol. 159, 1374–1391. https://doi.org/10.1111/j.1476-5381.2010.00645.x.
Zhang, H.W., Lin, Z.X., Xu, C., Leung, C., Chan, L.S., 2014. Astragalus (a traditional Chinese medicine) for treating chronic kidney disease. Cochrane Database Syst. Rev. 10, 1465–1858. https://doi.org/10.1002/14651858.CD008369.pub2.
Zhao, P., Liu, B., Wang, C., Acute Liver Failure Study, T., 2017. Hepatotoxicity evaluation of traditional Chinese medicines using a computational molecular model. Clin. Toxicol. 55, 996–1000. https://doi.org/10.1080/15563650.2017.1333123.
Zhong, D., Wang, H., Liu, M., Li, X., Huang, M., Zhou, H., Lin, S., Lin, Z., Yang, B., 2015. Ganoderma lucidum polysaccharide peptide prevents renal ischemia reperfusion injury via counteracting oxidative stress. Sci. Rep. 5, 16910. https://doi.org/10.1038/srep16910.
Zhu, X.W., Sedykh, A., Liu, S.S., 2014. Hybrid in silico models for drug-induced liver injury using chemical descriptors and in vitro cell-imaging information. J. Appl. Toxicol. 34, 281–288. https://doi.org/10.1002/jat.2879.