

QUANTITATIVE MODELS FOR PREDICTING ANTIOXIDANT CAPACITY IN
HERBS BASED ON MOLECULAR STRUCTURES AND COMPOSITIONS

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To Allah (SWT) and my beloved family

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In the name of Allah, the Most Gracious and the Most Merciful

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ABSTRACT

Herbs are considered as a vital source of natural antioxidants that can neutralise free radicals which cause harmful health effects to the human body. Researchers have found that the phenolic compounds are the major phytochemicals in herbs that contribute to their antioxidant capacity. However, even though the herbs are grown in the same conditions and geographic origin, the components and composition of phenolic compounds may differ for each sample, contributing to different antioxidant capacities. Previous researchers have only studied the interactions between either their molecular structures or composition of phenolic compounds. The interaction and synergistic effect of the combined components and composition of phenolic compounds contributing to their antioxidant property are still unknown. The aim of this research is to understand the synergistic effect between the structure and composition of phenolic compounds in herbs by developing a quantitative model. Firstly, a Quantitative Structure-Activity Relationship (QSAR) model was developed in three different approaches, namely general, consensus and comprehensive models using literature data set of traditional Chinese medicine. Previous research have developed the QSAR models using all generated molecular descriptors without any classification that might overlooked the important variable. In this research, the general and consensus models were built using the molecular descriptors from the DRAGON software. The general model utilised all the molecular descriptors, while the consensus model classified the molecular descriptors according to the phenolic compound groups. In addition, quantum-chemical descriptors from the Gauss View 5.0 and Gaussian 09 software which were also added into the model to include 3D descriptors in the model, and therefore, the model is known as the comprehensive model. Then, a new Quantitative Structure-Composition-Activity Relationship (QSCAR) model was developed by using the experimental data set to further correlate between the molecular structure (from QSAR model) and composition ratio for each significant phenolic compound in Misai Kucing. Three variable selections, namely forward stepwise, interval-partial least square (*i*-PLS) and genetic algorithm and two multi-linear regression analysis methods were combined to developed all models. The best performance QSCAR model based on the robustness, reliability and predictivity was selected and the result was compared with QSAR model and experimental results. As a result, the consensus model produced overall performance better than the general model. The increment of antioxidant activity is correlated with the phenolic compound size through measurement of the bond indices distance between the atom, shape that is specifically calculated in the proportion of path/walk in length 3 from molecular Randic shape index and the number of bridge edges. The high ratio between E_{HOMO} and E_{LUMO} , the low of stability and total energy values of phenolic compounds increased the antioxidant activity as well. The QSCAR could predict the antioxidant capacity with 13.88 % more accurately than the QSAR model. The QSCAR model shows that the high compositions of apigenin and dalspinosin while the low composition of caffeic, ferulic and rosmarinic acids increased the antioxidant capacity in Misai Kucing. In conclusion, a quantitative model has been developed to predict the antioxidant capacity in herbs by combining the comprehensive QSAR and QSCAR models. The QSAR model is generic for phenolic compounds, but QSCAR needs to be simulated again with the other herb composition ratios. Thus, the future researchers can use the models to predict antioxidant capacity for other herbs. The research may also be beneficial by extending the model for predicting other biological activities.

ABSTRAK

Herba dianggap sebagai sumber penting antioksidan semulajadi yang dapat meneutralkan radikal bebas yang menyebabkan kesan berbahaya kepada kesihatan tubuh manusia. Penyelidik mendapati bahawa sebatian fenolik adalah fitokimia utama dalam herba yang menyumbang kepada keupayaan antioksidan mereka. Walaupun herba ditanam dalam keadaan dan asal geografi yang sama, komponen dan komposisi sebatian fenolik mungkin berbeza bagi setiap sampel, menyumbang kepada keupayaan antioksidan yang berbeza. Penyelidik terdahulu hanya mengkaji interaksi antara sama ada struktur molekul atau komposisi sebatian fenolik. Kesan interaksi dan sinergistik gabungan komponen dan komposisi sebatian fenolik yang menyumbang kepada ciri antioksidan masih tidak diketahui. Tujuan kajian ini adalah untuk memahami kesan sinergi antara struktur dan komposisi sebatian fenolik dalam herba dengan membangunkan model Kuantitatif Hubungan Struktur-Aktiviti (QSAR) menggunakan tiga pendekatan berbeza, iaitu model umum, konsensus dan komprehensif menggunakan set data literatur perubatan tradisional Cina. Penyelidik terdahulu membangunkan model QSAR menggunakan semua deskriptor molekul tanpa sebarang pengkelasan yang mana mungkin mengabaikan pembolehubah penting. Dalam kajian ini, model umum dan konsensus dibina menggunakan deskriptor molekul dari perisian DRAGON. Model umum menggunakan semua deskriptor molekul, manakala model konsensus mengkelaskan deskriptor molekul berdasarkan kumpulan sebatian fenolik. Di samping itu, deskriptor kuantum-kimia daripada perisian Gauss View 5.0 dan Gaussian 09 dimasukkan juga ke dalam model bagi memasukkan deskriptor 3D ke dalam model, model ini dikenali sebagai model komprehensif. Kemudian, model Kuantitatif Hubungan Struktur-Komposisi-Aktiviti (QSCAR) yang baru dibangunkan menggunakan data set dari eksperimen untuk mengaitkan struktur molekul (dari model QSAR) dan nisbah komposisi untuk setiap sebatian fenolik penting dalam Misai Kucing. Tiga pilihan pembolehubah, iaitu ke hadapan langkah demi langkah, selang-sepaya kuasa dua terkecil (*i*-PLS) dan algoritma genetik dan dua kaedah regresi multi-linear digabungkan untuk membangunkan semua model. Prestasi terbaik model QSCAR berdasarkan ketahanan, kebolehpercayaan dan ramalan telah dipilih dan keputusan dibandingkan dengan model QSAR dan keputusan eksperimen. Keputusannya, model konsensus menghasilkan keseluruhan prestasi lebih baik daripada model umum. Peningkatan aktiviti antioksidan dikaitkan dengan saiz sebatian fenolik melalui ukuran indeks ikatan jarak antara atom, bentuk yang secara khusus dikira dalam perkadaran antara laluan/jalan dalam panjang 3 dari indeks molekular bentuk Randik dan bilangan penjurujambatan sebatian fenolik. Nisbah yang tinggi antara E_{HOMO} dan E_{LUMO} , kestabilan dan jumlah nilai tenaga sebatian fenolik yang rendah meningkatkan aktiviti antioksidan juga. Model QSCAR boleh meramalkan kapasiti antioksidan 13.88 % lebih tepat berbanding model QSAR. Model QSCAR menunjukkan komposisi tinggi apigenin dan dalspinosin manakala komposisi rendah asid kaffeik, asid ferulik dan asid rosmarinik meningkatkan antioksidan kapasiti dalam Misai Kucing. Sebagai kesimpulan, satu model kuantitatif telah dibangunkan untuk meramalkan kapasiti antioksidan dalam herba dengan menggabungkan model komprehensif QSAR dan QSCAR. Model QSAR adalah generik untuk sebatian fenolik, tetapi QSCAR perlu disimulasikan lagi dengan nisbah komposisi bagi herba yang lain. Oleh itu, penyelidik pada masa depan boleh menggunakan model untuk meramalkan kapasiti antioksidan untuk herba yang lain. Kajian ini juga boleh memberi manfaat dengan memperluaskan model bagi meramalkan aktiviti-aktiviti biologi lain.

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LIST OF ABBREVIATIONS

EPPs	-	Entry Point Projects
NKEAs	-	National Key Economic Areas
ETP	-	Economic Transformation Programme
GNI	-	Gross national income
E-DRAGON	-	Electronic-DRAGON
PCLIENT	-	Parameter Client
QSAR	-	Quantitative Structure-Activity Relationship
QCAR	-	Quantitative Composition-Activity Relationship
QSCAR	-	Quantitative Structure- Composition-Activity Relationship
ABTS ^{•+}	-	2,2'-azinobis-3-ethylbenzothiazoline-6-sulphonic acid radical
TEAC	-	Trolox Equivalent Antioxidant Capacity
0D	-	Zero dimensional
1D	-	One dimensional
2D	-	Two dimensional
3D	-	Three dimensional
UHPLC	-	Ultra-High Performance Liquid Chromatography
WHO	-	World Health Organisation
MEP	-	Mevalonic acid pathway
BHA	-	Butylated hydroxyanisole

BHT	-	Butylated hydroxytoluene
HPLC	-	High-performance liquid chromatography
NMR	-	Nuclear magnetic resonance
MS	-	Mass spectrophotometer
FTIR	-	Fourier-transform infrared spectroscopy
ROS	-	Reactive oxygen species
RNS	-	Reactive nitrogen species
GSHP _x	-	Glutathione peroxidase
SOD	-	Superoxide dismutase
CAT	-	Catalase
GSH	-	Glutathione
GS _t	-	Glutathione-S-transferase
PEROX	-	Peroxidase
NO	-	Nitric oxide
MDA	-	Malondialdehyde
TBARS	-	Thiobarbituric acid reactive substance
LPO	-	Lipid peroxidation
DPPH	-	2,2-Diphenyl-1-picrylhydrazyl
FRAP	-	Fluorescence Recovery after Photo-bleaching
ABTS	-	2,2'-azinobis-3-ethylbenzothiazoline-6-sulphonic acid
TRAP	-	Total radical trapping antioxidant parameter
ORAC	-	Oxygen radical absorbance capacity
CUPRAC	-	Cupric reducing antioxidant capacity
DPPH [•]	-	2,2-Diphenyl-1-picrylhydrazyl radical
HAT	-	Hydrogen atom transfer

ET	-	Electron transfer
LDL	-	Low-density lipoprotein
TBA	-	Thiobarbituric acid
IMR	-	Institute for Medical Research
PCA	-	principal component analysis
MDC	-	The most descriptive compounds
LMD	-	The largest minimum distance
AM1	-	Austin Model 1
PM3	-	Parametric Method 3
DFT	-	Density Functional Theory
HF	-	Hartree-Fork
BDE	-	Bond dissociation enthalpy
IP	-	Ionization potential
VCC-LAB	-	Virtual Computational Chemistry Laboratory
HTML	-	Hypertext Markup Language
VSA	-	Van der Waals surface area
<i>HOMO</i>	-	Highest Occupied Molecular Orbital
<i>LUMO</i>	-	Lowest Unoccupied Molecular Orbital
E_{HOMO}	-	Energy of the <i>HOMO</i>
E_{LUMO}	-	Energy of the <i>LUMO</i>
ΔE_{gap}	-	Difference between the E_{HOMO} and E_{LUMO}
TCM	-	Traditional Chinese Medicine
GC-MS	-	Gas chromatography–mass spectrometry
HPLC-MS	-	High-performance liquid chromatography-mass spectrophotometer
UPLC	-	Ultra-performance liquid chromatography

FDA	-	Food and Drug Administration
EMA	-	European Medicines Evaluation Agency
SFDA	-	State Food and Drug Administration
HCA	-	Hierarchical clustering analysis
MLR	-	Multiple Linear Regressions
PLS	-	Partial Least Square
OPLS	-	Orthogonal partial least squares
CCA	-	Canonical correlation analysis
SVR	-	Support vector regression
GRNN	-	Generalized regression neural network
SW	-	Stepwise
FSW	-	Forward stepwise
GA	-	Genetic algorithm
<i>i</i> -PLS	-	Interval-partial least squares
GFA	-	Genetic Function Approximation
FA	-	Factor Analysis
RM	-	Replacement Method
ERM	-	Enhanced Replacement Method
VIP	-	Variable Importance in the Projection
UVE	-	Uninformative Variable Elimination
CARS	-	Competitive Adaptive Reweighted Sampling
CovSel	-	Covariance Selection
LDA	-	Linear Discriminant Analysis
SVM	-	Support Vector Machine
ANN	-	Artificial Neural Net

LOO	-	Leave-one-out
LSO	-	Leave-several-out
LMO	-	Leave-many-out
MDC	-	The most descriptive compounds
LMD	-	The largest minimum distance
PRESS	-	Prediction error sum of squares
<i>RMSEC</i>	-	Root-mean-square error of calibration
<i>RMSECV</i>	-	Root-mean-square error of cross-validation
<i>RMSEP</i>	-	Root-mean-square error of prediction
GETAWAY	-	Geometry, Topology and Atom-Weights Assembly
RDF	-	Radial Distribution Function
MR	-	Molar refractivity
V_w	-	Van der Walls volume
H_f	-	Heat of formation
ΔH_f	-	The energy of electron abstraction
I	-	Indicator variable
MAXDP	-	Maximal electrotopological positive variation
E-state	-	Electronic topological state atom
FP	-	Frontal polygon
CoMSIA	-	Comparative molecular similarity indices analysis
HQSAR	-	Hologram QSAR
G-QSAR	-	Group-based QSAR
kNN	-	k-nearest neighbors
DF	-	Decision Forest
ESCC	-	Extended Site Composite Curve

MR	-	Molar refractivity
MM2	-	Molecular mechanics
MOPAC	-	Molecular Orbital Package
RMS	-	Root Mean Square
GUI	-	Graphical user interface
LV	-	Latent variable
NIPALS	-	Non-linear Iterative Partial Least Squares
TE	-	Total energy
MS/MS	-	Tandem mass spectrometry
AO-H	-	Antioxidant

LIST OF SYMBOLS

r	-	Regression coefficient
r^2	-	Squared regression coefficient
r_{cv}^2	-	Cross-validation squared correlation coefficient
$\bar{y}_{training}$	-	The mean activity value of the training set
r_{pred}^2	-	Prediction squared correlation coefficient
$y_{exp(test)}$	-	The experimental activity value for the test set of compounds
$y_{pred(test)}$	-	The predicted activity value for the test set of compounds
$n_{training}$	-	The number of the training set of compounds
n_{test}	-	The number of the test set of compounds
r_m^2	-	Metrics Squared regression coefficient
r_o^2	-	Squared correlation coefficient for the internal and external Predicted value without the intercept
$r_{m(overall)}^2$	-	The overall performance
r_r^2	-	The squared correlation coefficient value for each randomised model
S	-	Standard deviation
r_{adj}^2	-	Modification of r^2
$O_2^{\bullet-}$	-	Superoxide anion radical
H_2O_2	-	Hydrogen peroxide

ROO^\bullet	-	Peroxyl radical
HO^\bullet	-	Hydroxyl radical
NO^\bullet	-	Nitric oxide
OONO^-	-	Peroxynitrite anion
Fe^{2+}	-	Ferrous ion
${}^0\chi$	-	Zero-order connectivity index
IP _v	-	Vertical ionization
EA	-	Electro affinities
χ	-	Electronegativity
η	-	Hardness
S	-	Softness
ω	-	Electrophilic index
K_s	-	Reaction rate
mM	-	Milimolar
A_{blank}	-	The absorbance of the control
μ	-	Dipole moment
Log P	-	Octanol/water partition coefficient
IC ₅₀	-	Half maximal inhibitory concentration

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CHAPTER 1

INTRODUCTION

1.1 Research Background

Clinical and epidemiological studies have reported the consumption of herbs can prevent the occurrence of diseases caused by oxidative stresses, such as hepatic, cancer, diabetes and lungs. In Malaysia, herbal products generate substantial income where the annual sales for traditional medicines reported to increase from US\$ 385 million (RM 1 billion) to US\$ 1.29 billion (RM 4.5 billion) within five years from 2000 to 2005 (Kew *et al.*, 2015). The high demand for herbal products shows their potential in driving the sustainability of the Malaysian bio-economy sector. Thus, the Malaysian Government recognises the herbal development as one of the agriculture Entry Point Projects (EPPs) under the National Key Economic Areas (NKEAs) in the Economic Transformation Programme (ETP). One of the objectives of NKEA 11 (Agriculture) is to reach high gross national income (GNI) from RM 28.9 million to RM 49.1 million in 2020 (Wan Zaki and Mohd Rani, 2013). The usages of herbs are not only restricted for prevention and treatment purposes but also have been extended in cosmetics, nutraceuticals, flavourings, beverages, dyeing, repellents and industrial uses.

The literature findings revealed that herbs prevent and treat diseases because of their antioxidant function. As an example, antioxidant react to delay the deterioration by the action of oxygen in animal tissues. The phytochemicals that produced through secondary metabolites is attributed to the antioxidant action in

herbs. Herbs comprise 100,000 to 200,000 phytochemical components including terpenes and terpenoids, alkaloids and phenolic compounds (Pereira *et al.*, 2009). Phenolic compounds are one of the major and dominant components of antioxidant (Akbar *et al.*, 2014, Liu *et al.*, 2013, Selvaraj *et al.*, 2014, Shon *et al.*, 2003, Soobrattee *et al.*, 2005). Phenolic compounds consist of almost 10,000 structures (Kennedy and Wightman, 2011). The antioxidant in herbs possesses a broad range of biological activities, such as antibacterial (Kiran *et al.*, 2014, Janifer *et al.*, 2010), antimicrobial (Mocan *et al.*, 2014, Karimi *et al.*, 2011, Araujo *et al.*, 2012, Sharma *et al.*, 2014), anti-inflammatory (Huang *et al.*, 2006) and antidiabetic (Kumar *et al.*, 2014). Thus, the evaluation of antioxidant capacity is a fundamental assessment to determine the potential of herbs for exhibiting other biological activities.

The *in-vivo* and *in-vitro* methods are frequently used for evaluating antioxidant capacity. These experimental approaches are time-consuming and costly, especially when many samples are involved in obtaining an accurate and stable value. Therefore, the approach of quantitative methodology has the potential to decrease the time and cost substantially by predicting the antioxidant capacity prior to the experimental methods. This approach is known as *in-silico* method which has been widely applied in medical fields especially in medicinal chemistry or pharmaceutical companies for discovering new medicine as well as improving their efficacy. In fact, the increasing computational powers together with advances in computer technology further stimulate the development of the quantitative method (Wang *et al.*, 2006). Nevertheless, the *in-silico* method is rarely applied in the herbal industry. The limitation might be due to the inconsistent phytochemicals content that resulted in the difficulty in collecting the data (Chew *et al.*, 2011).

The *in-silico* method is applied to transform the relationship between a dependent variable (antioxidant activity or capacity) and independent variables (phenolic compounds) of herbs into a mathematically quantified equation by employing a significant number of statistical tools through the regression analysis methods. The developed model can be utilised to predict activities of compounds that are not included in the model development. The molecular structures and compositions of components of phenolic compounds are commonly used as

independent variables to derive correlation with the antioxidant value in herbs. The studies of these factors provide an opportunity for researchers to build quantitative models using various types of independent variables for determining and analysing thoroughly the correlation of phenolic compounds and antioxidant in the different point of views.

Sometimes, researchers have applied single type of independent variables to study the effect of particular properties of phenolic compounds towards the antioxidant (Wei *et al.*, 2015, Cheng *et al.*, 2002b, Cheng *et al.*, 2002a, Wright *et al.*, 2001, Lien *et al.*, 1999, Sergediene *et al.*, 1999). Meanwhile, some researchers have combined different types of independent variables for viewing numerous properties of phenolic compounds affecting antioxidant value (Prokai *et al.*, 2013, Mitra *et al.*, 2011, Lucas *et al.*, 2010, Mitra *et al.*, 2010, Rastija and Medic-Saric, 2009, Ray *et al.*, 2008a, Reis *et al.*, 2007). It is evident that various properties from variations of the molecular structure of phenolic compounds influencing antioxidant value are widely studied. Normally, molecular descriptors that are generated by various types of software, such as Electronic-DRAGON (E-DRAGON), Parameter Client (PCLIENT), DRAGON, Cerius2, CORINA and Padel are used to characterise the properties of molecular structures. By using the molecular descriptors, Quantitative Structure-Activity Relationship (QSAR) models are specifically developed. The biggest challenge in QSAR studies is to obtain the best performance of a model. The problem might be due to the limited numbers of data set, distribution of data set, the types of independent variables, unsuitable analysis method and overfitting. As an example, Sergediene *et al.* (1999) considered only thirteen phenolic compounds belonged to flavanoids, derivatives of gallic and caffeic acids. Due to that, many researchers study and explore the development of the QSAR model by considering all the problems for improving their model performance.

The Quantitative Composition-Activity Relationship (QCAR) models have been developed to investigate the synergistic effects among different components of phenolic compounds contributing to the antioxidant capacity in a herb (Wang *et al.*, 2006). By using the QCAR model, the prediction of activity of herbal medicine and the optimal combination of active components to form more effective herbal

medicine prior to the experimental procedure can be made. In other words, the new herbal medicine can also be designed. For example, Wang et al. (2006) formulated the new proportion of two active components of *Qi-Xue-Bing-Zhi-Fang* for cardiovascular diseases where the efficiency in each condition of proportion predicted by the QCAR model. Due to the beneficial applications of the quantitative models, it will be developed in this research, especially for herbs in Malaysia.

1.2 Problem Statement

Herbs show considerable variation in antioxidant capacities, which could be ascribed to soil fertility levels, age of the plants and variation in sample sourcing. Due to that, the antioxidant pattern is generally complex. Thus, the quantitative model has been developed to correlate between antioxidant capacities with one of the vital phytochemicals in herbs *i.e.* phenolic compounds. The main focus is to develop a model with the best performance. Most of the developed quantitative models by previous researchers only focused on one single criteria either only molecular structures (QSAR model) or compositions (QCAR model) of phenolic compounds alone. However, in herbs, both the molecular structures and compositions can affect the antioxidant capacity. The QSAR models have been widely developed in literature (Roy and Mitra, 2009, Cherkasov *et al.*, 2014). In contrast, the QCAR model is limited. The limitation may be due to inconsistent composition and complex components of phenolic compounds in a herb (Zang *et al.*, 2011). Consequently, the collection of similar components of phenolic compounds for each sample become more difficult. Thus, the challenge in developing the QCAR model is the scarce numbers of data set reported on the compositions of phenolic compounds for many samples of a herb. Therefore, this research aims to develop a new quantitative model of Quantitative Structure-Composition Activity Relationship (QSCAR) that can correlate both the molecular structures and compositions with antioxidant capacity. Not only that, this model can also demonstrate the synergistic effects among the different components of phenolic compounds that can also contribute to the antioxidant capacity. Hence, it is vital to develop a comprehensive QSAR model that can include all the significant features of phenolic compounds structure.

Theoretically, only the homologous set of molecules which has similar structure analogues is effective for QSAR development rather than the large structure variation of the data sets. The QSAR models are normally developed using large variation of structure from various components of phenolic compounds without any classification. This circumstance makes the construction of the best model becomes increasingly difficult. Thus, an alternative approach is required to perform QSAR on structurally diverse compounds.

1.3 Research Objective

The main objective of this research is to develop a quantitative model for predicting antioxidant capacity in a herb by considering the interaction between the molecular structure and composition of phenolic compounds. Therefore, three sub-objectives are as follow:

- 1) To develop a QSAR model to determine antioxidant activity by considering the grouping of molecular descriptors.
- 2) To develop a comprehensive QSAR model to further determine antioxidant activity by considering the grouping of molecular descriptors and quantum-chemical descriptors.
- 3) To develop a quantitative model that combined the molecular structure and composition of phenolic compounds to predict antioxidant capacity.
- 4) To validate the developed models with experimental work.

1.4 Scope of Research

The following are the scope of research to achieve each sub-objectives:

- 1) To develop a QSAR model to determine the antioxidant capacity of the herb by considering the grouping of molecular descriptors.

- i) Data set from literature of Cai *et al.* (2006) consists of 89 phenolic compounds with antioxidant activity is used to develop the QSAR model.
- ii) The antioxidant activity is evaluated through the 2,2'-azinobis-3-ethylbenzothiazoline-6-sulphonic acid radical (ABTS^{•+}) assay in Trolox Equivalent Antioxidant Capacities (TEAC).
- iii) The structures of phenolic compounds are pre-optimised geometrically by minimising energy using molecular mechanics (MM2) force field until the Root Mean Square (RMS) gradient value reaches a value smaller than 0.1 Kcal/mol.
- iv) The models are built using MATLAB (Mathwork_Inc., 2013) as the platform together with the latest version of PLS Toolbox 7.9.5 (Eigenvector_Research_Inc., 2010).
- v) Five combinations of variable selection as well as regression analysis methods are used in developing the all the models and then the suitable combination method is determined.
- vi) The activity-based ranking method is used to split the data set into 2:1 for training and test set, respectively.
- vii) The 29 blocks of molecular descriptors from the DRAGON software that are categorised based on their dimensional properties (0-dimensional (0D), 1-dimensional (1D), 2-dimensional (2D) and 3-dimensional (3D)) are recategorised into three combinations groups, namely group 1 (0D, 1D, 2D and 3D) , group 2 (0D, 1D and 2D) and group 3 (3D) to build the general QSAR model.
- viii) The individual models are developed using the generated molecular descriptors from six groups of phenolic compounds and then the models are integrated to produce the consensus model.
- ix) The performance of developed models are analysed based on the robustness, reliability and prediction potential using the internal and external validation as well as *Y*-randomisation test that is represented by the statistical parameters.
- x) The performance of the general and consensus models are compared.

- 2) To develop a comprehensive QSAR model to further determine the antioxidant capacity of the herb by considering the grouping of molecular descriptors and quantum-chemical descriptors.
 - i) The quantum-chemical descriptors that is generated by the Gauss View 5.0 and Gaussian 09 software (Gaussian, 2003) in two different semi-empirical methods are combined with the significant molecular descriptors from the consensus model to develop the comprehensive model.
 - ii) The appropriate semi-empirical method is determined based on the performance of developed models using the internal and external validation as well as *Y*-randomisation test that is represented by the statistical parameters.

- 3) To develop a quantitative model that combined the molecular structure and composition relationship of phenolic compounds to predict antioxidant capacity.
 - i) 16 Misai Kucing samples in different geographical origins are used to develop QSCAR model.
 - ii) The antioxidant capacity is evaluated through the ABTS^{•+} assay in TEAC.
 - iii) The components and compositions of phenolic compounds are analysed using Ultra-High Performance Liquid Chromatography (UHPLC) system (Perkin Elmer Model Flexar FX-15) coupled with a hybrid triple quadrupole-linear ion trap-tandem mass spectrometer (3200 QTRAP, AB/Sciex, Canada).
 - iv) The composition ratio is obtained by determining the peak and total peak areas of the components of phenolic compounds and then combined with their predicted antioxidant activity from the comprehensive QSAR model to represent the independent variables.
 - v) Three different splitting ratios of training and test sets (1:1, 2:1 and 3:1) are implemented using activity-based ranking method and the best ratio is determined based on the robustness, reliability and prediction potential

- 4) To validate the developed models with experimental work.
 - i) The antioxidant capacity of three samples of Misai Kucing is evaluated through the ABTS^{•+} assay in TEAC.
 - ii) The significant components and their composition of phenolic compounds in three samples are analysed using Ultra-High Performance Liquid Chromatography (UHPLC) system (Perkin Elmer Model Flexar FX-15) coupled with a hybrid triple quadrupole-linear ion trap-tandem mass spectrometer (3200 QTRAP, AB/Sciex, Canada).
 - iii) The prediction accuracy of the comprehensive QSAR and QSCAR models is determined by comparing with their experimental value of antioxidant capacity.

1.5 Significance of Research

The key specific contributions from this research include:

- 1) A new approach to develop a quantitative model using molecular descriptors based on the group of phenolic compounds.
- 2) A new method for developing a quantitative model by correlating the molecular structure and composition ratio of phenolic compounds.
- 3) A new quantitative model for predicting antioxidant capacity in herbs.

1.6 Thesis Outline

This thesis is organised into six chapters. Chapter 1 provides the introduction. It begins with the background of the research followed by the respective problem statements and research objectives. In addition, the scope and significance of the research have been presented as well.

In Chapter 2, the literature reviews are discussed the specific areas or issues pertinent to this research which include the scenario of herbal development, antioxidant, model development (data set, independent variables, variable selection methods and validation process) along with the overview of the QSAR as well QCAR studies are analysed. The subsequent section covers the research gaps for the current development model.

Chapter 3 presents the detailed methodology used throughout the study. The development of QSAR models that are categorised into three different parts (Part A, B and C) and QSCAR models is explained in detail. Besides that, the techniques on model validation are discussed as well. The subsequent study applied the developed QSAR and QSCAR models to validate their accuracy in predicting the antioxidant capacity of three samples of Misai Kucing.

Results and discussion are divided into two chapters. Chapter 4 discusses the development of general, consensus and comprehensive QSAR models that take into account the molecular descriptors generated by the DRAGON software as well as the quantum-chemical descriptors generated by the Gauss View 5.0 and Gaussian 09 software. The general (Part A) and the consensus (Part B) QSAR models are initially developed using molecular descriptors from the DRAGON software. The comprehensive model (Part C) are then developed using the quantum-chemical descriptors and molecular descriptors from the consensus model. The performance of developed models are analysed based on the robustness, reliability and prediction potential using the internal (leave-one-out) and external validation as well as *Y*-randomisation test that is represented by the statistical parameters. Moreover, the QSCAR model that take into account the components structure and composition of phenolic compounds that identified from 16 samples of Misai Kucing in different geographical origin is discussed. The analysed compositions of phenolic compounds together with their predicted antioxidant activity (from the comprehensive QSAR model) are used to generate the data set. The models have been developed using three different splitting ratios of training and test set. The performance of QSCAR models is also compared and discussed based on the robustness, reliability and prediction potential.

Chapter 5 presents the validation of the developed comprehensive QSAR and QSCAR models for predicting the antioxidant capacity of three samples of Misai Kucing. The prediction accuracy for both models is evaluated by comparing with their experimental values of antioxidant capacity. Finally, Chapter 6 concludes the study with a brief discussion and summary of the results from each topic or analysis of the research. It highlights the novelty of the findings, achievement and contribution of this research. In addition, the limitations and some recommendations for future research are also discussed.

REFERENCES

- Afantitis, A., Melagraki, G., Sarimveis, H., Koutentis, P. A., Markopoulou, J. and Markopoulou, O. I. (2006). A Novel QSAR Model for Predicting Induction of Apoptosis by 4-aryl-4H-chromenes. *Bioorganic & Medicinal Chemistry* 14, 6686–6694.
- Akbar, P. N., Jahan, I. A., Hossain, M. H., Banik, R., Nur, H. P. and Hossain, M. T. (2014). Antioxidant Capacity of *Piper Longum* and *Piper Nigrum* Fruits Grown in Bangladesh. *World Journal of Pharmaceutical Sciences*, 2, 931-941.
- Akhbar, P. N., Jahan, I. A., Hossain, M. H., Banik, R., Nur, H. P. and Hossain, M. T. (2014). Antioxidant Capacity of *Piper longum* and *Piper nigrum* Fruits Grown in Bangladesh. *World Journal of Pharmaceutical Sciences*, 2, 931-941.
- Akowuah, G. A., Ismail, Z., Norhayati, I. and Sadikun, A. (2005). The Effects of Different Extraction Solvents of Varying Polarities on Polyphenols of *Orthosiphon Stamineus* and Evaluation of The Free Radical-Scavenging Activity. *Food Chemistry*, 93, 311-317.
- Akowuah, G. A., Zhari, I., Norhayati, I., Sadikun, A. and Khamsah, S. M. (2004). Sinensetin, Eupatorin, 3'-hydroxy-5, 6, 7, 4'-tetramethoxyflavone and Rosmarinic Acid Contents and Antioxidative Effect of *Orthosiphon stamineus* from Malaysia. *Food Chemistry* 87, 559-566.
- Aksoy, L., E., K., Agilano, Y., Aslan, Z. and Kargıoglu, M. (2013). Free Radical Scavenging Activity, Total Phenolic Content, Total Antioxidant Status, and Total Oxidant Status of Endemic *Thermopsis turcica*. *Saudi Journal of Biological Sciences* 20, 235-239.
- Alam, M. N., Bristi, N. J. and Rafiquzzaman, M. (2013). Review on *In-vivo* and *In-vitro* Methods Evaluation of Antioxidant Activity. *Saudi Pharmaceutical Journal*, 21, 143-152.
- Amarowicz, R., Pegg, R. B., Rahimi-Moghaddam, P., Barl, B. and Weil, J. A. (2004). Free-radical Scavenging Capacity and Antioxidant Activity of Selected Plant Species from the Canadian Prairies. *Food Chemistry*, 84, 551-562.

- Ameer, O. Z., Salman, I. M., Asmawi, M. Z., Ibraheem, Z. O. and Yam, M. F. (2012). *Orthosiphon stamienus*: Traditional Uses, Phytochemistry, Pharmacology, and Toxicology: A Review. *Journal of Medicinal Food*, 15, 1-13.
- Amic, D., Davidovic-Amic, D., Beslo, D. and Trinajstić, N. (2003). Structure-Radical Scavenging Activity Relationships of Flavonoids. *Croatia Chemica Acta* 76, 55-61.
- Andrade, C. H., Pasqualoto, K. F., Ferreira, E. I. and Hopfinger, A. J. (2010). 4D-QSAR: Perspectives in Drug Design. *Molecules*, 15, 3281-94.
- Anthony, K., Subramanya, G., Uprichard, S., Hammouda, F. and Saleh, M. (2013). Antioxidant and Anti-Hepatitis C Viral Activities of Commercial *Milk thistle* Food Supplements. *Antioxidants* 2, 23-36.
- Aouachria, S., Boumerfeg, S., Benslama, A., Benbacha, F., Guemmez, T., Khennouf, S., Arrar, L. and Baghiani, A. (2017). Acute, Sub-Acute Toxicity and Antioxidant Activities (*In-vitro* And *In-vivo*) of *Reichardia picroide* Crude Extract. *Journal of Ethnopharmacology*, 208, 105-116.
- Aoudia, H., Oomah, B. D., Zaidi, F., Zaidi-Yahiaoui, R., Drover, J. C. and Harrison, J. E. (2013). Phenolics, Antioxidant and Anti-inflammatory Activities of *Melia azedarach* Extracts. *International Journal of Applied Research in Natural Products*, 6, 19-29.
- Aqil, F., Ahmad, I. and Mehmood, Z. (2006). Antioxidant and Free Radical Scavenging Properties of Twelve Traditionally Used Indian Medicinal Plants. *Turki Journal Biology*, 30, 177-183.
- Araujo, M. G. D. F., Hilario, F., Vilegas, W., Santos, L. C. D., Brunetti, I. L., Sotomayor, C. E. and Bauab, T. M. (2012). Correlation among Antioxidant, Antimicrobial, Hemolytic, and Antiproliferative Properties of *Leiothrix spiralis* Leaves Extract. *International Journal Molecular Science* 13, 9260-9277.
- Arnao, M. B., Cano, A. and Acosta, M. (2016). Methods to Measure the Antioxidant Activity in Plant Material. A Comparative Discussion. *Free Radical Research*, 31, 89-96.
- Asadollahi, T., Dadfarnia, S., Shabani, A. M. and Ghasemi, J. B. (2014). Use of the Genetic Algorithm for Variable Selection of PLS Regression in a QSAR Study on [4,5-d] Pyrimidine Derivatives as Antagonist of CXCR2. *Communications in Mathematical and in Computer Chemistry*, 71, 287-304.

- Azmir, J., Zaidul, I. S. M., Rahman, M. M., Sharif, K. M., Mohamed, A., Sahena, F., Jahurul, M. H. A., Ghafoor, K., Norulaini, N. A. N. and Omar, A. K. M. (2013). Techniques for Extraction of Bioactive Compounds from Plant Materials: A Review. *Journal of Food Engineering* 117, 426-436.
- Bakhari, N. A., Abdullah, A. R., Osman, H. and Nordin, N. H. The Relationship between Phenolic, Tannin and Flavonoid Content with the Antioxidant Activity of *Pereskia bleo* (Kunth). *International Conference on Science and Social Research* 5-7 Dec. 2010 2010, 494-498.
- Bakhtiyor, F. R., Nasrulla, D. A., Syrov, V. N. and Jerzy, L. (2005). A Quantitative Structure-Activity Relationship (QSAR) Study of the Antioxidant Activity of Flavonoids. *QSAR & Combinatorial Science*, 24, 1056-1065.
- Balasundram, N., Sundram, K. and Samman, S. (2006). Phenolic Compounds in Plants and Agri-industrial by Products: Antioxidant Activity, Occurrence and Potential Uses. *Food Chemistry*, 99, 191-203.
- Bendary, E., Francis, R. R., Ali, H. M. G., Sarwat, M. I. and Hady, S. E. (2013). Antioxidant and Structure-Activity Relationship (SARs) of Some Phenolic and Anilines Compounds. *Annals of Agriculture Science*, 58, 173-181.
- Bernhoft, A. (2010). A Brief Review on Bioactive Compounds in Plants. *The Norwegian Academy of Science and Letters*, 11-17.
- Biskup, I., Golonka, I., Gamian, A. and Sroka, Z. (2013). Antioxidant Activity of Selected Phenols Estimated by ABTS and FRAP Methods. *Postepy Hig Med Dosw* 67, 958-963.
- Boligon, A. A., Machado, M. M. and Athayde, M. L. (2014). Technical Evaluation of Antioxidant Activity. *Medicinal Chemistry*, 4, 517-522.
- Bouayed, J., Piri, K., Rammal, H., Dicko, A., Desor, F., Younos, C. and Soulimani, R. (2007). Comparative Evaluation of the Antioxidant Potential of Some Iranian Medicinal Plants. *Food Chemistry* 104, 364-368.
- Boutennoun, H., L., B., Rawashdeh, A., Al-Qaoud, K., Abdelhafez, S., Kebieche, M. and Madani, K. (2017). *In-vitro* Cytotoxic and Antioxidant Activities of Phenolic Components of Algerian *Achillea odorata* Leaves. *Arabian Journal of Chemistry* 10, 403-409.
- Boyle, N. O., Banck, M., James, C. A., Morley, C., Vandermeersch, T. and Hutchison, G. R. (2011). Open Babel: An Open Chemical Toolbox. *Journal of cheminformatics*, 3.

- Brereton, R. G. (2003). *Chemometrics: Data Analysis for the Laboratory and Chemical Plant*. Chichester, UK: John Wiley & Sons, Ltd.
- Cai, Y., Luo, Q., Sun, M. and Corke, H. (2004). Antioxidant Activity and Phenolic Compounds of 112 Traditional Chinese Medicinal Plants Associated with Anticancer. *Life Science*, 74, 2157-2184.
- Cai, Y., Sun, M., Xing, J., Luo, Q. and Corke, H. (2006). Structural-Radical Scavenging Activity Relationship of Phenolic Compounds from Traditional Chinese Medical Plants. *Life Sciences* 78, 2872-2888.
- CambridgeSoft, C. (2003a). Chem3D Ultra. Cambridge, USA: ChemOffice.
- CambridgeSoft, C. (2003b). ChemDraw Ultra. 2002 ed. Massachusetts, USA: ChemOffice.
- Campos, L. J. D. and Melo, E. B. D. (2014). Modeling Structure-Activity Relationships of Prodiginines with Antimalarial Activity using GA/MLR and OPS/PLS. *Journal of Molecular Graphics and Modelling*, 54, 19-31.
- Chanda, S. and Dave, R. (2009). *In-vitro* Models for Antioxidant Activity Evaluation and Some Medicinal Plants Possessing Antioxidant Properties: An Overview. *African Journal of Microbiology Research* 3, 981-996.
- Chen, B., Zhu, Z., Chen, M., Dong, W. and Li, Z. (2014). Three-dimensional Quantitative Structure-Activity Relationship Study on Antioxidant Capacity of Curcumin Analogues. *Journal of Molecular Structure*, 1061, 134-139.
- Chen, Q., Wu, L., Liu, W., Xing, L. and Fan, X. (2013). Enhanced QSAR Model Performance by Integrating Structural and Gene Expression Information. *Molecules*, 18, 10789-10801.
- Chen, Y., Huang, B., He, J., Han, L., Zhan, Y. and Wang, Y. (2011). *In-vitro* and *In-vivo* Antioxidant Effects of the Ethanolic Extract of *Swertia chirayita*. *Journal of Ethnopharmacology* 136, 309-315.
- Cheng, Y., Wang, Y. and Wang, X. (2006). A Causal Relationship Discovery-Based Approach to Identifying Active Components of Herbal Medicine. *Computational Biology and Chemistry* 30, 148-154.
- Cheng, Z., Ren, J., Li, Y., Chang, W. and Chen, Z. (2002a). Establishment of a Quantitative Structure-Activity Relationship Model for Evaluating and Predicting the Protective Potentials of Phenolic Antioxidants on Lipid Peroxidation. *Journal of Pharmaceutical Sciences*, 92, 475-484.

- Cheng, Z., Ren, J., Li, Y., Chang, W. and Chen, Z. (2002b). Study on the Multiple Mechanisms Underlying the Reaction between Hydroxyl Radical and Phenolic Compounds by Qualitative Structure and Activity Relationship. *Bioorganic & Medicinal Chemistry* 10, 4067-4073.
- Cherkasov, A., Muratov, E. N., Fourches, D., Varnek, A., Baskin, II, Cronin, M., Dearden, J., Gramatica, P., Martin, Y. C., Todeschini, R., Consonni, V., Kuz'min, V. E., Cramer, R., Benigni, R., Yang, C., Rathman, J., Terfloth, L., Gasteiger, J., Richard, A. and Tropsha, A. (2014). QSAR Modeling: Where Have You Been? Where Are You Going to? *J Med Chem*, 57, 4977-5010.
- Chew, Y. L., Chan, E. W. L., Tan, P. L., Lim, Y. Y., Stanslas, J. and Goh, J. K. (2011). Assessment of Phytochemical Content, Polyphenolic Composition, Antioxidant and Antibacterial Activities of *Leguminosae* Medicinal Plants in Peninsular Malaysia. *BMC Complementary and Alternative Medicine* 11, 1-10.
- Chirinos, R., Pedreschi, R., Rogez, H., Larondelle, Y. and Campos, D. (2013). Phenolic Compound Contents and Antioxidant Activity in Plants with Nutritional and/or Medicinal Properties from the *Peruvian andean* Region. *Industrial Crops and Products*, 47, 145-152.
- Choi, C. W., Kim, S. C., Hwang, S. S., Choi, B. K., Ahn, H. J., Lee, M. Y., Park, S. H. and Kim, S. K. (2002). Antioxidant Activity and Free Radical Scavenging Capacity between Korean Medical Plants and Flavonoids by Assay-guided Comparison. *Plant Science*, 163, 1161-1168.
- Choudhary, M. I. and Sharma, B. K. (2015). QSAR Rationales for the Isoindolone Derivatives as 5-HT_{2C} Receptor Antagonists. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 6, 1725-1736.
- Dawidowicz, A. L. and Olszowy, M. (2012). Mechanisms Change in Estimating of Antioxidant Activity of Phenolic Compounds. *Talanta* 97, 312-317.
- De, B., Adhikari, I., Nandy, A., Saha, A. and Goswami, B. B. (2017). *In-silico* Modelling of Thiazolidine Derivatives with Antioxidant Potency: Models Quantify the Degree of Contribution of Molecular Fragments towards the Free Radical Scavenging Ability. *Journal of Molecular Structure* 1138, 17-26.
- Dewi, V. S. and Rao, M. G. (2014). *Alpinia Speciosa*: A Gold Ornamental Plant – A Review. *World Journal of Pharmaceutical Research*, 3, 169-177.
- Divatia, S., Chhabaria, M. T., Parmar, K. and Patel, H. (2016). QSAR Study of Benzimidazole-hydrazine Carbothioamide Derivatives as Potent Anti-malaria

- Agents against *Plasmodium Falciparum*. *Indian Journal of Chemistry*, 55B, 486-491.
- Djeridane, A., Yousfi, M., Nadjemi, B., Boutassouna, D., Stocker, P. and Vidal, N. (2006). Antioxidant Activity of Some Algerian Medicinal Plants Extracts Containing Phenolic Compounds. *Food Chemistry*, 97 654-660.
- Dudonne, S., Vitrac, X., Coutiere, P., Woillez, M. and Merillon, J. M. (2009). Comparative Study on Antioxidant Properties and Total Phenolic Content of 30 Plant Extracts of Industrial Interest using DPPH, ABTS, FRAP, SOD and ORAC assays. *Journal of Agricultural Food Chemistry*, 57, 1768-1774.
- Durand, A. C., Farce, A., Carato, P., Dilly, S., Yous, S., Berthelot, P. and Chavvatte, P. (2007). Quantitative Structure-Activity Relationship Studies of Antioxidant Hexahydropyridoinoles and Flavonoid Derivatives. *Journal of Enzyme Inhibition and Medicinal Chemistry* 22, 556-562.
- Eghdami, A., Piri, H., Sirati-Sabet, M. and Ilghari, D. (2013). Investigation of Anti Proliferative Properties and Antioxidant Activity of Aerial Parts Ethanolic Extract of *Hypericum perforatum L.* by Breast Cancer 4T1 Cell Lines. *International Journal of Biosciences*, 3, 265-272.
- Eigenvector_Research_ Inc. (2010). PLS_Toolbox. Washington, USA.
- Eklund, M., Norinder, U., Boyer, S. and Carlsson, L. (2012). Benchmarking Variable Selection in QSAR. *Molecular Informatics*, 31, 173-179.
- Eklund, M., Norinder, U., Boyer, S. and Carlsson, L. (2014). Choosing Feature Selection and Learning Algorithms in QSAR. *Journal of Chemical Information and Modeling*, 54, 837-43.
- Estrada, E., Quincoces, J. A. and Patlewicz, G. (2004). Creating Molecular Diversity from Antioxidants in Brazilian Propolis. *Molecular Diversity*, 8, 21-33.
- Fan, J., Feng, H., Yu, Y., Sun, M., Liu, Y., Li, T., Sun, X., Liu, S. and Sun, M. (2017). Antioxidant Activities of the Polysaccharides of *Chuanminshen violaceum*. *Carbohydrate Polymers* 157, 629-636.
- Farkas, O., Jakus, J. and Héberger, K. (2004). Quantitative Structure–Antioxidant Activity Relationships of Flavonoid Compounds. *Molecules* 9, 1079-1088.
- Fernandez, M., Caballero, J., Helguera, A. M., Castro, E. A. and Gonzalez, M. P. (2005). Quantitative Structure-Antioxidant Activity Relationships to Predict Differential Inhibition of Aldose Reductase by Flavonoid Compounds. *Bioorganic & Medical Chemistry*, 13, 3269-3277.

- Filipovic, M., Markovic, Z., Dorovic, J., Markovic, J. D., Lucic, B. and Amic, D. (2015). QSAR of the Free Radical Scavenging Potency of Selected Hydroxybenzoic Acids and Simple Phenolics. *Comptes Rendus Chimie*, 18 492-498.
- Forman, H. J. (2016). Redox Signaling: An Evolution from Free Radicals to Aging. *Free Radical Biology and Medicine* 97, 398-407.
- Froufe, H. J. C., Abreu, R. M. V. and Ferreira, C. F. R. (2011). QCAR Model to Predict Wild Mushroom Radical Scavenging Activity, Reducing Power and Lipid Peroxidation Inhibition. *Chemometrics and Intelligent Laboratory Systems*, 109, 192-196.
- Gaussian, I. (2003). GaussView. Wallingford, USA.
- Ghasemzadeh, A. and Ghasemzadeh, N. (2011). Flavonoids and Phenolic Acids: Role and Biochemical activity in Plants and Human. *Journal of Medicinal Plants Research*, 5.
- Ghiotto, R. C. T., Lavarda, F. C. and Ferreira, F. J. B. (1998). Antioxidant Activity of Flavonols. *International Journal Quantum Chemistry*, 97, 949-952.
- Golbraikh, A., Shen, M., Xiao, Z., Xiao, Y. D., K.H., L. and Tropsha, A. (2003). Rational Selection of Training and Test sets for the Development of Validated QSAR Models. *Journal of Computer-Aided Molecular design*, 17, 241-253.
- Gonzalez, M. P., Teran, C., Saiz-Urra, L. and Teixeira, M. (2008). Variable Selection Methods in QSAR: An Overview. *Current Topics in Medicinal Chemistry*, 8, 1606-1627.
- Goodarzi, M., Funar-Timofei, S. and Heyden, Y. V. (2013). Towards Better Understanding of Feature Selection or Reduction Techniques for Quantitative Structure-Activity Relationship Models. *Trends in Analytical Chemistry*, 42, 49-63.
- Gramatica, P. (2007). Principles of QSAR Models Validation: Internal and External. *QSAR & Combinatorial Science*, 26, 694-701.
- Grochowski, G. M., Uysal, S., Aktumsek, A., Granicac, S., Zengin, G., Ceylan, R., Locatelli, M. and Tomczyk, M. (2017). *In-vitro* Enzyme Inhibitory Properties, Antioxidant Activities and Phytochemical Profile of *Potentilla thuringiaca*. *Phytochemistry Letters* 20, 365-372.
- Gurib-Fakim, A. (2006). Medicinal Plants: Traditions of Yesterday and Drugs of Tomorrow. *Molecular Aspects and Medicine*, 27, 1-93.

- Harborne, J. B. (1998). *Phytochemicals Methods*. London: Chapman & Hall.
- Hasegawa, K. and Funatsu, K. (1998). GA Strategy for Variable Selection in QSAR Studies: GAPLS and D-optimal Designs for Predictive QSAR Model. *Journal of Molecular Structure (Theochem)*, 425, 255-262.
- Hassanpour, S., Maheri, N., Eshratkhah, B. and F.B., M. (2011). Plant and Secondary Metabolites (Tannin): A Review. *International Journal of Forest, Soil and Erosion*, 1, 47-53.
- He, J., Huang, B., Ban, X., Tian, J., Zhu, L. and Wang, L. (2012). *In-vitro* and *In-vivo* Antioxidant Activity of the Ethanolic Extract from *Meconopsis quintuplinervia*. *Journal of Ethnopharmacology* 141, 104-110.
- Heim, K. E., Tagliaferro, A. R. and Bobilya, D. J. (2002). Flavonoid Antioxidants: Chemistry, Metabolism and Structure-Activity Relationships. *Journal of Nutritional Biochemistry*, 13, 572-584.
- Helguera, A. M., Combes, R. D., Gonzalez, M. P. and Cordeiro, N. D. S. (2008). Application of 2D Descriptors in Drug Design: a DRAGON Tale. *Current Topics in Medicinal Chemistry*, 8, 1628-1655.
- Hewitt, M., Cronin, M. T. D., Madden, J. C., Rowe, P. H., Johnson, C., Obi, A. and Enoch, S. J. (2007). Consensus QSAR Models: Do the Benefits Outweigh the Complexity? *Journal of Chemical Information and Modeling*, 47, 1460-1468.
- Hiraganahalli, B. D., Chinampudur, V. C., Dethe, S., Mundkinajeddu, D., Pandre, M. K., Balachandran, J. and Agarwal, A. (2012). Hepatoprotective and Antioxidant Activity of Standardized Herbal Extracts. *Pharmacognosy Magazine*, 8, 116-23.
- Hong, H., Xie, Q., Ge, W., Qian, F., Fang, H., Shi, L., Su, Z., Perkins, R. and Tong, W. (2008). Mold², Molecular Descriptors from 2D Structures for Chemoinformatics and Toxicoinformatics. *Journal Chemical Information and Modeling*, 48, 1337-1344.
- Hoskuldsson, A. (2001). Variable and Subset Selection in PLS Regression. *Chemometrics and Intelligent Laboratory Systems* 55, 23-38.
- Hossain, M. A. and Rahman, S. M. M. (2015). Isolation and Characterization of Flavonoids from the Leaves of Medical plant *Orthosiphon stamineus*. *Arabian Journal of Chemistry*, 8, 218-221.
- Huang, B., Ke, H., He, J., Ban, X., Zeng, H. and Wang, Y. (2011). Extracts of *Halenia elliptica* Exhibit Antioxidant Properties *In-vitro* And *In-vivo*. *Food and Chemical Toxicology* 49, 185-190.

- Huang, D., Ou, B. and Prior, R. L. (2005). The Chemistry behind Antioxidant Capacity Assays. *Journal of Agricultural Food Chemistry*, 53, 1841-1856.
- Huang, W. H., Lee, A. R. and Yang, C. H. (2006). Antioxidant and Anti-inflammatory Activities of Polyhydroxyflavonoids of *Scutellaria baicalensis* Georgi. *Bioscience, Biotechnology, and Biochemistry*, 70, 2371-2380.
- Huang, W. Y., Cai, Y. Z. and Zhang, Y. (2009). Natural Phenolic Compounds from Medicinal Herbs and Dietary Plants: Potential Use for Cancer Prevention. *Nutrition and cancer*, 62, 1-20.
- Hui Gan, S., Tham, T. C., Ng, M. X., Chua, L. S., Aziz, R., Baba, M. R., Abdullah, L. C., Ong, S. P. and Law, C. L. (2016). Study on Retention of Metabolites Composition in Misai Kucing (*Orthosiphon Stamineus*) by Heat Pump Assisted Solar Drying. *Journal of Food Processing and Preservation*, 1-9.
- Ibrahim, A. A. and Abdalrazaq, E. A. (2009). Physical Properties of Phenol Compound: Semi-empirical Calculation of Substituent Effects [Part One]. *American Journal of Applied Sciences* 6, 1385-1389.
- Ignat, I., Volf, I. and Popa, V. I. (2011). A Critical Review of Methods for Characterisation of Polyphenolic Compounds in Fruits and Vegetables. *Food Chemistry*, 126, 1821–1835.
- Jain, S., Jain, D. K. and Balekar, N. (2012). *In-vivo* Antioxidant Activity of Ethanolic Extract of *Mentha pulegium* Leaf against CCl₄ Induced Toxicity in Rats. *Asian Pacific Journal of Tropical Biomedicine* 737-740.
- Jamaludin, R. and Hasan, M. N. (2010). Quantitative Structure-Activity Relationship for Antimalaria Activity of Artemisinin. *Journal of Fundamental Sciences*, 6, 76-83.
- Janifer, R. X., Bajpai, P. K., Phani, K. G., Pal, M. M., Jitendra, K., Chaourasia, O. P. and Shashi, B. S. (2010). Determination of Total Phenols, Free Radical Scavenging and Antibacterial Activities of *Mentha longifolia* Linn. Hudson from the Cold Desert, Ladakh, India. *Pharmacognosy Journal*, 2, 470-475.
- Jenifer, R. X., Bajpai, P. K., Murugan, M. P. and Srivastava, R. B. (2012). Antioxidant Activity of *Urtica hyperborea* from Cold Arid Desert Ladakh. *The Madras Agricultural Journal*, 99 181-184.
- Jiang, J. L., Zhang, H., Zhou, P. P., Han, S. N., Han, Y. D. and Yuan, Y. J. (2013). Composition–Activity Relationship Modeling to Predict The Antitumor Activity

- for Quality Control of Curcuminoids from *Curcuma Longa L.* (Turmeric). *Analytical Methods*, 5, 641-647.
- Kahkonen, M. P., Hopia, A. I., Vuorela, H. J., Rauha, J. P., Pihlaja, K., Kujala, T. S. and Heinonen, M. (1999). Antioxidant Activity of Plant Extract Containing Phenolic Compounds. *Journal of Agricultural and Food Chemistry*, 47, 3954-3962.
- Kar, S., Gajewicz, A., Puzyn, T. and Roy, K. (2014). Nano-quantitative Structure-Activity Relationship Modeling Using Easily Computable and Interpretable Descriptors for Uptake of Magnetofluorescent Engineered Nanoparticles in Pancreatic Cancer Cells. *Toxicology In-vitro*, 28, 600-606.
- Karelson, M., Lobanov, V. S. and Katritzky, A. R. (1996). Quantum-Chemical Descriptors in QSAR/QSPR Studies. *Chemical Reviews*, 96, 1027-1044.
- Karimi, E., Jaafar, H. Z. E. and Ahmad, S. (2011). Phytochemical Analysis and Antimicrobial Activities of Methanolic Extracts of Leaf, Stem and Root from Different Varieties of *Labisa pumila Benth.* *Molecules*, 16, 4438-4450.
- Katalinic, V., M., M., Kulisic, T. and Jukic, M. (2006). Screening of 70 Medicinal Plant Extracts for Antioxidant Capacity and Total Phenols. *Food Chemistry* 94, 550-557.
- Kennedy, D. O. and Wightman, E. L. (2011). Herbal Extracts and Phytochemicals: Plant Secondary Metabolites and the Enhancement of Human Brain Function. *American Society for Nutrition*, 2, 32-50.
- Kew, Y., Chia, Y. K., Lai, S. M., Chong, K. Y., Ho, X. L., Liew, D. W., Moy, F. M. and Selvarajah, S. (2015). Traditional and Complementary Medicine (TCM) among Study Population with Cardiovascular Risk; Use and Substitution for Conventional Medicine in Pahang, Malaysia. *Medical Journal Malaysia* 70.
- Khlebnikov, A. I., Schepetkin, I. A., Domina, N. G., Kirpotina, L. N. and Quinn, M. T. (2007). Improved Quantitative Structure–Activity Relationship Models to Predict Antioxidant Activity of Flavonoids in Chemical, Enzymatic, and Cellular Systems. *Bioorganic & Medicinal Chemistry* 15, 1749-1770.
- Kiralj, R. and Ferreira, M. M. C. (2009). Basic Validation Procedures for Regression Models in QSAR and QSPR Studies: Theory and Application. *Journal of The Brazil Chemical Society*, 20, 770-787.
- Kiran, B., Lalitha, V. and Raveesha, K. A. (2014). Phytochemical Screening and Antibacterial Activity of Leaves of *Eclipta alba* (L.) Hask on Important Species

- of Bacteria. *International Journal of Chemistry and Pharmaceutical Sciences*, 2, 1107-1110.
- Komeri, R., Thankam, F. G. and Muthu, J. (2017). Free Radical Scavenging Injectable Hydrogels for Regenerative Therapy. *Materials Science and Engineering*, 71, 100-110.
- Krishnaiah, D., Sarbatly, R. and Nithyanandam, R. (2011). A Review of the Antioxidant Potential of Medicinal Plant Species. *Food And Bioproducts Processing* 89, 217-233.
- Kumar, V., Anwar, F., Ahmed, D., Verma, A., Ahmed, A., Damanhour, Z. A., Mishra, V., Ramteke, P. W., Bhatt, P. C. and Mujeeb, M. (2014). *Paederia foetida* Linn. leaf extract: an antihyperlipidemic, antihyperglycaemic and antioxidant activity. *BMC Complement Altern Med*, 14, 76.
- Labute, P. (2000). A Widely Applicable Set of Descriptors. *Journal of Molecular Graphics and Modelling*, 18, 464-477.
- Leach, A. R. and Gillet, V. J. (2003). *An Introduction to Chemometrics*. Dordrecht: Kluwer Academic Publishers.
- Leardi, R. (2007). Genetic Algorithms in Chemistry. *Journal of Chromatography A*, 1158, 226-233.
- Leardi, R. and Gonzalez, A. L. (1998). Genetic Algorithms Applied to Feature Selection in PLS Regression: How and When to Use Them. *Chemometrics and Intelligent Laboratory Systems*, 41, 195-207.
- Lee, W. L. and Chan, L. K. (2004). Plant Regeneration from Stem Nodal Segment of *Orthosiphon stamineus* Benth: a Medical Plant with Diuretic Activity. *In Vitro Cellular & Developmental Biology* 40, 115-118.
- Leszczynski, J., Puzyn, T. and Cronin, M. T. D. (2010). *Challenges and Advances in Computational Chemistry and Physics* Springer.
- Li, H. B., Wong, C. C., Cheng, K. W. and Chen, F. (2008). Antioxidant Properties *In-vitro* and Total Phenolic Contents in Methanol Extracts from Medicinal Plants. *LWT* 41, 385-390.
- Li, J. Y., Wang, X. B., Luo, J. G. and Kong, L. Y. (2015). Seasonal Variation of Alkaloid Contents and Anti-Inflammatory Activity of *Rhizoma coptidis* Based on Fingerprints Combined with Chemometrics Methods. *Journal of Chromatographic Science*, 53, 1131-1139.

- Li, W. J., Cheng, X. L., Liu, J., Lin, R. C., Wang, G. L., Du, S. S. and Liu, Z. L. (2012). Phenolic Compounds and Antioxidant Activities of *Liriope muscari*. *Molecules*, 17, 1797-1808.
- Li, Z., Wan, H., Shi, Y. and Ouyang, P. (2004). Personal Experience with Four Kinds of Chemical Structure Drawing Software: Review on ChemDraw, ChemWindow, ISIS/Draw and ChemSketch. *Journal of Chemical Information and Computer Science*, 44, 1886-1890.
- Li, Z. D., S.N., H., Jiang, J. L., Zhang, X. H., Li, Y. L., Chen, H. and Yuan, Y. J. (2013). Antitumor Compound Identification from *Zanthoxylum Bungeanum* Essential Oil Based on Composition-Activity Relationship. *Chemical Research in Chinese Universities*, 29, 1068-1071.
- Liao, H., Banbury, L. K. and Leach, D. N. (2008). Antioxidant Activity of 45 Chinese Herbs and the Relationship with their TCM Characteristics. *Evidence-Based Complementary and Alternative Medicine*, 5, 429-434.
- Lien, E. J., Ren, S., Bui, H. H. and Wang, R. (1999). Quantitative Structure-Activity Relationship Analysis of Phenolic Antioxidants. *Free Radical Biological Medicine*, 26, 285-294.
- Lin, J. T., Liu, S. C., Kuo, L. C. and Yang, D. J. (2018). Composition of Phenolic Compounds and Antioxidant Attributes of *Cyclea gracillima* Diels Extracts. *Journal of Food and Drug Analysis* 26, 193-200.
- Liochev, S. I. (2013). Reactive Oxygen Species and the Free Radical Theory of Aging. *Free Radical Biology and Medicine* 60, 1-4.
- Liu, X., Wu, W. Y., Jiang, B. H., Yang, M. and Guo, D. A. (2013). Pharmacological Tools for The Development of Traditional Chinese Medicine. *Trends in Pharmacological Sciences*, 34, 620-628.
- Loganayaki, N., Siddhuraju, P. and Manian, S. (2013). Antioxidant activity and free radical scavenging capacity of phenolic extracts from *Helicteres isora* L. and *Ceiba pentandra* L. *Journal Food Science Technology*, 50, 687-695.
- Losada-Barreiro, S. and Bravo-Díaz, C. (2017). Free Radicals and Polyphenols: The Redox Chemistry of Neurodegenerative Diseases. *European Journal of Medicinal Chemistry* 133, 379-402.
- Lu, J. M., Lin, P. H., Yao, Q. and Chen, C. (2010). Chemical and Molecular Mechanisms of Antioxidants: Experimental Approaches and Model Systems. *Journal Cell. Molecular Medicine*, 14, 840-860.

- Lucas, V. B. H., Bruno, A. C. H., Jocley, Q. A., Magaly, G. A., Ricardo, B. A. and Joaquim, F. M. S. (2010). Quantitative Structure-Activity Relationships of Antioxidant Phenolic Compounds. *Journal of Chemical and Pharmaceutical Research*, 2, 291-306.
- Lynch, N. and Berry, D. (2007). Differences in Perceived Risks and Benefits of Herbal, Over-the-counter Conventional, and Prescribed Conventional, Medicines, and the Implications of this for the Safe and Effective Use of Herbal Products. *Complementary Therapies in Medicine*, 15, 84-91.
- MacDonald, L. K., Wood, L. G. and Garg, M. L. (2006). Methodology for the Determination of Biological Antioxidant Capacity *In vitro*: a Review. *Journal of the Science of Food and Agriculture*, 86, 2046-2056.
- Mansouri, K., Ringsted, T., Ballabio, D., Todeschini, R. and Consonni, V. (2013). Quantitative Structure-Activity Relationship Models for Ready Biodegradability of Chemicals. *Journal Chemical Information and Modeling*, 53, 867-878.
- Mantle, D., Eddeb, F. and Pickering, A. T. (2000). Comparison of Relative Antioxidant Activities of British Medicinal Plant Species *In-vitro*. *Journal of Ethnopharmacology* 72 47-51.
- Martins, N., Barros, L., Santos-Buelga, C., Henriques, M., Silva, S. and Ferreira, I. C. F. R. (2015). Evaluation of Bioactive Properties and Phenolic Compounds in Different Extracts Prepared from *Salvia officinalis* L. *Food Chemistry*, 170, 378-385.
- Mathwork_Inc. (2013). Natick, MA.
- Mauri, A., Consonni, V., Pavan, M. and Todeschini, R. (2006). DRAGON Software: An Easy Approach to Molecular Descriptor Calculations *Communications in Mathematical and in Computer Chemistry*, 56, 237-248.
- Mercader, A. G., Duchowicz, P. R., Fernandez, F. M., Castro, E. A., Bennardi, D. O., Autino, J. C. and Romanelli, G. P. (2008). QSAR Prediction of Inhibition of Aldose Reductase for Flavonoids. *Bioorganic & Medicinal Chemistry*, 16, 7470-7476.
- Miliauskas, G., Venskutonis, P. R. and Van Beek, T. A. (2004). Screening of Radical Scavenging Activity of Some Medicinal and Aromatic Plant Extracts. *Food Chemistry*, 85 231-237.
- Mishra, P., Tripathi, V. and Yadav, B. S. (2010). *In-silico* QSAR Modeling and Drug Development Process. *GERF Bulletin of Biosciences*, 1, 37-40.

- Mitra, I., Saha, A. and Roy, K. (2010). Exploring Quantitative Structure–Activity Relationship Studies of Antioxidant Phenolic Compounds Obtained from Traditional Chinese Medicinal Plants. *Molecular Simulation*, 36, 1067-1079.
- Mitra, I., Saha, A. and Roy, K. (2011). Chemometric QSAR Modeling and *In-silico* Design of Antioxidant No Donor Phenols. *Scientia Pharmaceutica*, 79, 31-57.
- Mitra, I., Saha, A. and Roy, K. (2012). Development of Multiple QSAR Models for Consensus Predictions and Unified Mechanistic Interpretations of the Free-radical Scavenging Activities of Chromone Derivatives. *Journal Molecular Modeling*, 18, 1819-1840.
- Mocan, A., Crisan, G., Vlase, L., Crisan, O., Vodnar, D. C., Raita, O., Gheldiu, A. M., Toiu, A., Oprean, R. and Tilea, I. (2014). Comparative Studies on Polyphenolic Composition, Antioxidant and Antimicrobial Activities of Schisandra chinensis Leaves and Fruits. *Molecules*, 19, 15162-15179.
- Mohamed, K. A., Saida, A. E. and Mohammed, H. R. (2013). Quantitative Structure-Trypanocidal Activity Relationship Analysis of Phenothiazine Derivatives. *Indian Journal of Applied Research*, 3, 65-68.
- Montoro, P., Braca, A., Pizza, C. and Tommasi, N. D. (2005). Structure-Antioxidant Activity Relationships of Flavanoids Isolated from Different Plant Species. *Food Chemistry*, 92, 349-355.
- Mota, S. G. R., Barros, T. F. and Castilho, M. S. (2009). 2D QSAR Studies on a Series of Bifonazole Derivatives with Antifungal Activity. *Journal Brazil Chemical Society*, 20, 452-459.
- Mustafa, R. A., Abdul, H. A., Mohamed, S. and Bakar, F. A. (2010). Total Phenolic Compounds, Flavonoids, and Radical Scavenging Activity of 21 Selected Tropical Plants. *Journal Food Science*, 75, 28-35.
- Nayak, S. K., Patra, P. K., Padhi, P. and Panda, A. (2010). Optimization of Herbal Drugs using Soft Computing Approach *International Journal of Logic and Computation* 1, 34-39.
- Nowaczyk, A. and Kulig, K. (2012). QSAR Studies on a Number of Pyrrolidin-2-one Antiarrhythmic Arylpiperazinyls. *Medical Chemistry Research* 21, 373-381.
- Onoja, S. O., Omeh, Y. N., Ezeja, M. I. and Chukwu, M. N. (2014). Evaluation of the *In-vitro* and *In-vivo* Antioxidant Potentials of *Aframomum melegueta* Methanolic Seed Extract. *Journal of Tropical Medicine*, 1-6.

- Osman, A. M., Wong, K. K. Y. and Fernyhough, A. (2006). ABTS radical-driven oxidation of polyphenols: Isolation and structural elucidation of covalent adducts. *Biochemical and Biophysical Research Communications* 346, 321-329.
- Oyedemi, S. O., Bradley, G. and Afolayan, A. J. (2010). *In-vitro* and *In-vivo* Antioxidant Activities of Aqueous Extract of *Strychnos henningsii* Gilg. *African Journal of Pharmacy and Pharmacology*, 4, 70-78.
- Pan, S. Y., Zhou, S. F., Gao, S. H., Yu, Z. L., Zhang, S. F., Tang, M. K., Sun, J. N., Ma, D. L., Han, Y. F., Fong, W. F. and Ko, K. M. (2013). New Perspectives on How to Discover Drugs from Herbal Medicines: CAM's Outstanding Contribution to Modern Therapeutics. *Evidence-Based Complementary and Alternative Medicine*, 1, 1-25.
- Patel, P. D., Patel, M. R., Kaushik-Basu, N. and Talele, T. T. (2008). 3D QSAR and Molecular Docking Studies of Benzimidazole Derivatives as Hepatitis C Virus NS5B Polymerase Inhibitors. *Journal of Chemical Information and Modeling*, 48, 42-55.
- Patel, V. R., Patel, P. R. and Kajal, S. S. (2010). Antioxidant Activity of Some Selected Medicinal Plants in Western Region of India. *Advance in Biological Research*, 4, 23-26.
- Pauku, Y., Rasulev, B., Syrov, V., Khushbaktova, Z. and Leszczynski, J. (2009). Structure-Hepatoprotective Activity Relationship Study of Sesquiterpene Lactones: A QSAR Analysis. *International Journal of Quantum Chemistry*, 109, 17-27.
- Pereira, D. M., Valentao, P., J.A., P. and Andrade, P. B. (2009). Phenolics: From Chemistry to Biology. *Molecules*, 14, 2202-2211.
- Pourbasheer, E., Aalizadeh, R., Tabar, S. S., Ganjali, M. R., Norouzi, P. and Shadmanesh, J. (2014). 2D and 3D-QSAR Study of Hepatitis C Virus NS5B Polymerase Inhibitors by CoMFA and CoMSIA Methods. *Journal of Chemical Information and Modeling*, 1-56.
- Pourmorad, F., Hosseinimehr, S. J. and Shahabimajd, N. (2006). Antioxidant Activity, Phenol and Flavonoids Content of Some Selected Iranian Medical Plants. *African Journal of Biotechnology*, 5, 1142-1145.
- Prokai, L., Rivera-Portalatin, N. M. and Prokai-Tatrai, K. (2013). Quantitative Structure-Activity Relationship Predicting the Antioxidant Potency of 17 β -

- Estradiol-Related Polycyclic Phenols to Inhibit Lipid Peroxidation. *International Journal of Molecular Sciences*, 14, 1443-1454.
- Promden, W., Monthakantirat, O., Umehara, K., Noguchi, H. and De-Eknamkul, W. (2014). Structure and Antioxidant Activity Relationships of Isoflavonoids from *Dalbergia parviflora*. *Molecules*, 19, 2226-37.
- Raheel, R., Saddiqe, Z., Iram, M. and Afzal, S. (2017). *In-vitro* antimutagenic, antiproliferative and antioxidant activity of stem bark extracts of *Ficus benghalensis* L. *South African Journal of Botany*, 111, 248-257.
- Rajurkar, N. S. and Hande, S. M. (2011). Estimation of Phytochemical Content and Antioxidant Activity of Some Selected Traditional Indian Medicinal Plants. *Indian Journal of Pharmaceutical Science*, 73, 146-151.
- Randic, M. (2001). Novel Shape Descriptors for Molecular Graphs. *Journal of Chemical Information and Modeling*, 41, 607-613.
- Rastija, V. and Medic-Saric, M. (2009). QSAR Study of Antioxidant Activity of Wine Polyphenols. *European Journal of Medicinal Chemistry*, 44 400-408.
- Rasulev, B. F., Abdullaev, N. D., Syrov, V. N. and Leszczynski, J. (2005). A Quantitative Structure-Activity Relationship (QSAR) Study of the Antioxidant Activity of Flavonoids. *QSAR & Combinatorial Science*, 24, 1056-1065.
- Ray, S., De, K., Sengupta, C. and Roy, K. (2008a). QSAR Study of Lipid Peroxidation-Inhibition Potential of Some Phenolic Antioxidants. *Indian Journal of Biochemistry & Biophysics*, 45, 198-205.
- Ray, S., Sengupta, C. and Roy, K. (2007). QSAR Modeling of Antiradical and Antioxidant Activities of Flavonoids Using Electrotopological State (E-State) Atom Parameters. *Central European Journal of Chemistry*, 5, 1094-1113.
- Ray, S., Sengupta, C. and Roy, K. (2008b). QSAR Modelling for Lipid Peroxidation Inhibition Potential of Flavonoids using Topological and Structural Parameters. *Central European Journal of Chemistry*, 5, 267-276.
- Razali, N., Mat-Junit, S., Abdul-Mutalib, A. F., Subramaniam, S. and Abdul-Aziz, A. (2012). Effects of Various Solvents on the Extraction of Antioxidant Phenolics from the Leaves, Seeds, Veins and Skins of *Tamarindus indica* L. . *Food Chemistry*, 131, 441-448.
- Re, R., Pellegrini, N., Proteggente, A., Pannala, A., Yang, M. and Evans, C. R. (1999). Antioxidant Activity Applying an Improved ABTS Radical Cation Decolorization Assay. *Free Radical Biology & Medicine*, 26, 1231-1237.

- Rebaya, A., Belghith, S. I., Baghdikian, B., Leddet, V. M., Mabrouki, F., Olivier, E., Cherif, J. K. and Ayadi, M. T. (2014). Total Phenolic, Total Flavonoid, Tannin Content, and Antioxidant Capacity of *Halimium halimifolium* (Cistaceae). *Journal of Applied Pharmaceutical Science* 5, 52-57.
- Reilly, S. M., Goel, R., Trushin, N., Elias, R. J., Foulds, J., Muscat, J., Liao, J. and Richie, J. P. (2017). Brand Variation in Oxidant Production in Mainstream Cigarette Smoke: Carbonyls and Free Radicals. *Food and Chemical Toxicology* 106, 147-154.
- Reis, M., Lobato, B., Lameira, J., Santos, A. S. and Alves, C. N. (2007). A Theoretical Study of Phenolic Compounds with Antioxidant Properties. *European Journal of Medicinal Chemistry*, 42, 440-446.
- Rice-Evan, C. A., Miller, N. J. and Paganga, G. (1996). Structure-Antioxidant Activity Relationships of Flavonoids and Phenolic Acids. *Free Radical Biology & Medicine*, 20, 933-956.
- Rispail, N., Morris, P. and Webb, K. J. (2005). *Phenolic compounds extraction and analysis*. Wales: Lotus japonicus Handbook.
- Roy, K., Kar, S. and Das, R. N. (2015). *A Primer on QSAR/QSPR Modeling: Fundamental Concepts*. Springer International Publishing.
- Roy, K. and Mitra, I. (2009). Advances in Quantitative Structure–Activity Relationship Models of Antioxidants. *Expert Opinion: Drug Discovery* 4, 1157-1175.
- Roy, K. and Roy, P. P. (2008). Comparative QSAR Studies of CYP1A2 Inhibitor Flavonoids Using 2D and 3D Descriptors. *Chemical Biology Drug Design* 72, 370-382.
- Roy, P. P., Leonard, J. T. and Roy, K. (2008). Exploring the Impact of Size of Training Sets for the Development of Predictive QSAR Models. *Chemometrics and Intelligent Laboratory Systems* 90, 31-42.
- Roy, P. P., Paul, S., Mitra, I. and Roy, K. (2009). On Two Novel Parameters for Validation of Predictive QSAR Models. *Molecules*, 14, 1660-1701.
- Saeed, N., Khan, M. R. and Shabbir, M. (2012). Antioxidant Activity, Total Phenolic and Total Flavonoid Contents of Whole Plant Extracts *Torilis leptophylla* L. *BMC Complementary and Alternative Medicine* 12, 1-12.
- Saleem, U., Ahmad, B., Ahmad, M., Hussain, K. and Bukhari, N. I. (2014). Investigation of *In-vivo* Antioxidant Activity of *Euphorbia helioscopia* Latex

- and Leaves Methanol Extract: A Target Against Oxidative Stress Induced Toxicity. *Asian Pacific Journal of Tropical Medicine*, 369-375.
- Sanilkumar, R. and Muthu, A. K. (2013). Evaluation of *In-vivo* Antioxidant Activity of Methanolic Extract of *Triumfetta rotundifolia* (Linn.) on Streptozotocin induced Oxidative Stress in Wistar Rats. *Journal Pharmaceutical Science & Research* 5, 249-253.
- Santos, C. B. R., Lobato, C. C., Braga, F. S., Morais, S. S. S., Santos, C. F., Fernandes, C. P., Brasil, S. B., Hage-Melim, L. I. S., Macedo, W. J. C. and Carvalho, J. C. T. (2014). Application of Hartree-Fock Methos for Modeling of Bioactive Molecules using SAR and QSPR. *Computatial Molecular Bioscience*, 4, 1-24.
- Saxena, A. K. and Prathipati, P. (2003). Comparison of MLR, PLS and GA-MLR in QSAR Analysis. *SAR and QSAR in Environmental Research*, 14, 433-445.
- Selvaraj, S., Chittibabu, C. V. and Janarthnam, B. (2014). Studies on Phytochemical Screening, Antioxidant Activity and Extraction of Active Compound (swertiamarin) from Leaf Extract of *Enicostemma littorale*. *Asian Journal of Pharmaceutical and Clinical Research*, 7, 240-244.
- Senese, C. L. and Cronin, M. T. D. (2008). Application of the Modelling Power Approach to Variable Subset Selection for GA-PLS QSAR Models. *Analytical Chimica Acta*, 609, 169-174.
- Senguttuvan, J., Paulsamy, S. and Karthika, K. (2014). Phytochemical Analysis and Evaluation of Leaf and Root Parts of the Medicinal Herb, *Hypochoeris radicata* L. for *In-vitro* Antioxidant Activities. *Asian Pacific Journal of Tropical Biomedicine* 4, 359-367.
- Sergediene, E., Johnsson, K., Szymisiak, H., Tyrakowska, B., Rietjens, I. M. C. M. and Cenas, N. (1999). Prooxidant Toxicity of Polyphenolic Antioxidant to HL-60 cells: Description of Quantitative Structure-Activity Relationships. *FEBS Letters* 462, 392-396.
- Serviddio, G., Bellanti, F. and Vendemiale, G. (2013). Free Radical Biology for Medicine: Learning from Nonalcoholic Fatty Liver Disease. *Free Radical Biology and Medicine*, 65, 952-968.
- Shahlaei, M. (2013). Descriptor Selection Methods in Quantitative Structure-Activity Relationship Studies: A Review Study. *Chemical Review*, 113, 8093-8103.

- Sharma, S., Satpathy, G. and Gupta, R. K. (2014). Nutritional, Phytochemical, Antioxidant and Antimicrobial Activity of *Prunus armenicus*. *Journal of Pharmacognosy and Phytochemistry*, 3, 23-28.
- Shayanfar, A. and Shayanfar, S. (2014). Is regression Through Origin Useful in External Validation of QSAR Model? *European Journal of Pharmaceutical Science*.
- Shon, M. Y., Kim, Y. H. and Sung, N. J. (2003). Antioxidant and Free Radical Scavenging Activity of *Phellinus baumii* (*Phellinus* of *Hymenochaetaceae*) Extract. *Food Chemistry*, 82, 593-597.
- Sivakumar, P. M., Prabhakar, P. K. and Doble, M. (2011). Synthesis, Antioxidant Evaluation, and Quantitative Structure-Activity Relationship Studies of Chalcone. *Medical Chemistry Research*, 20, 482-492.
- Soobrattee, M. A., Neergheen, V. S., Luximon-Ramma, A., Aruoma, O. I. and Bahorun, T. (2005). Phenolics as Potential Antioxidant Therapeutic Agents: Mechanism and Actions. *Mutation Research*, 579, 200-213.
- Stalikas, C. D. (2007). Extraction, Separation and Detection Methods for Phenolic Acids and Flavonoids. *Journal of Separation Science*, 30, 3268-3295.
- Sumanth, M. and Rana, A. C. (2006). *In-vivo* Antioxidant Activity of Hydroalcoholic Extract of *Taraxacum officinale* Roots in Rats. *Indian Journal Pharmacological* 38, 54-55.
- Surveswaran, S., Cai, Y. Z., Corke, H. and Sun, M. (2007). Systematic Evaluation of Natural Phenolics Antioxidants from 133 Indian Medicinal Plants. *Food Chemistry*, 102, 938-953.
- Surveswaran, S., Cai, Y. Z., Xing, J., Corke, H. and Sun, M. (2010). Antioxidant Properties and Principal Phenolic Phytochemicals of Indian Medical Plants from *Asclepiadoideae* and *Periplocoideae*. *Natural Product Research*, 24, 206-221.
- Tachakittirungrod, S., Okonogi, S. and Chowwanapoonpohn, S. (2007). Study on Antioxidant Activity of Certain Plants in Thailand: Mechanism of Antioxidant Action of Guava Leaf Extract. *Food Chemistry* 103, 381-388.
- Takeda, H., Tsuji, M., Miyamoto, J. and Matsumiya, T. (2002). Rosmarinic Acid and Caffeic Acid Reduce the Defensive Freezing behaviour of Mice Exposed to Conditioned Fear Stress. *Psychopharmacology* 164, 233-235.
- Tang, H., Wang, X. S., Huang, X. P., Roth, B. L., Butler, K. V., Kozikowski, A., P., Jung, M. and Tropsha, A. (2009). Novel Inhibitors of Human Histone

- Deacetylase (HDAC) Identified by QSAR Modeling of Known Inhibitors, Virtual Screening, and Experimental Validation. *Journal of Chemical Information and Modeling*, 49, 461-476.
- Tanwar, B. and Modgil, R. (2012). Flavonoids: Dietary Occurrence and Health Benefits. *Spatula DD*, 2, 59-68.
- Tasdemir, D., Kaiser, M., Brun, R., Yardley, V., Schmidt, T. J., Tosun, F. and Ruedi, P. (2006). Antitrypanosomal and Antileishmanial Activities of Flavonoids and Their Analogues: *In-vitro*, *In-vivo*, Structure-Activity Relationship and Quantitative Structure-Activity Relationship Studies. *Antimicrobial Agents and Chemotherapy*, 50, 1352-1364.
- TCMD, M. o. H. M. (2015). Traditional and Complementary Medicine (T&CM) Act. National Regulatory Conference 2015. Retrieved on 4 January 2016, from <https://npra.moh.gov.my/images/Announcement/2015/NRC-2015-day2/TMHS08-P-Ms-TehLiYin-31-07-15.pdf>.
- Tetko, I. V., Gasteiger, J., Todeschini, R., Mauri, A., Livingstone, D., Ertl, P., V.A., P., Radchenko, E. V., Zefirov, N. S., A.S., M., Tanchuk, V. Y. and Prokopenko, V. V. (2005). Virtual Computational Chemistry Laboratory-Design and Description. *Journal of Computer-Aided Molecular Design*, 19, 453-463.
- Tibaut, T., Drgan, V. and Marjana, N. (2018). Application of SAR Methods toward Inhibition of Bacterial Peptidoglycan Metabolizing Enzymes. *Journal of Chemometrics*, 32, 1-11.
- Todeschini, R. and Consonni, V. (2000). *Handbook of Molecular Descriptors*. Germany: Wiley-VCH, Weinheim.
- Todeschini, R. and Consonni, V. (2003). *Descriptors from Molecular Geometry. Handbook of Chemoinformatics*. Germany: Wiley-VCH, Weinheim.
- Todeschini, R. and Consonni, V. (2009). *Molecular Descriptors for Chemoinformatics* Germany: WILEY-VCH, Weinheim.
- Todeschini, R., Consonni, V., Mauri, A. and Pavan, M. (2010). DRAGON - Software for Molecular Descriptor Calculations (Version 6.0 for Windows). *Milan, Italy: Talete srl*.
- Tropsha, A. (2010). Best Practices for QSAR Model Development, Validation and Exploitation. *Molecular Information*, 29, 476-488.
- Usman, B., Maarof, H., Abdallah, H. H. and Aziz, M. (2015). Computational Evaluation of the Effect of Structural Parameters of 3-Fluoro Thiophene and 3-

- thiophene Malonic Acid on Corrosion Inhibition Efficiency of Mild Steel in Acidic Media. *International Journal of Electrochemical Science*, 10, 3223-3229.
- Usman, B., Maarof, H., Abdallah, H. H., Jamaludin, R., Al-Fakih, A. M. and Aziz, M. (2014). Corrosion Inhibition Efficiency of Thiophene Derivatives on Mold Steel: A QSAR Model. *International Journal Electrochemical Science*, 9, 1678 - 1689.
- Vanommeslaeghe, K., Guvench, O. and MacKerell, A. D. (2014). Molecular Mechanics. *Current Pharmaceutical Design*, 20, 3281-3292.
- Velkov, Z. A., Kolev, M. K. and Tadjer, A. V. (2007). Modeling and Statistical Analysis of DPPH Scavenging Activity of Phenolics. *Collection of Czechoslovak Chemical Communications*, 72, 1461-1471.
- Verma, A. R., Vijayakumar, M., Mathela, C. S. and Rao, C. V. (2009). *In-vitro* and *In-vivo* Antioxidant Properties of Different Fractions of *Moringa oleifera* Leaves. *Food and Chemical Toxicology* 47, 2196-2201.
- Vinholes, J., Rudnitskaya, A., Goncalves, P., Martel, F., Coimbra, M. A. and Rocha, S. M. (2014). Hepatoprotection of Sesquiterpenoids: a Quantitative Structure-Activity Relationship (QSAR) Approach. *Food Chemistry*, 146, 78-84.
- Votano, J. R., Parham, M., Hall, L. H., Kier, L. B., Oloff, S., Tropsha, A., Xie, Q. and Tong, W. (2004). Three New Consensus QSAR Models for the Prediction of Ames Genotoxicity. *Mutagenesis*, 19, 365-377.
- Wan Zaki, W. M. and Mohd Rani, A. (2013). Country Status Report on Medicinal and Aromatic Plants in Malaysia. *Proceedings of Expert Consultation on MAP in the Asia-Pacific Region*, 174-185.
- Wang, Y., Wang, X. and Cheng, Y. (2006). A Computational Approach to Botanical Drug Design by Modeling Quantitative Composition–Activity Relationship. *Chemical Biology & Drug Design*, 68, 166-172.
- Weber, K. C., Honorio, K. M., Bruni, A. T. and da Silva, A. B. (2006). The Use of Classification Methods for Modeling the Antioxidant Activity of Flavonoid Compounds. *Journal Molecule Model*, 12, 915-920.
- Wei, J. B., Li, X., Song, H., Liang, Y. H., Y.Z., P., Ruan, J. X., Qin, X., Chen, Y. X., Nong, C. L. and Su, Z. H. (2015). Characterization and Determination of Antioxidant Components in The Leaves of *Camellia Chrysantha* (Hu) *Tuyama* Based on Composition-activity Relationship Approach. *Journal of Food and Drug Analysis*, 23, 40-48.

- WHO. (2000). General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine. Retrieved on 11 December 2016, from http://apps.who.int/iris/bitstream/10665/66783/1/WHO_EDM_TRM_2000.1.pdf.
- Wise, B. M., Gallagher, N. B., Bro, R., Shaver, J. M., Winding, W. and Koch, R. S. (2006). *PLS _Toolbox 4.0 for Use with MATLAB*. Wenatchee, WA: Eigenvector Research, Inc.
- Wojdylo, A., Oszmianski, J. and Czemerts, R. (2007). Antioxidant Activity and Phenolic Compounds in 32 Selected Herbs. *Food Chemistry*, 105, 940-949.
- Wojtunik-Kulesza, K. A., Oniszczyk, A., Oniszczyk, T. and Waksmundzka-Hajnos, M. (2016). The Influence of Common Free Radicals and Antioxidants on Development of Alzheimer's Disease. *Biomedicine & Pharmacotherapy* 78, 39-49.
- Wold, S. (1991). Validation of QSAR's. *Quantitative Structure-Activity Relationship* 10, 191-193.
- Wold, S., Sjostrom, M. and Eriksson, L. (2001). PLS-regression: a Basic Tool of Chemometrics. *Chemometrics and Intelligent Laboratory Systems* 58, 109-130.
- Wong, K. C., Wang, C. and Wu, L. (1936). *History of Chinese Medicine: Being a Chronicle of Medical Happenings in China from Ancient Times to the Present Period*. Tientsin Press.
- Wright, J. S., Johnson, E. R. and DiLabio, G. A. (2001). Predicting the Activity of Phenolic Antioxidants: Theoretical Method, Analysis of Substituent Effects and Application to Major Families of Antioxidants. *Journal of The American Chemical Society*, 123, 1173-1183.
- Wu, J. A., Attele, A. S., Zhang, L. and Yuan, C. S. (2001). Anti-HIV Activity of Medicinal Herbs: Usage and Potential Deveomennt. *American Journal of Chinese Medicine*, 29, 69-81.
- Xiao, S., Fei, C. Z., Zhang, L. F., Zheng, W. L., Zhang, K. Y. and Xue, F. Q. (2014). Spectrum-Effect Relationship between High Performance Liquid Chromatography Fingerprints and Anticoccidial Activities of a Compound Chinese Medicine. *Journal of Integrative Agriculture*, 13, 1082-1089.
- Xiao, S., Zhang, L. F., Zhang, X., Li, S. M. and Xue, F. Q. (2013). Tracing Antibacterial Compounds from *Acalypha Australis* Linn. by Spectrum-Effect Relationships and Semi-Preparative HPLC. *Journal of Separation Science* 36, 1667-1676.

- Xiaobo, Z., Jiewen, Z., Povey, M. J. W., Holmes, M. and Hanpin, M. (2010). Variables Selection Methods in Near-Infrared Spectroscopy. *Analytica Chimica Acta*, 667 14-32.
- Xu, J., Huang, S., Luo, H., Li, G., Bao, J., Cai, S. and Wang, Y. (2010). QSAR Studies on Andrographolide Derivatives as Alpha-glucosidase Inhibitors. *International Journal of Molecular Sciences*, 11, 880-895.
- Yadav, R. and Nandi, S. (2014). QSAR and Anticancer Drug Design of β -Carboline Compounds Utilizing Computed Molecular Descriptors *Journal of Computational Methods in Molecular Design*, 4, 92-105.
- Yan, S. K., Lin, Z. Y., Dai, W. X., Shi, Q. R., Liu, X. H., Jin, H. Z. and Zhang, W. D. (2010). Chemometric-based Approach to Modeling Quantitative Composition-Activity for *Radix Tinosporae*. *Interdiscip Science Computer and Life Science*, 2, 221-227.
- Ye, Y., Luo, Y. and Wang, Y. (2012). Antioxidant Activity of Related Compounds Besides Polyphenols in Chinese Herabs. In: Ieee (ed.) *International Conference on Biomedical Engineering and Biotechnology*.
- Yee, L. C. and Wei, Y. C. (2012). *Current Modeling Methods Used in QSAR/QSPR*. In: M. Dehmer, K. V. a. D. B. (ed.) *Statistical Modeling of Molecular Descriptors in QSAR/QSPR*. (1-31). First ed.: Wiley-VCH Verlag GmbH & Co.
- Zang, Q. C., Wang, J. B., Kong, W. J., Jin, C., Ma, Z. J., Chen, J., Gong, Q. F. and Xiao, X. H. (2011). Searching for The Main Anti-Bacterial Components in Artificial Calculus Bovis using UPLC and Microcalorimetry Coupled with Multi-Linear Regression Analysis. *J. Sep. Sci.* , 34, 3330-3338.
- Zheng, Q., Zhao, Y., Wang, J., Liu, T., Zhang, B., Gong, M., Li, J., Liu, H., Han, B., Zhang, Y., Song, X., Li, Y. and Xiao, X. (2014). Spectrum-Effect Relationships between UPLC Fingerprints and Bioactivities of Crude Secondary Roots of *Aconitum Carmichaelii Debeaux (Fuzi)* and its Three Processed Products on Mitochondrial Growth Coupled with Canonical Correlation Analysis. *Journal of Ethnopharmacology* 153, 615-623.
- Zheng, W. and Wang, S. Y. (2001). Antioxidant Activity and Phenolic Compounds in Selected Herbs. *Journal Agriculture Food Chemical*, 49 5165-5170
- Zhou, G., Chen, Y., Liu, S., Yao, X. and Wang, Y. (2013). *In-vitro* and *In-vivo* Hepatoprotective and Antioxidant Activity of Ethanolic Extract from

Meconopsis integrifolia (Maxim.) Franch. *Journal of Ethnopharmacology* 148, 664-670.