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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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-separa 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 penjuru jambatan 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
$ABTS^{\bullet+}$	-	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 peroxidise
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
$DPPH^{\bullet}$	-	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
HOMO	-	Highest Occupied Molecular Orbital
LUMO	-	Lowest Unoccupied Molecular Orbital
E_{HOMO}	-	Energy of the *HOMO*
E_{LUMO}	-	Energy of the *LUMO*
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
EMEA	-	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-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
RMSEC	-	Root-mean-square error of calibration
RMSECV	-	Root-mean-square error of cross-validation
RMSEP	-	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 used 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
IPv	-	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 ($ABTS^{\bullet+}$) 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 $ABTS^{\bullet+}$ 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 rangking 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 $ABTS^{\bullet+}$ assay in TEAC.
   ii) The signifcant 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 compouds.
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.

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